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Travel Advice for HIV-Infected Individuals

By Robin McKenzie, M.D.

A growing number of HIV-infected individuals are traveling to developing countries for vacations, business, or visits with friends and family. This article discusses ways to reduce the risk of travel for immunosuppressed patients.

Vaccines

Pre-travel preparation includes updating routine vaccines and administering "travel" vaccines that are specific for the regions to be visited. Since most of the pre- and post-marketing data for these vaccines were obtained in healthy individuals, there are concerns about safety and efficacy when vaccines are given to immunocompromised travelers. In general, vaccines that are not "live" can be given safely to HIV-infected persons, but their immunogenicity may be reduced, roughly in proportion to the reduction in CD4 count.

A summary of vaccine recommendations is contained in the [Table on page 18](#). Before travel all routinely recommended vaccines should be updated. Each traveler should be fully immunized against tetanus-diphtheria, which requires booster injections every 10 years. If available, an annual influenza vaccine should be given, since influenza occurs year-around in the tropics. While pneumococcal infection is not considered to be a travel-related illness, HIV-infected individuals are at greater risk for pneumococcal disease and should be vaccinated, probably with a booster

every five years. Even though hepatitis B virus (HBV) infection is more common in developing countries, HBV infection is not commonly acquired by travelers. HBV vaccine is recommended, however, for those who will be exposed to blood products, those who will have sexual contact or daily physical contact with the local population, and those who may receive medical or dental care while abroad. Additionally, HBV vaccine is standard-of-care in non-immune HIV-infected individuals. For travel to areas with high levels of endemic HBV infection, the longer the trip and the greater the contact with the local population, the greater the risk. The hepatitis B vaccine is given in 3 doses at 0, 1 and 6 months. In young, healthy adults antibody develops in about 60%, 80% and 95% of vaccinees after the first, second and third dose respectively. For HIV-infected individuals these rates are probably lower. Even though one dose may give some protection, it is clearly preferable to complete the series. Occasionally vaccination is completed abroad.

Measles occurs commonly in developing countries and in some developed countries in Europe and Asia. In general, individuals born in the US before 1957 are naturally immune. Healthy travelers born after 1957 should have confirmation of immunity, either based on a history of two doses of measles, mumps, and rubella vaccine (MMR, the first dose of which is usually given at 12-15 months of age) or a

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Discordants Able to Get HIV-Free Babies

Byline: The East African Standard

Couples in a discordant relationship are able to have children with minimal risk of exposure to HIV infection, experts say.

A research conducted by the World Federation of Haemophilia in the United Kingdom confirms that alternative methods of conception are available for couples in a relationship where the male is HIV-positive and female is negative.

These methods drastically reduce the risk of HIV-negative females becoming infected by semen as they try to conceive. Couples, however, have to undergo a Highly Effective Anti-Retroviral Therapy (HAART) to achieve this.

Before couples attempt any prescribed methods of conception, they have to undergo fertility assessment in a specialist unit. This is mainly to ensure pregnancy is possible and that chances of HIV infection are minimal. Both the male and female undergo genital tract infection screening so that any infection can be treated, therefore reducing the risk of transmission.

According to the World Health Organization, the minimum criteria is a sperm count. There must be more than 20 million cells per ml, with more than 50 per cent of the sperms being mobile.

Female partners must have open fallopian tubes and a normal uterine cavity. These can be assessed by either a special X-ray test, combined with a direct inspection of the cavity of the uterus using a scope passed up the birth canal and through the cervix. Normal ovulation must also be demonstrated.

Both the male and female have to undergo infection screening, which entails a thorough health examination and screening for concurrent sexually transmitted infection (STD). This should be performed on the female before fertility investigations.

Treatment of any STI detected in the male has been shown to significantly reduce the HIV load in semen. Therefore, if infection is detected, it should be eradicated before conception is attempted.

Female partners should have an HIV test performed to ensure they are not infected. If either partner has a history of genital herpes, both should be taking appropriate anti-viral medication at the time of unprotected intercourse to prevent infection spread to the uninfected partner.

If a decision is made to proceed with conception, routine pre-pregnancy measures should be initiated. These include the female taking the vitamin folic acid (0.4mg a day), three months prior to the planned conception date and continuing until at least week 12 of pregnancy. The female should also be up-to-date with her cervical screening.

Timed ovulatory intercourse

Using this method, the risk of HIV transmission is the same as that of unprotected sexual intercourse. However, this method probably offers the best chance of conception and is arguably the only reasonable alternative (provided all possible measures have been taken to minimize transmission risk) when other methods are not available or not acceptable.

Before attempting this method, it is recommended that fertility rests should be confirmed as being normal and genital infection in either partner is appropriately treated.

A semen HIV load should be checked regardless of whether or not the man is on HAART. If HIV is not detected in the semen or the viral load is low, it should be checked on one or two further occasions to exclude the possibility that he is a "super shedder."

Men on HAART with undetectable HIV in blood and semen should not be considered risk-free. While there

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HealthWise by Lucinda K. Porter, RN, CCRC

The high price of health care is dominating some of my social conversations. Other than gasoline, perhaps nothing more essential is so obviously inflated. Rising health care costs are occurring at many levels. Hospital, laboratory, and professional fees are increasing. Insurance is costing more but covering less. According to a report released by the Kaiser Family Foundation, health insurance premiums rose more than 11% this year. Insurance plan deductibles and co-payment amounts keep rising. Medicare premiums will increase by 17% in 2005. Prescription drug costs are going up.

These rising costs, particularly of prescriptions drugs are affecting us all, chiseling away at our earnings. Patricia Barry writes poignantly in an article appearing in the October 2003 AARP Bulletin, "A widow recently sold her wedding ring to pay for medicine. Another sometimes begs for prescription drugs left by friends who've died. Another on occasion uses pills prescribed for her dog." The Medicare Prescription Drug Law and the Medicare Prescription Discount card were intended to reduce prescription drug costs and to some extent they have. Unfortunately, these programs are confusing and are not serving those who need the most help.

In my work with patients, I frequently see examples of how the high cost of prescription drugs and health care can drive people to creative or desperate measures. Treatment for chronic hepatitis C virus (HCV) infection is expensive. Patients without insurance and other economic means or with high deductibles and prescription co-pay amounts, simply cannot afford HCV treatment. Some call Stanford Medical Center and other hospitals in the country, looking for clinical trials that treat their conditions and provide free medication, lab tests, and clinic visits. Although not all clinical trials offer free medication and treatment, when they do this can be an excellent resource. Before participating in a clinical trial, it is important to be informed of the entire process before agreeing to be in a drug trial. In order to judge the feasibility of a study from a financial standpoint, some questions to ask are:

What is the purpose of the study?

What is the drug or combination of drugs being tested?

What are the potential benefits or risks of my participation in the study?

Will I incur any costs? Will the treatment or tests be free?

Is a placebo being used? If so, what are the chances of receiving the study drug versus the placebo? If I receive the placebo, will I be offered the study drug at the end of the trial period?

Current treatment for chronic HCV uses peginterferon alfa combined with ribavirin. Peginterferon alfa is currently marketed by two companies, Hoffmann-La Roche and Schering. No generic form of peginterferon alfa is available. Hoffmann-La Roche and Schering also sell their own brands of ribavirin, but there is a generic form available. At this time, generic ribavirin is not necessarily a cheaper alternative. Hopefully competition will have a healthy influence on the ribavirin market. For more information about HCV medications, see "[A Simple Guide to Understanding the Cost of HCV Medications](#)," by Alan Franciscus, HCV Advocate (May 2003).

Patients are looking for cheaper drugs for all of their medical problems, not just HCV. The following are some cost-saving ideas to consider:

- Ask your doctor if there is a cheaper version of your medication, such as a generic form
- Inquire about free samples
- See if you qualify for a pharmaceutical patient assistance program. For more information contact Needy Meds www.needymeds.com or try www.helpingpatients.org
- Shop for the best drug price, such as through Costco, wholesale, or reliable Internet-based pharmacies
- Look for discounted drug prices, such as through your insurance plan, or AARP. Insurance pharmacy mail order plans can really cut costs. Some pharmaceutical companies, such as Pfizer, offer discounted drug prices for everyone without prescription drug coverage. For more about this, look for information at the website of the pharmaceutical company that sells the medication you are taking.
- If it's a drug you are confident you will be taking for some time and at a steady dose, see if a 90 day supply costs less than a 30 day supply.
- Join a discount pharmacy program. These programs offer discounted drug prices for an annual membership fee. If you are interested in this option, make sure the membership fee is reasonable and that the program carries the medications you are taking.
- Compare the price of different strengths of the drug. Ask your doctor if the pill can be prescribed at a higher dose and safely divided in half. For instance, if you are supposed to take a 5 mg dose of a medication every day, it may be cost effective to purchase a 30-day supply of a 10 mg dose and divide it in two. This would stretch the medication over a 60 day time period. Do not do this without your doctor's knowledge because some pills should not be cut.

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Healthwise (continued)

- A lesser known option is a program called The Medicine Program. For a fee of \$5.00 per medication, this service is staffed by volunteers who attempt to find free-of-charges prescriptions. This service can be reached at (573) 996-7300 www.themedicineprogram.com

For more information about Medicare programs, call Medicare at 1-800-MEDICARE (1-800-633-4227) or go to www.medicare.gov/MedicareReform. Kaiser Family Foundation provides some interesting information about this program and other health topics at www.kff.org.

Lately there has been a lot in the press about purchasing prescription drugs in Canada, Mexico, or overseas. In some cases this is perfectly legal and other cases it is not. The laws about this vary, depending on the medication and how it is being used. Medication from another country is not always the same or safe and not necessarily cheaper. However, sometimes it can be the same drug priced at a substantial savings. One resource that can provide more information about this option is www.medicineassist.org

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Editor's Note: Lucinda Porter made reference to voting on 11/2/04. Due to the date in reprinting this article, two paragraphs have not been included.

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Hepatitis C Treatment Recommended for Shorter Course of Therapy

Schering Plough recently announced that the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion for the approval of a shorter, 24-week course of peginterferon alfa-2b and ribavirin combination therapy for the treatment of hepatitis C virus genotypes 2 and 3. Previously, peginterferon alfa-2b was approved in the European Union for a 48-week course in combination with ribavirin. The safety of effectiveness of the 24-week treatment was compared with that of historical control patients receiving the 48-week course.

R&D Focus Drug News

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Discordants Able to Get HIV-Free Babies (continued)

have been no studies to assess transmission risk in this situation, it is likely to be very low.

Artificial insemination with washed sperm

This process greatly minimizes the risk of HIV transmission to the female, and at present, it is considered to be the preferred conception method for HIV-discordant couples.

The clinical application of this method was pioneered by Prof Semprini from Milan, Italy, who has been offering assisted conception for HIV-discordant couples using this technique since 1989.

A sperm-washing conception service is very expensive to establish and run, and therefore very few other centers worldwide have so far set up a similar service. It is unlikely that such a service will be available in Kenya in the near future.

Centers currently offering sperm-washing conception service include the Chelsea and Westminster Hospital, London, Munich (Germany); and Barcelona (Spain). Since early 2001, more than 300 cycles of sperm washing and intrauterine insemination or in-vitro fertilization have been performed in these centers.

There have been more than 300 live births and no reported transmission of HIV to any of the female partners or children.

Usually, couples will have to pay to enter a sperm-washing conception program, as it is exceptional for funding to be obtained from other sources. In the UK, for example, couples are not funded by the National Health Service. The cost of sperm-washing conception may be prohibitive for many of them. In the UK, the cost of the procedure is at least £1,000 (Approximately Sh143,000).

Sperm washing involves centrifugation of semen, with subsequent removal of seminal plasma and non- seminal cells and resuspension of sperm in a sterile fluid. A number of groups have demonstrated the effectiveness of this procedure in reducing the amount of transmissible HIV in semen, experts say.

In a study performed at the Chelsea and Westminster Hospital, 10 of 11 HIV-infected men were found to have HIV in their semen. Following sperm washing using a very sensitive detection technique, HIV was no longer present in any of the sperm samples that were positive before washing.

Once the pre-screening tests and counseling are completed, a timetable for the procedure is agreed upon. Insemination of the washed sperm can be performed during a natural menstrual cycle following ovulation, which is confirmed using a kit that detects hormone level changes in the urine. Twenty-four hours after ovulation, the male partner is invited to donate semen by masturbation. The semen is collected into a sterile container and "washed." A sample of washed semen is taken and screened for the presence of HIV. If the test is negative, the sperm is inseminated into the female using a soft catheter inserted through the cervix into the uterus.

A pregnancy test is performed two weeks later and, if it is positive, the female is closely screened for HIV throughout the rest of the pregnancy. Based on available data, chances of pregnancy using this technique are about 10 per cent. Several attempts may therefore have to be performed.

Although it is now considered routine to test washed sperm for HIV prior to insemination due to the rapidity with which the result is required, the technique used is extremely expensive.

This is a major cost element in the establishment of a sperm-washing service and the price of the procedure.

However, as large numbers of couples were treated by Semprini prior to the introduction of post-wash HIV testing with no HIV transmission, it would appear that washing technique is fully effective at removing any living virus. Therefore, a strong case can be made for omitting post-wash testing, which considerably reduces the cost of the procedure.

Male-positive-female-negative HIV discordant couples wishing to have children should be offered appropriate counseling and advice before attempting conception.

They should make a decision as to which option to choose, based on balancing the chances of conception against risk of HIV transmission. Of the two main alternatives, artificial insemination with washed sperm is the safer option.

If sperm washing conception is not feasible or acceptable, couples can consider timed ovulatory intercourse, which, although not completely without risk, may be considered a risk worth taking because of the higher chance of conception.

Africa News
July 26, 2004

Acetaminophen and Your Liver

by Liz Highleyman

The pain-reliever acetaminophen is one of the best-selling over-the-counter medications, used by 100 million people each year. It is sold under many brand names, including Tylenol, and is an ingredient in hundreds of combination medications, both over-the-counter (such as Excedrin, Midol, NyQuil, and Sudafed) and prescription (such as Vicodin).

Most people believe that acetaminophen is safe, but it can cause serious liver damage—and even acute liver failure—if it is taken in high enough doses. In fact, it is one of the leading causes of liver failure in the United States, accounting for more than 56,000 emergency room visits and 100 deaths each year. *Unsafe At Any Dose?*

Most people are only at risk for liver toxicity if they take more than the normal recommended amount of acetaminophen. Most cases of liver damage occur in people who have taken at least 10-15 grams—more than twice the recommended dose. Many of the emergency room visits and deaths linked to acetaminophen poisoning are due to accidental or intentional overdoses (for example, suicide attempts).

But some people are more susceptible to acetaminophen toxicity and can experience liver damage even at the recommended dose. A study by the U.S. Food and Drug Administration (FDA) showed that about 20% of people with acetaminophen-related liver toxicity had taken less than the recommended daily amount. For other people, a dangerous dose is not much higher than the recommended dose—that is, the “window” between a therapeutic dose and a toxic dose is smaller for acetaminophen than it is for many other drugs. Some experts also believe that taking acetaminophen for several days in a row may cause a dangerous build-up of the drug in the body.

Acetaminophen is more likely to cause liver toxicity at near-normal doses when used by people who drink alcohol. In fact, people who drink regularly may be more prone to liver damage even if they do not consume alcohol and acetaminophen at the same time. There appears to be added risk even if people take acetaminophen a few hours, or in some cases longer, before or after drinking. Since the mid-1990s, the Tylenol package has included a warning against drinking alcohol when using the drug.

How Acetaminophen Harms the Liver

Like many drugs, acetaminophen is metabolized by

the liver. If the normal processing pathway is overwhelmed by a high dose, a different pathway known as the cytochrome P450 enzyme system kicks in. When this happens, a toxic metabolic byproduct called NAPQI is produced that can kill liver cells. Alcohol and many other drugs also use the cytochrome P450 processing system, and the risk of a “bottleneck” is greater if the liver has to deal with both acetaminophen and these other substances at the same time.

Acetaminophen poisoning has three stages. During the first 12-24 hours after taking the drug, a person may experience nausea and vomiting. During the second phase, from 24-48 hours, the person usually feels better. After 48-72 hours, however, liver enzyme (ALT and AST) levels start to rise, indicating liver injury. In the most severe cases, a person may develop acid buildup in the blood, excessive bleeding, and coma. At this stage, only a liver transplant can prevent death.

Fortunately, there is an antidote for acetaminophen poisoning. NAPQI is normally detoxified by a naturally occurring antioxidant called glutathione. But if too much acetaminophen is present, the body's supply of glutathione can be used up. An amino acid called N-acetylcysteine (NAC), which restores glutathione in the cells, can be administered to reverse acetaminophen toxicity. NAC is most effective when used within 16 hours after taking acetaminophen; however, people often do not recognize that gastrointestinal symptoms could be an early sign of acetaminophen poisoning.

Fair Warning?

An FDA advisory panel recommended several times (most recently in September 2002) that products containing acetaminophen should carry a warning on the label about the risk of liver toxicity. In January 2004, the FDA launched a new public education campaign warning consumers about the potential risks of acetaminophen and other pain-relievers. Some companies now clearly label their products containing acetaminophen. This is important because unintentional overdoses can occur when people take two or more medications together without realizing they all contain acetaminophen. However, the FDA still does not require that such products carry a warning label concerning liver toxicity.

Acetaminophen for People with Hepatitis

What does all this mean for people with chronic hepatitis

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What are Fibrosis and Cirrhosis?

by Liz Highleyman

Chronic infection with hepatitis C or hepatitis B virus (HCV or HBV) can lead to long-term liver damage including fibrosis, cirrhosis, and hepatocellular carcinoma (liver cancer). It is estimated that about 20 percent of people with chronic hepatitis C will develop cirrhosis, a process that usually takes 20-30 years.

The Fibrosis Process

Liver fibrosis refers to the accumulation of fibrous scar tissue in the liver. The formation of scar tissue is a normal bodily response to injury, but in fibrosis this healing process goes awry. When hepatocytes (functional liver cells) are injured due to viral infection, alcohol consumption, toxins, trauma, or other factors the immune system is activated and the repair process swings into gear. The injury or death (necrosis) of hepatocytes stimulates inflammatory immune cells to release cytokines, growth factors, and other chemicals. These chemical messengers direct support cells in the liver called hepatic stellate cells to activate and produce collagen, glycoproteins (such as fibronectin), proteoglycans, and other substances. These substances are deposited in the liver, causing the buildup of extracellular matrix (nonfunctional connective tissue). At the same time, the process of breaking down or degrading collagen is impaired. In a healthy liver, the synthesis (fibrogenesis) and breakdown (fibrolysis) of matrix tissue are in balance. Fibrosis occurs when excessive scar tissue builds up faster than it can be broken down.

Fibrosis Risk Factors

Liver fibrosis does not occur at the same rate in all individuals, and in some people fibrosis remains stable or may even regress over time. Several factors influence fibrosis progression. Fibrosis occurs more rapidly in men than in women, and also in older people, particularly those over age 50. Progression does not seem to be linear; that is, the process appears to accelerate later in the course of disease. Immune system compromise for example, due to coinfection with HIV or use of immunosuppressive drugs after a liver transplant also has been shown to accelerate fibrosis. Heavy alcohol consumption is strongly associated with worsening fibrosis and cirrhosis. Finally, studies indicate that steatosis (fatty liver) and insulin resistance are associated with more rapid and severe fibrosis. In contrast, HCV or HBV viral load and HCV genotype do not appear to have much effect on fibrosis progression (although genotype 3 is associated with a higher risk of steatosis).

Advanced Fibrosis and Cirrhosis

Early in the course of fibrosis, a person usually will ex-

perience few or no symptoms. Over years or decades, however, the liver can become excessively scarred, developing nodules and thick bands of fibrous tissue (septa) that extend from one area or portal of the liver to another—a condition known as cirrhosis. As cirrhosis sets in, scar tissue replaces working hepatocytes and the basic architecture or structure of the liver changes, affecting the organ's ability to function. One such change is the obstruction of the normal flow of blood through the liver. Early on, this can deprive hepatocytes of nutrients, causing increased cell death. In an attempt to restore circulation, new blood vessels form. But these new vessels do not drain efficiently and accumulating scar tissue may put pressure on other vessels, causing blood to back up in the portal vein (portal hypertension). One symptom is stretched and weakened blood vessels (varices) in the esophagus and stomach, which may burst and bleed. Compensated cirrhosis occurs when the liver is heavily scarred but can still function relatively normally. Decompensated cirrhosis occurs when the liver is so damaged that its vital functions are impaired. The organ loses its ability to filter toxins from the blood and to synthesize important proteins, leading to clinical symptoms such as cognitive dysfunction (hepatic encephalopathy), accumulation of fluid in the abdomen (ascites), and prolonged bleeding. In the most severe cases, cirrhosis may progress to hepato-cellular carcinoma or end-stage liver disease (liver failure), necessitating a transplant.

Grading Fibrosis and Cirrhosis

Early fibrosis can be difficult to diagnose because it is often asymptomatic. Various techniques are under study to detect fibrosis using noninvasive blood tests, for example by measuring markers of fibrogenesis and fibrolysis. But the current "gold standard" for determining the extent of liver disease is liver biopsy, in which a small sample of tissue is removed with a needle, stained, and examined under a microscope. In order to monitor progression in a timely manner, most experts recommend repeat biopsies every 3-5 years.

Various systems are used to grade fibrosis and cirrhosis. These include the Knodell Histological Activity Index (HAI), a modified HAI known as the Ishak system, and the METAVIR system. All three systems include separate scores for histological activity (necrosis and inflammation) and fibrosis; inflammation itself is not a reliable predictor of fibrosis severity. The Knodell system includes four components, for periportal/bridging

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Maintaining a Positive Attitude

Alan Franciscus, Editor-in-Chief

HCV therapy is not easy for many people. The side effects that people experience on therapy range from mild to severe. In addition to the physical side effects, one may experience a multitude of psychological problems that can be triggered by interferon and ribavirin. In order to get through therapy, sometimes it is simply a matter of equipping yourself with the necessary tools and strategies.

Maintaining a positive attitude while on treatment may be difficult, but it is essential and should be at the top of your list for side effect management. Although there is no scientific data at this time to support the notion that a positive attitude will have an impact on hepatitis C or treatment outcome, many patients report that attitude was an important part of staying on therapy. Strive to maintain a positive attitude, but it would be unrealistic to assume that you will achieve perfection 100% of the time. The point is that a positive attitude is a process and not the goal. Be realistic and don't set yourself up for failure because this is the time that you need to be gentle with yourself.

Attitude

How do you maintain a positive attitude? There are many steps you can take:

Before beginning therapy write a list of the reasons why you are being treated and read the list often.

Reasons to undergo therapy are:

- To improve health
- Live longer
- To feel that you have done all that you can do
- To be alive for your children, grandchildren and loved ones
- To experience life and all it has to offer
- To simply get rid of the virus
- To put the treatment or hepatitis C behind you
- To have children
- To reduce symptoms and increase quality of life
- To help reach personal and professional goals
- To avoid being a burden to others

Starting the day off with a positive attitude is half the battle. When you wake up in the morning try to think of one thing you are grateful for in your life. Examples:

- I feel grateful that I have the opportunity to take this treatment
- I am grateful for the people in my life
- I am grateful I have a roof over my head or a bed

to sleep in at night

Try restructuring your thought processes. For example:

- Instead of saying "I'm overwhelmed," say and believe "I am doing the best that I can"
- If you find yourself thinking "I'm tired," try saying to yourself "This will eventually pass"
- When you say "I can't do this," try saying "I can do this because it is only temporary"

In the evening when you are going to sleep, look back at your day and define what made you feel better and what made you feel worse. Congratulate yourself for getting through the day! Remind yourself that you are one more day closer to completing treatment and your goal.

Support

Staying positive while on therapy would be almost impossible if a person did not have a very good support system established and in place well before starting therapy. Support from as many areas as possible is critical. Support comes in many forms, including family, friends, co-workers, and from peers found in support groups. If you do not already attend a support group, consider joining one before starting therapy.

Personal Appearance

Keeping a positive attitude requires that you take really good care of your body, including your appearance. When you look good you generally feel better. If you wake up in the morning and feel achy and out of sorts generally, it will help you feel better if you take the necessary steps to stay well groomed. Starting your day off feeling fresh will create a positive influence on your emotions for the entire day.

Try these strategies:

- Shower or bathe daily. Spoil yourself with bathing products that smell and feel good. Light a candle and listen to soothing music
- Take care of the hands and nails
- Moisturize, moisturize, moisturize!
- Consider getting a different hair style that would be attractive, easy to take care of and flattering in case there is hair loss
- Brush and floss your teeth regularly
- Men - shower and shave or trim facial hair
- Women - if you regularly use make-up, then continue while on treatment
- Keep finger and toe nails well groomed

- Get dressed even if you will be laying on the couch (wear comfortable clothing)
- Wear colors that make you feel good

Exercise

Exercise is one of the most important components of health maintenance, even on therapy. It will help you stay positive, focused and improve your general well-being. Moderation is the key to physical activity. Exercise comes in many forms and does not mean that you have to spend an enormous amount of money or run a marathon to stay fit.



Examples:
Stretching
Walking
Hula-hooping
Swimming
Yoga
Pilates

Social Events

Treatment-related side effects and the everyday demands of life can create some uncertainty. Maintain a social life but be realistic when scheduling dates or appointments. The surest way to become depressed is to isolate yourself from family and friends. However, it is important to talk with family and friends before starting treatment so that they can be supportive if you need to cancel or adjust any plans. Sometimes just the knowledge that you can cancel or leave a social activity early will help to reduce the stress. Relax and enjoy the time spent with family and friends.

Daily Strategies

Engage in activities that make you laugh. Choose movies that are comedies rather than movies with painful themes. Read the comics, watch sitcoms, use humor - use it during the difficult moments to get a better perspective. In-

clude in a favorite hobby, but, most of all, learn to pamper yourself.

www.hcvadvocate.org October 2004. Reprint permission is granted and encouraged with credit to the Hepatitis C Support Group.

Relaxation

Being on HCV medication is stressful. Trying to remember to take all of the medications, dealing with side effects, a job and family can greatly overwhelm most people. It is important that people build in relaxation strategies. Try some of these to help you with relaxing:

- Meditation—try saying "may I be well" while you take a deep breath, say "may others be well" when you exhale
- Prayer—practice your spiritual preference at least once a day
- Light a candle and listen to music
- Many people hold their breath when they are stressed out. During these periods try gently breathing in and out
- Sit or walk in a place of natural beauty, such as a beach, garden, or park

HIV-HCV Notes

Vitamins May Slow HIV Disease

(From *The New York Times*, 7/1/04)

A nutritious diet, possibly supplemented by vitamin pills, may extend the life of HIV-positives. The use of vitamins has been studied as a stop-gap therapy in poor, developing countries where patients, often vitamin-deficient, have little hope of getting anti-viral drugs. Researchers in Africa and Asia, principally studying nutritionally vulnerable men and women, found that the use of supplements delayed the progress of AIDS in patients and lowered mortality. One study emphasized B, C and B-complex vitamins.

A professor of nutrition and epidemiology at Harvard, the lead author of an eight-year study of women, said that those who benefited from vitamins did so "regardless of whether they were undernourished or not."

HIV/HCV Coinfection

(By B. Andrew Plant, *Hepatitis*, April-June 2004)

As you probably know, the key measure of success in HCV treatment, regardless of mono-infection or coinfection, is sustained virologic response (usually defined as having an undetectable viral load six months after ending therapy). To a greater extent than ever before, research is indicating that fewer coinfecting people will have a truly sustained response than if they were mono-infected.

Researchers are realizing that people who initially respond to treatment later experience "viral rebound." Previously, research tended to report results from the middle or end of therapy/test periods; results from the same test subjects, measured later, indicate that fewer than previously thought actually had a sustained response.

A study designed to measure the effectiveness of pegylated interferon alone or combined with ribavirin in the treatment of coinfecting individuals compared with mono-infected people was recently reported in the *Journal of Infectious Diseases*. Though the viral dynamics of coinfecting and mono-infected people are, of course, different, treatment response generally seems similar.

Even so, there does seem to be somewhat of an added difficulty for a person whose body must "clear" both HIV and HCV. This was indicated by slower first (treatment) phase results, and it is assumed, therefore,

that HIV slows HCV-specific immune responses. That in turn could slow the clearance of HCV and may result in a shorter sustained period of clearing overall.

Another explanation simply might be that coinfecting individuals tend to have a higher pretreatment HCV viral load to begin with, likely due to the presence of HIV. It is important to know that only a small number of test subjects was involved in this study. Perhaps, the results will inspire similar, larger research of the same nature.

Until then, it is likely the "answers" remain the same as they have been assumed to be for some time in terms of coinfection treatment, which often involves higher doses (at least during the first few weeks of treatment) for longer periods and with more frequent retreatment.

Transplantation

The occurrence of end-stage liver disease is increasing among HIV-infected people due to the fact that they are living longer in general and because their organs can be imperiled by the very medications that are extending their lives. Organ transplantation in HIV-positive people is gaining acceptance. It has been demonstrated that HCV-infected people, whether or not they are HIV-positive, have a somewhat shortened survival rate, post-transplant. However, at least two recent studies indicate that a key difference may be related, in large part, to the nature of post-transplant treatment received.

There is increased difficulty in tolerating both HIV and HCV treatment after transplantation. Multiple studies underscore the fact that it is crucial to select the optimal combination of HIV drugs so that the transplanted liver is not challenged more than is necessary. Added to that are indications that survival rates tend to improve if a patient is allowed to stabilize a bit before HIV and HCV treatment is reintroduced, even though the recurrence rate of HCV infection post-transplant is quite high. Previously, a common practice was to treat the HCV fairly early after a transplant – even empirically (that is, before symptoms were noted) – in order to head off the recurrence of HCV.

That said, research continues to indicate poorer post-transplant survival rates for people with end-stage liver disease, whether they are mono-infected or coinfecting, meaning we are more likely to see liver transplants occur earlier in treatment or, at least, in indi-

viduals who have not yet reached the more severe stages of liver disease.

Reason to Monitor the Thyroid

Spanish research first reported late last year seems to indicate that pegylated interferon may be related with higher incidence of thyroid dysfunction, particularly in people coinfecting with HIV/HCV. Just under ten percent experienced this apparent side effect.

However study participants who were found during HCV treatment (with pegylated interferon and ribavirin) to have thyroid disease were able to complete their courses of treatment. So the primary indication from the study seems to be that regular thyroid monitoring in coinfecting people is a good idea, principally during their HCV treatment.

One of the great challenges in reporting on coinfection is that a great deal of research on the topic is taking place. While it is tough to report all of the breaking coinfection news, the good news is simply that there is an appreciable amount of focus in this area.

HIV/HCV Coinfection: Summary from ICAAC & AASLD by Liz Highleyman

Several presentations at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the American Association for the Study of Liver Diseases (AASLD) meeting, both held in late October—early November 2004, dealt with hepatitis C and HIV coinfection.

Treatment of Coinfected Individuals

Following on the heels of the APRICOT and ACTG 5071 studies, the PRESCO (Pegasys Plus Ribavirin for HCV Treatment in HIV/HCV Coinfection) trial (ICAAC abstract V-1148) again showed promising results using pegylated interferon plus ribavirin to treat HIV/HCV-coinfected individuals. This ongoing multicenter study by M. Núñez and colleagues from Madrid's Hospital Carlos III includes about 350 subjects with well-controlled HIV disease and good overall health; about half have hard-to-treat HCV genotype 1, about 40% have genotypes 2 or 3, and about 10% have genotype 4. This study used relatively high weight-adjusted doses of ribavirin (low initial doses of ribavirin may have contributed to the high relapse rate seen in ACTG 5071). The present analysis included nearly 200 patients who completed 24 weeks of therapy. After 24 weeks, an intent-to-treat analysis revealed that 63% of all subjects and 50% of those with genotype 1 achieved

undetectable HCV viral loads. As-treated response rates were higher (71% overall and 61% for genotype 1), since this analysis excluded the approximately 20% of subjects who discontinued therapy early due to adverse events or other causes. While this response rate for genotype 1 patients is higher than those seen with the same duration of treatment in other coinfection studies, longer follow-up is needed to determine whether participants will go on to achieve sustained virological response (SVR) 24 weeks after the completion of therapy.

When to Stop HCV Treatment

Given the difficult side effects and high cost of hepatitis C treatment, it would be useful to predict which patients are likely to achieve SVR so therapy can be stopped early in people who will not benefit. Two presentations at ICAAC showed that—as is the case with HCV-monoinfected individuals—coinfecting patients who respond poorly early in the course of therapy usually do not go on to achieve SVR. Maribel Rodríguez-Torres and colleagues (ICAAC abstract H-1751) analyzed data from a subset of nearly 300 subjects in the APRICOT study (about 60% with genotype 1). They found that while a good response (at least a 2-log drop in HCV RNA) at week 4 or week 12 did not necessarily predict SVR (positive predictive value of 66% and 56%, respectively), a poor response at these time points did predict lack of SVR (negative predictive value of 88% at week 4 and 98% at week 12). The researchers concluded that 12 weeks was the best time to assess progress and make a decision about continuing therapy, since four weeks seemed to be too early and missed some people who would later achieve SVR. Early response data from the PRESCO study (ICAAC abstract H-1753) support a similar conclusion. Manel Crespo presented similar findings at AASLD (abstract 428), again validating a 2-log HCV RNA decrease at week 12 as a useful predictor of ultimate treatment success. In contrast, however, a small study by E. Shaw and colleagues (ICAAC abstract H-1752) found that no patients who failed to demonstrate at least a 1-log drop in HCV RNA by week 4 later achieved SVR (negative predictive value of 100%).

Low-Dose Interferon

Another way to limit side effects related to hepatitis C treatment is to use lower doses of interferon and/or ribavirin, but there is concern that this strategy may compromise the effectiveness of therapy. Ghassan Hammoud reported at AASLD (abstract 520) that in a study of 63 coinfecting individuals (about half black, about 1/4 with genotype 1), subjects who received low-dose (1.0 mcg/kg/week) pegylated interferon (Peg-Intron) plus weight-adjusted ribavirin for 48 weeks re-

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sponded about as well as those who received a higher Peg-Intron dose (1.5 mcg/kg/week). These results must be interpreted with caution since both end-of-treatment response and SVR rates were unusually low (27% and 11%, respectively) in this study compared to those seen in other recent coinfection trials.

Histological Response

Looking at histological response in the APRICOT trial, Eduardo Lissen and colleagues (AASLD abstract 174) found that while SVR (40% overall) correlated with improved liver fibrosis, a "substantial proportion" of patients experienced histological improvement even in the absence of SVR. Improvement in liver health was seen in 69% of those who achieved SVR and in 43% of those who did not achieve a sustained response.

Side Effects of HCV Therapy

L. Moreno and colleagues (ICAAC abstract V-0784) reported that many coinfecting individuals with advanced fibrosis experience severe side effects when using interferon plus ribavirin, but some can still benefit from hepatitis C treatment. In this prospective study of 56 subjects, 88% were on combination anti-HIV therapy and most had well-controlled HIV disease (although 18% had an AIDS diagnosis); 59% had genotype 1 HCV, and 43% had evidence of cirrhosis. At the end of HCV treatment (just over three-quarters with pegylated interferon), 29% experienced an end-of-treatment response, but only 14% achieved SVR. More than one-quarter (29%) discontinued treatment due to side effects; one-fifth of the subjects were hospitalized and two (4%) died during therapy. Blood cell deficiencies were particularly common: neutropenia, 73%; thrombocytopenia, 61%; anemia, 38%. The poor results seen in this study may be related to the fact that a substantial number of the subjects had a history of injection drug use and returned to active use during HCV treatment. Because some individuals responded well to treatment, however, the researchers suggested interferon plus ribavirin could be a viable option for patients with advanced liver disease.

In other side effects reports, Ana Rendón, also from the Hospital Carlos III team, reported that levels of ribavirin in the blood could predict which patients would develop anemia during treatment (ICAAC abstract H-1754). Although all 49 people in this analysis received the same weight-adjusted doses of ribavirin (1000 mg if under 75 kg, 1200 if above this weight), blood levels of the drug varied widely among individuals. Not surprisingly, patients with higher ribavirin blood concentrations were more likely to develop anemia. These results suggest that drug level monitoring could play a role in managing

HCV treatment side effects. In related research, Lev Ginzburg (AASLD abstract 397) reported that women and people over age 55 were at higher risk of anemia while taking ribavirin than men and younger individuals.

Liver Toxicity Due to HIV Therapy

In terms of liver toxicity related to HIV therapy, C. Cooper and colleagues (ICAAC abstract H-1759) found that, based on a chart review of HCV positive patients at Ottawa Hospital treated with anti-HIV drugs between January 1994 and December 2003, severe liver toxicity was uncommon. Just 7% developed an ALT level more than five times the upper limit of normal, and only 3% switched or discontinued HIV medications due to liver problems (all of these were taking full-dose protease inhibitors, not non-nucleoside reverse transcriptase inhibitors or low "boosting" doses of ritonavir [Norvir]). L. Aranzabal from Ramón y Cajal Hospital in Madrid (ICAAC abstract H-1760) reported, based on a study of 107 coinfecting patients, that individuals with moderate-to-advanced liver damage (Knodel fibrosis scores of 3 or 4) were nearly three times more likely to experience severely elevated ALT than patients with less fibrosis. In related research, J. Sasadeusz (AASLD abstract 372) reported that Pegasys plus ribavirin "appears to be safe and well-tolerated" in coinfecting subjects in the APRICOT trial who had compensated cirrhosis. However, two subjects with decompensated cirrhosis died during the study, leading the researchers to urge caution in such patients.

Liver Transplantation

Several studies to date have shown that people with HIV have liver transplant outcomes nearly or as good as those of HIV-negative people. But new research indicates that current algorithms for allocating donor organs may work to the disadvantage of HIV positive and coinfecting individuals. A study by M. Sánchez-Conde from the Hospital Carlos III team (ICAAC abstract H1758) found a disproportionately high mortality rate among coinfecting HIV patients on liver transplant waiting lists (4 out of 20, or 20%), and suggested that HIV positive individuals with cirrhosis should be assessed and added to waiting lists "much earlier" than their HIV-negative counterparts. In related news, Isabelle Pache (AASLD abstract 442) reported that more than half (58%) of HIV/HCV-coinfecting patients with cirrhosis met the criteria for transplantation, but that 29% died either before evaluation or while waiting for a new liver. Pache and colleagues suggested that since liver damage progresses more rapidly in coinfecting individuals, a "more specific and sensitive criteria" than the MELD score should be defined for coinfecting patients, and that such individuals "should be referred early in the course of the liver disease to a liver transplantation unit."

AASLD 2004: Part 2

By Alan Franciscus, Editor-in-Chief

Longer Duration of Treatment

The current standard of care for treating hepatitis C (HCV) is the combination of pegylated interferon and ribavirin, which results in an overall sustained virological response (SVR, continued undetectable HCV viral load 6 months after the completion of therapy) of up to 50% in genotype 1 and up to 90% in genotype 2 and 3 patients. Standard treatment protocol is to treat genotype 1 patients for 48 weeks and genotype 2 and 3 patients for 24 weeks. However, more and more research is indicating that there are other important factors to consider when treating HCV, such as viral load, liver histology, gender, body mass index and steatosis. In HCV genotype 1 patients there is a high relapse rate in patients treated with pegylated interferon and ribavirin when patients are treated for 48 weeks. The reasons for the relapse are unknown, but one speculation is that these difficult to treat patients may require an even longer course of therapy.

Thomas Berg and colleagues reported on a German multicentre study of 456 patients with HCV genotype 1 infection treated with 180 ug peginterferon alfa-2a (Pegasys) plus 800 mg ribavirin for either 48 weeks (231 patients) or 72 weeks (225 patients).

The results of this study reported that the relapse rate for all patients who responded to the course of therapy was 23%. There was a slight difference in the relapse rate in patients treated for 48 weeks (26% relapse) vs. 72 weeks (19% relapse). However, a significant difference in relapse rates was found in patients with a late virological response, defined as HCV RNA greater than 1000 U/L at week 4 or 12, and negative at week 24. In the group that was treated for 48 weeks with a late virological response the relapse rate was 46% or 82% compared to 29% or 44% in patients who were treated for 72 weeks.

The authors concluded that a small but significant number of genotype 1 patients with detectable HCV RNA at week 4 or 12, but who became HCV RNA negative by week 24, would benefit from a longer duration of therapy. There is a larger prospective study underway to confirm these findings.

Durability of SVR

Sustained virological response is defined as becoming HCV RNA (viral load) negative during treatment with continued negative HCV RNA following 6 months after the completion of HCV therapy. SVR is considered by some experts to be a "cure" even though some reports have shown that a minority of patients (approximately 2-3%) of patients become HCV RNA detectible after

achieving an SVR. The reason for the return of detectable viral load has not been well studied, but some unknown variables such as re-infection of HCV, sensitivity of HCV RNA tests or lab error may exist. Because pegylated interferon plus ribavirin therapy has been studied for a shorter period of time, the durability of sustained virological response for pegylated interferon plus ribavirin therapy is unknown. The interim results of a study of peginterferon alfa-2a (Pegasys) plus ribavirin (Copegus) SVR durability were reported.

Mark Swain and colleagues reported on the interim results of 845 patients who achieved an SVR and on those of more than 40 patients have been followed for 5 years or longer. Of the total number of patients enrolled in this follow-up trial, 174 patients received peginterferon alfa-2a (Pegasys) monotherapy and 671 received various doses of peginterferon alfa-2a (Pegasys) plus ribavirin (Copegus). Overall, 838 of the 845 patients (99.2%) remained HCV RNA negative during the long term follow-up period. The authors concluded that "An SVR achieved with peginterferon alfa-2a (40KD) (Pegasys), alone or in combination with ribavirin (Copegus) is durable for up to 5 years after completion of therapy." The authors also reported that there were no obvious common risk or treatment factors associated with detection of HCV RNA during follow-up, but that further investigation is underway to determine the reason for the reemergence of the HCV virus.

Pegylated Interferon Long Term Maintenance

There is much research to determine the benefits of long term peginterferon maintenance therapy to delay or reverse HCV disease progression. Two ongoing trials are of interest: the HALT-C trial using Pegasys, and the COPILOT study using Colchicine (COLC) vs. Peg-Intron (PEG).

Colchicine vs. Peg-Intron

The interim analysis of clinical outcomes at Year 2 of the COPILOT study was reported at AASLD. Colchicine (KOL-chi-seen) is used to prevent or treat attacks of gout (also called gouty arthritis). Colchicine does not cure gout or take the place of other medicines that lower the amount of uric acid in the body. It prevents or relieves gout attacks by reducing inflammation. In the study, the effectiveness (slowing HCV disease progression) of colchicine (6 mg po bid) was compared with low dose Peg-Intron (0.5mg/kg/wk) in patients with advanced fibrosis (Ishak >3), who failed prior interferon based therapies.

534 patients are enrolled in the study to date. Of these, 264 received colchicine and 270 received Peg-Intron.

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Patient characteristics were well matched. 70% of the patients have received 2 years of therapy or have reached an endpoint. 59 patients (39 treated with colchicine; 20 treated Peg-Intron) have reached a clinical verified endpoint for an annual event rate of approx. 5%. (The primary endpoints are death, liver failure, variceal bleeding, liver cancer or liver transplant). The authors found that the primary endpoint showed a benefit in favor of Peg-Intron when compared to colchicine.

Overall 83 patients (14%) failed to comply with the study and are being followed off treatment or on alternative treatment. 38 (7%) discontinued for an adverse event (15 of colchicine; 23 of Peg-Intron). There were no unexpected or unusual serious adverse events in either group.

The authors concluded that "Low dose maintenance PEG is superior to COLC in preventing clinical complications of cirrhosis over 2 years of treatment, particularly in patients with portal hypertension and hypoalbuminemia. Maintenance therapy with PEG may be an option in cirrhotic patients who fail interferon based therapies.

Pegasys

The results of the use of Pegasys in the HALT-C trial are eagerly awaited. In the meantime, the results of a study conducted by Gregory Everson and colleagues on the benefits of Pegasys monotherapy on histologic improvement was reported on at AASLD.

The data for this study was obtained from a randomized controlled trial that compared 48 weeks of treatment with peginterferon alfa 2a (Pegasys) 90 ug/week or 180 ug/week or interferon alfa-2a (Roferon) 3 million units 3x a week in 271 patients with cirrhosis or bridging fibrosis. Of these, pre- and post-treatment biopsies were available from 184 patients graded and staged (Metavir) by one pathologist blinded to treatment and to time of biopsy.

The primary end-points were improvement in fibrosis stage (defined as = 1 stage improvement) and inflammatory grade (defined as = 1 grade improvement) from baseline. The patient characteristics were similar between the three groups. The results of this study found that the SVR rates were higher in the Pegasys 180 ug/week group. In addition, the most significant decrease in the inflammatory grade was 27.9% in the Pegasys 180 ug/week group; 31.1% in the Pegasys 90 ug/week group and 10.9% in the Roferon group. Improvement in the fibrosis score was seen in 35.3% of the Pegasys 180 ug/week group; 24.6% of the Pegasys 90 ug/week group and in 27.3% of Roferon group. The greatest decrease in the inflammation and fibrosis scores was seen in all patients who achieved an SVR.

The authors concluded that "although the greatest benefits were seen in patients with an SVR, patients with virological relapse and non-response also obtained moderate histologic improvement."

Retreatment

Consensus interferon (Infergen) plus ribavirin is being studied for the treatment of naïve patients and the re-treatment of prior interferon non-responders. Stephan Kaiser and colleagues reported on the positive results of a clinical trial of 120 patients (91% genotype 1). The average weight of patients was 79 kg. Liver biopsy was performed in all patients, with 28% of patients reported as having bridging fibrosis or cirrhosis. The patients were either treated with Infergen 18 ug daily for 4 weeks, followed by Infergen 9 ug daily for 8 weeks (group A), or with Infergen 27 ug daily for 4 weeks, followed by 8 weeks of Infergen 18 ug daily (group B). Groups A and B were then treated with Infergen 9 ug daily plus weight-based ribavirin for another 36 weeks.

The SVR results were 39% for group A and 44% for group B, which are impressive results for retreatment of non-responders. In this study 17% of patients had to be dose reduced and treatment was discontinued in 6% of patients. The most common cause for dose reductions were significant reductions in white blood cells and platelet counts, especially in the 27 ug Infergen group. No growth factors were used in this study. The overall tolerability of Group A was comparable to standard therapy, while Group B was less tolerable during the high dose induction period. Patient drop out rates were not different between the two groups.

Ribavirin

Ribavirin monotherapy has minimal antiviral activity against the hepatitis C virus, but when combined with interferon the combination greatly improves SVR. The reason for the synergy of interferon and ribavirin is not clear. However, it has been speculated that the ribavirin acts against the HCV polymerase to create HCV mutants that make the HCV virus ineffective. An NIH study of randomized, placebo controlled trials of ribavirin monotherapy between 1992-1994, in which patients were treated for 48 weeks was reported on at AASLD. There were 31 patients (20 men, mean age 43.3 years) of whom 18 patients received ribavirin (1,000-1200 mg/day) and 13 patients received placebo. It was found that there were no significant differences in the clinical, virologic or histologic findings between the two groups. Comparing the ribavirin treated group to the placebo patients, there were no significant differences in the error generation rate, or the total number of mutations. The authors concluded that "Error catastrophe as a result of lethal mutagenesis is unlikely to be the mechanism of action of ribavirin during therapy for chronic HCV." www.hcvadvocate.org, Jan 2005, Reprint permission is granted and encouraged with credit to the Hepatitis C Support Group.

HCV Persistence & Long-Term Response to Therapy

by Liz Highleyman

When evaluating medical treatments for hepatitis C, many patients and health-care providers speak of sustained virological response (SVR) – continued undetectable HCV viral load 24 weeks after completing therapy – as a “cure.” But with the availability of new testing technology, a growing body of evidence suggests that a true cure may remain elusive.

The good news is that most individuals who achieve SVR do, in fact, have a durable response – at least according to traditional measures. At the annual meeting of the American Association for the Study of Liver Diseases this past October, Mark Swain and colleagues reported on 845 participants in Phase II/III trials of pegylated interferon (Pegasys). After follow-up periods as long as five years, more than 99% of sustained responders still had undetectable serum HCV, with just seven subjects showing renewed evidence of HCV relapse or reinfection.

In another study, after up to 7.5 years of follow-up, 96% of sustained responders maintained undetectable serum HCV RNA; only 4% relapsed over the next six years if they did not do so within the six-month period immediately following completion of therapy. Similarly, John McHutchison and colleagues found that about 4% of sustained responders had detectable HCV RNA in their livers 24 weeks after the end of therapy, and only about 1.2% had a return of detectable serum HCV RNA after up to 3.5 years of follow-up.

The most long-term data comes from Natsuko Tsuda and colleagues in Osaka, who reported in the November 2004 *Journal of Medical Virology* that HCV clearance was sustained for up to 12 years after completion of therapy in all 38 sustained responders studied. Nor was HCV RNA detectable in the livers of any of the 15 SVR patients who had biopsies. “Collectively, these findings suggest that HCV seroclearance at six months after [interferon] therapy withdrawal would usually imply virological cure.”

SVR appears durable even in HCV/HIV coinfecting individuals, who tend to respond less well to therapy and are more prone to relapse. In a study by Vincent Soriano and colleagues published in the December 2004 issue of *Antiviral Therapy*, both HCV replication and liver damage appeared “permanently halted” in coinfecting subjects who achieved SVR. After an average follow-up of about four years, none of the 77 sustained responders showed HCV relapse, elevated liver enzymes, hepatocellular carcinoma, or decompensated cirrhosis.

But closer examination reveals a more complex picture.

Most studies to date, including those described above, have used standard, commercially available reverse transcription-polymerase chain reaction (RT-PCR) tests to measure HCV genetic material (RNA) in patients’ blood serum. Other testing methods may detect smaller amounts of HCV lurking in white blood cells or elsewhere in the body.

In a study by T. Watkins-Riedel and colleagues published in the December 2004 *Clinical Infectious Diseases*, researchers used four different types of RT-PCR assays (including the commonly used Cobas Amplicor) to measure HCV in whole blood, serum, and plasma from 56 previous nonresponders retreated with interferon/ribavirin. (Serum is the liquid portion of blood after coagulation; plasma is blood with the cells removed). At the end of treatment, serum and plasma specimens indicated that 18 subjects had undetectable HCV viral load. But analysis of their whole-blood samples showed that 12 of these (about 66%) did in fact have evidence of low-level HCV RNA. Testing of only serum or plasma “underestimates the true circulating HCV load and leads to an overestimation of antiviral response rates,” the researchers concluded.

In addition to looking for HCV beyond the blood serum, more sensitive assays can also reveal heretofore hidden virus. In a study reported in the January 1, 2004 *Journal of Infectious Diseases*, Immaculada Castillo and colleagues used an extra-sensitive RT-PCR assay and in situ hybridization to test peripheral blood mononuclear cells (PBMCs, a type of immune system white blood cell) and liver biopsy specimens. They detected “occult” (hidden) HCV in the liver cells of more than one-half of subjects (57 out of 100) with persistently elevated liver enzymes but no evidence of HCV infection using commercially available serum tests; in addition, 40 subjects had HCV RNA in their PBMCs.

Similarly, in the June 2004 *Journal of Virology*, Tram Pham and colleagues reported that low-level virus remains present up to five years after apparent spontaneous or treatment-induced HCV “clearance.” Using an extra-sensitive RT-PCR-nucleic acid hybridization assay, the researchers detected residual HCV RNA in serum or PBMC samples from all 16 subjects examined; six of seven tested also showed evidence of HCV RNA in their monocyte-derived dendritic cells (another type of white blood cell). Furthermore, in about 75% of subjects the researchers found traces of negative-strand HCV RNA, an intermediate form of genetic material that suggests ongoing viral replication.

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Travel Advice (continued)

laboratory test showing antibodies. Even though MMR is a live vaccine, measles can be severe in HIV-infected individuals, and the CDC recommends MMR vaccination for all asymptomatic non-immune HIV-infected individuals. (Asymptomatic children do not need to be tested for HIV.) Adults with CD4 counts <200 cells/mm³ or CD4% $<14\%$ should not be vaccinated with MMR but can consider receiving immune globulin.

In addition to the routinely recommended vaccines, specific travel vaccines may be needed. Hepatitis A is one of the most common vaccine-preventable illnesses among travelers. The inactivated vaccine is given as two doses. The first dose produces an antibody response in $\geq 95\%$ of healthy adults and should be administered to all persons who travel to developing countries. The second dose, given 6 to 12 months later, promotes long-term protection. If the second dose is delayed, the series does not need to be restarted. The two brands, *Havrix* and *Vaqta*, can be interchanged. Hepatitis A and B vaccines is also available in a combined formulation (*Twinrix*), which is given as a series of 3 injections (months 0, 1, and 6). HIV-infected individuals with low CD4 counts may not develop antibody after vaccination and may need intramuscular immune globulin instead of, or in addition to, vaccine.

Polio has been eradicated from most of the world except parts of Africa and Asia. Most transmission occurs in five countries: Afghanistan, India, Pakistan, Nigeria, and Niger. In addition, outbreaks of vaccine-derived polio occurred recently in Haiti, the Dominican Republic, and the Philippines. Before traveling to endemic areas, adults should have completed the primary vaccine series (usually completed by age 6 years) and have one booster as an adult of inactivated polio vaccine. (Oral, live polio vaccine is no longer available in this the U.S.)

Typhoid fever is not a common illness in travelers, but vaccination is recommended for those planning to eat adventurously, to stray off the five-star tourist track, or to travel longer than three weeks. Risk is greater in some areas, especially the Indian subcontinent. HIV-infected individuals should receive the inactivated rather than the live typhoid vaccine.

The quadrivalent ACYW-135 vaccine for meningococcal disease is indicated for travel during the dry season (Dec—June) to the "meningitis belt" of Africa, which stretches from Senegal to Ethiopia. In addition, vaccination is required for those visiting Mecca during the Hajj.

Two other vaccines are recommended under certain circumstances. Rabies vaccine should be given to those who will be working with animals, to spelunkers, and to

those who are visiting endemic areas long-term, especially remote areas where post-exposure prophylaxis with both rabies immune globulin and a safe, effective vaccine may not be available. Japanese encephalitis (JE) vaccine is indicated for expatriates and some long-term travelers to certain Asian countries. Risk of infection with JE virus increases with evening and nighttime outdoor exposure, especially in rural areas. Thus, vaccination might be recommended for campers or others with long-term exposure to mosquitoes in rural areas, but generally not for short-term trips or trips to urban areas. There may be some confusion about the availability of JE vaccine. Fortunately, it is and has been available. Alternatively, the vaccine for tickborne encephalitis, which occurs mainly in Europe and the former USSR, is not available in this country.

Since the above "travel" vaccines are not live, they present no increased risk for HIV-infected persons. The same is not true, however, for yellow fever vaccine. Yellow fever, a mosquito-borne illness, is endemic in large parts of tropical South America and sub-Saharan Africa. Some countries require proof of vaccination for entry. An official stamp is provided by clinics that are approved yellow fever vaccine centers. Since the yellow fever vaccine is a live vaccine, immunocompromized persons may be at risk for dissemination of the vaccine strain. In Thailand a 53-year-old man with a low CD4 count developed fatal myeloencephalitis [Kengsakul K, et al. *J Med Assoc Thai* 2002;85(1):131 <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12075714>]. On the other hand, two HIV-infected individuals with high CD4 counts (674 and 1000 cells/mm³) were successfully immunized [Receveur MC, et al. *Clin Infect Dis* 2000;31:e7-8 <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11017859>]. In a French study, 44 HIV-infected persons with CD4 counts >200 cells/mm³ were given yellow fever vaccine without adverse events [Goujon C, et al. *J Travel Med* 1995; 2:145]. Since the risk for dissemination of the vaccine strain varies with the degree of immunosuppression, those with CD4 counts <200 cells/mm³ should not be vaccinated and should avoid travel to endemic areas if possible. If travel to an endemic area is unavoidable and the CD4 count is high, vaccination is an option. The CDC does not encourage vaccination but states that those with "adequate immune system function" who "cannot avoid potential exposure to yellow fever virus" should be offered the choice of vaccination (<<http://www.cdc.gov/travel>>). Otherwise, HIV-infected persons who must travel to an endemic area should be instructed in ways to avoid mosquito bites and should obtain a waiver letter from their physician, or, better yet, a travel physician with an official stamp, stating the contraindication to vaccination. This letter should be cleared by the embassy or consulate of the country to be visited.

For travelers, the risk of acquiring cholera is very low and currently, cholera vaccine is no longer available in the US. Two vaccines are available in other countries: Dukoral made by Active Biotec in Sweden and Mutacol manufactured by Berna in Switzerland. Previously, cholera vaccine was required by some countries, but now, no country or territory requires vaccination for entry or exit.

The possibility of reduced immunogenicity is an additional concern for all vaccines given to HIV-infected persons. Antibody levels following vaccination may be lower than for HIV seronegative individuals, especially for those with low CD4 counts. In some instances passive antibody is an alternative. Immune globulin, for example, can be given instead of or in addition to hepatitis A vaccine.

Malaria Prophylaxis

Malaria transmission occurs in large parts of Africa, Asia, and Central and South America. Chloroquine remains effective only in parts of Mexico, Central America, Egypt, and some countries in the Middle East. Chloroquine occasionally causes skin eruptions, pruritus, and gastrointestinal symptoms; it is contraindicated in individuals with psoriasis.

For malaria prophylaxis in countries with chloroquine-resistant *Plasmodium falciparum*, four medications are available in the US: mefloquine (*Larium*), atovaquone/proguanil (*Malarone*), doxycycline, and primaquine. While mefloquine has the advantage of weekly dosing, it has the disadvantage of possible CNS side effects, prolongation of the QT interval, and bradycardia. Mefloquine is contraindicated in those with active depression, anxiety, other major psychiatric disorders, and seizures. Atovaquone/proguanil is a more expensive alternative with fewer side effects. Doxycycline is less expensive but increases the risk of sun sensitivity, gastrointestinal symptoms, and *Candida* vaginitis. Primaquine is usually recommended only for someone unable to take the other prophylactic medications and requires documentation of a normal G6PD level. One or two doses of the prophylactic medication should be taken before entering a malarious area. The daily medications, atovaquone/proguanil, doxycycline, and primaquine, should be started 1-2 days before possible malaria exposure; and the weekly medications, chloroquine and mefloquine, 1-2 weeks before arrival. Whereas atovaquone/proguanil and primaquine can be stopped a week after leaving the malarious area, chloroquine, mefloquine and doxycycline should be continued for a month.

A major concern for HIV-infected persons is drug interactions. For mefloquine and chloroquine, a potential

interaction exists with other medications that might prolong the QT interval, such as trimethoprim-sulfamethoxazole, fluconazole, and clarithromycin. Ritonavir may decrease atovaquone and proguanil levels. Atovaquone/proguanil increases AZT levels by about 30%. In subjects at risk for bone marrow suppression, the AZT dose could be lowered by 1/3. Specific advice from the CDC can be obtained from the Malaria Hotline at 770-488-7788.

Diarrhea Treatment

All travelers to developing countries should practice dietary discretion by avoiding raw vegetables and fruits unless peeled by the traveler, unpasteurized dairy products, rare meat, raw seafood, and prepared food kept at room temperature for several hours. Water should be bottled or boiled. Ice is risky unless known to be prepared from clean water.

In spite of ample dietary advice, travelers' diarrhea is still very common. In general, treatment has replaced prophylaxis. Prophylaxis may be indicated for some special occasions, for instance, a short trip with an important presentation or meeting. Otherwise, travelers to developing countries should carry antibiotics for self-treatment. A fluoroquinolone such as ciprofloxacin (500 mg bid for 1-3 days) is often given to immunocompetent travelers. HIV-infected individuals may need a longer course of 5-7 days. For travel in Thailand, which has high rates of fluoroquinolone-resistant *Campylobacter* spp., azithromycin is preferred. Short-term treatment with loperamide or another antimotility agent is acceptable when there is no fever or blood in the stools. Dehydration, the main consequence of severe diarrhea, can be prevented and treated with oral rehydration salts. Packets are usually available at travel clinics and are easy to carry. If there is no improvement in several days, medical attention should be sought.

Other Travel-Related Issues

DEET is essential for the tropics. Insect repellents with DEET help protect against malaria and other arthropod-borne illnesses, such as dengue, leishmaniasis, yellow fever, Japanese encephalitis, and rickettsial infections. Permethrin, an insecticide applied to clothing, provides additional protection from mosquito bites and is more effective against ticks.

At altitudes >9,000 feet, acetazolamide may help prevent altitude sickness. In areas with schistosomiasis, fresh-water swimming should be avoided. Sunburn should be prevented with the use of sunscreen, hats,

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and sunglasses. Since animals may not be vaccinated against rabies, contact with domestic and wild animals should be avoided. If a potentially rabid animal bite occurs, the wound should be washed thoroughly and medical attention obtained immediately to determine whether rabies immune globulin and vaccine are indicated.

Other Special Advice for HIV-Infected Travelers

Persons carrying antiretroviral medications may be denied entry to some countries. Moreover, some countries screen for HIV infection in incoming travelers, especially travelers arriving for prolonged work or study. An unofficial list can be found at the following address: <http://www.travel.state.gov/HIVtestingreqs.html>, but individuals planning a prolonged visit should contact the country's consul in advance.

When possible, avoid changes in medications shortly before travel. Bring an adequate supply of medication along with copies of prescriptions. Refrigeration of medication may be difficult to obtain.

Since medical insurance plans often do not cover travel-related illness, additional travel insurance may be needed. Pre-existing conditions, however, may not be covered. Medical facilities in areas to be visited should be identified in advance.

Vacations may encourage sexual activity. To avoid transmitting HIV infection to others and to avoid acquiring additional HIV strains or other sexually transmitted diseases, HIV-infected individuals should, as always, only engage in safer sexual practices. Condom quality is not guaranteed in all countries; it's best to take them along.

The Yellow Book, CDC's *Health Information for International Travel*, available online at <http://www.cdc.gov/travel>, contains information on vaccines, malaria prophylaxis, and other topics, including "HIV and Travel". Advance planning and consultation with a travel health practitioner can minimize risks.

Summary

In conclusion, vaccines may be less immunogenic in HIV-infected persons. Live vaccines should be avoided, especially when the CD4 count is low. The need for malaria prophylaxis is based upon travel destination and the agent should be chosen based on side effects, convenience, cost, and medication interactions. Insect precautions, including application of both DEET and permethrin, will diminish the risk of acquiring yellow fever, malaria and other insect-transmitted diseases. Medication for treatment, rather than prophylaxis, of travelers' diarrhea is usually preferred. The Hopkins HIV Report, May 2004

Table: Vaccinations for HIV-Infected Travelers to Underdeveloped Countries

Disease	Recommendation/Comment
Routine vaccines	Update routinely recommended vaccines
Tetanus-diphtheria*	Give booster every 10 years.
Influenza	Give annually. Influenza occurs year-around in the tropics.
Pneumococcus	Give initial vaccine & booster 5 years later.
Hepatitis B	Immunize if exposure to blood, high-risk activity, or long-term stay anticipated.
Measles (live vaccine)	Confirm immunity or vaccinate if CD4 count is not low.
Travel Vaccines	Give for travel to specific areas or for high-risk exposure.
Hepatitis A	Immunize all travelers.
Polio*	Administer an adult booster if traveling to an endemic area.
Typhoid Fever	Give inactivated vaccine if trip is long or exposure risk is high.
Meningococcus	Give for Hajj or travel to meningitis belt of Africa.
Rabies	Vaccinate if risk is high & access to post-exposure vaccine & rabies immune globulin is unavailable.
Japanese encephalitis	Vaccinate before long-term travel to rural, endemic areas of Asia.
Yellow fever (live vaccine)	Not generally recommended. Consider only if CD4 count is high.

*Primary series should be given if not given previously.

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B or C? Doctors often recommend acetaminophen to relieve symptoms such as body aches and fever, which

Acetaminophen and Your Liver (continued)

are common side effects of interferon therapy. For most people, acetaminophen is safe and effective. According to the FDA's Dr. John Senior, "It's very clear the average dose for the average person is very safe. But we are not all average people." For many individuals, acetaminophen is still a good choice, especially considering that other over-the-counter pain-relievers can cause problems of their own (such as stomach bleeding with aspirin and nonsteroidal anti-inflammatory drugs).

The following tips can help prevent acetaminophen-related liver toxicity:

- ◆ Do not take more than the recommended dose of 4 grams within a 24-hour period (for example, 12 regular strength or 8 extra strength Tylenol tablets)

- ◆ Do not take the full day's dose at one time; space it out over the course of the day
- ◆ Do not take acetaminophen for more than 10 days in a row
- ◆ Avoid drinking alcohol; this is important for people with hepatitis whether or not they use acetaminophen
- ◆ People who do consume 2-3 alcoholic drinks per day should not take more than half the usual recommended dose of acetaminophen (2 grams within 24 hours)
- ◆ People with advanced liver fibrosis or cirrhosis should avoid acetaminophen
- ◆ Write down how much acetaminophen you take, and when, if you have trouble remembering
- ◆ Check the labels of all medications; small doses of acetaminophen in combination remedies can add up to big trouble.

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What are Fibrosis and Cirrhosis (continued)

necrosis, interlobular degeneration/focal necrosis, portal inflammation, and fibrosis, which are added together to yield a combined score from 0-18. The METAVIR system includes one score for inflammation (grades 0-4) and one for fibrosis (stages F0-F4).

METAVIR Fibrosis Stages

F0: no fibrosis

F1: minimal fibrosis in one portal of the liver, with no septa

F2: some fibrosis in one portal, with rare septa

F3: bridging fibrosis (septae that extend over adjacent portals)

F4: cirrhosis with loss of normal liver architecture

Another system, known as Child-Pugh, is used to grade the severity of cirrhosis on the basis of laboratory findings and clinical symptoms including ascites, hepatic encephalopathy, bilirubin and serum albumin levels, and prothrombin time (a measure of blood clotting ability).

Treatment and Future Prospects

It was once thought that fibrosis was irreversible, but more recent research indicates that treatment for hepatitis C or B can slow or halt fibrosis progression and even reverse existing liver damage. Studies have shown that fibrosis stabilization and regression are most likely when HCV positive individuals treated with interferon-based therapy achieve a sustained virologi-

cal response (SVR, continued undetectable HCV viral load six months after the completion of therapy), but improvement has also been seen in some partial responders or nonresponders. In the May 2002 issue of *Gastroenterology*, for example, Thierry Poynard and colleagues reported that among patients with repeated biopsies, 80% who achieved SVR with pegylated interferon plus ribavirin as well as 34% of nonresponders showed evidence of improved fibrosis.

It is likely that interferon improves fibrosis by suppressing HCV replication, allowing the liver to repair itself. But other medications and herbal remedies appear to have a direct antifibrotic effect. For example, in the August 1, 2004 issue of the *Journal of Hepatology*, Yukihiro Imanishi and colleagues reported that a traditional Japanese herbal preparation called *inchin-ko-to* (TJ-135) down-regulated the activity of hepatic stellate cells, suppressed the production of collagen and fibronectin, and inhibited the development of fibrosis in rats. Much research is ongoing in this area, including a study of long-term interferon maintenance therapy called HALT-C. With a better understanding of the mechanisms underlying fibrogenesis and fibrolysis, it may become possible to design specific therapies to prevent or reverse fibrosis and cirrhosis.

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HCV Persistence (continued)

A study in the January 2005 Hepatology confirmed Pham's findings. Marek Radkowski and colleagues looked for HCV RNA in serum and PBMC samples from patients who achieved SVR after interferon/ribavirin treatment; they also examined liver biopsy specimens from 11 subjects. After an average follow-up of five years (range 40-90 months), also using an extra-sensitive RT-PCR test, they detected HCV RNA in 15 out of the 17 subjects studied (11 with HCV in macrophages, 7 in lymphocytes, 4 in serum, and 2 in liver tissue). Negative-strand HCV RNA was detected in the white blood cells of six subjects, but in none of the liver samples. "[O]ur results suggest that in patients with SVR after therapy, small quantities of HCV RNA may persist in the liver or macrophages and lymphocytes for up to nine years," the authors concluded.

In an editorial accompanying Radkowski's article, Jordan Feld and T. Jake Liang from the National Institute of Diabetes and Digestive and Kidney Diseases reviewed what the latest studies tell us about HCV persistence and long-term response to therapy, concluding that HCV may persist at low levels after apparently successful therapy, but that the clinical significance of this occult virus remains unclear.

Some studies suggest that residual HCV may have a deleterious effect, although data are inconsistent. In Castillo's study, patients with evidence of occult HCV were more likely to have fibrosis and necroinflammatory activity compared to subjects with no evidence of residual virus, though most had only mild liver damage or steatosis (fatty liver). In Radkowski's study, subjects with residual HCV RNA in their livers showed no histological improvement, while those with no evidence of occult virus had reduced fibrosis and lower inflammatory scores. In addition, the presence of occult HCV may explain why some patients experience hepatitis C recurrence after a liver transplant even if they were apparently successfully treated prior to the procedure, and sheds light on why people retain HCV-specific CD4 and CD8 T-cell immune activity long after apparent spontaneous or treatment-induced viral "clearance."

Little is known about the treatment of occult HCV, or even whether it would be beneficial. Since HCV destroys liver cells as it replicates, any substantial reduction in viral load should have a protective effect against cirrhosis, liver cancer, and liver failure. Studies are now underway looking at new therapies for retreatment of nonresponders – including consensus interferon (Infergen) and interferon gamma (Actimmune) – and evaluating whether long-term interferon maintenance therapy can help prevent liver disease progression in people who continue to have detectable HCV RNA (the HALT-C and

COPILLOT trials). Treatments that prove beneficial for individuals classed as nonresponders using traditional measures will likely also help those with occult HCV.

Many questions remains to be answered about HCV persistence and long-term response (for example, whether people with residual, low-level HCV can transmit the virus to others). While research continues, Feld and Liang remind us, "the word 'cure' must not be used prematurely."

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HCV Advocate, March 2005

Are You at Risk for Hepatitis C?

by Alan Franciscus, Editor-in-Chief and Paula Fener

This article is designed to help you stay healthy by letting you know about those things that can put you at risk for getting HCV. Avoiding the situations listed below can greatly reduce your risk of getting HCV as well as other diseases that are transmitted by blood-to-blood-contact.

Direct Blood-to-Blood Contact

HCV is spread by direct blood-to-blood contact. Anything that places another person's blood in direct contact with your blood, or vice versa, should be handled with care. Being careful and using common sense in any situation where blood is present (yours or someone else's) will help protect you from HCV as well as other blood-borne diseases.

Sharing Drug Using Equipment

Sharing equipment for injection and non-injection drugs such as needles, cottons, cookers, ties, straws, pipes and even water are some of the easiest ways to get HCV. Even the smallest amounts of blood that you may not be able to see can transmit the virus. Making sure your equipment stays personal and isn't shared with anyone will help you stay healthy. If you have ever injected street drugs or shared a needle with another person—even just once—you should be tested for HCV.

Blood Transfusions/Medical Procedures Before 1992

Before 1992, many people contracted HCV through blood or blood product transfusions. If you had a medical procedure where blood or blood products were used you could have been at risk. Now the blood supply is considered safe. The likelihood of contracting HCV through infected blood is less than 0.01%. The risk of getting HCV from a medical procedure is rare, but safety procedures have to be followed carefully.

Medical & Dental Procedures Performed in Some Foreign Countries

Immigrants from foreign countries are at risk for HCV if the country that they immigrated from does not follow standard safety precautions to prevent transmission of HCV in any situation where blood is involved. Talk to your medical provider if you believe you are at risk.

Blood Clotting Factors Before 1987

People who received blood clotting factors before 1987 should be tested for HCV.

Hemodialysis

People who receive hemodialysis should be tested for HCV.

Children Born To HCV Positive Women

The likelihood of transmitting HCV from a HCV positive mother to her child is very low. Current studies have

found that about 5% of babies born to HCV positive mothers get HCV. If your mother is HCV positive you should be tested.

Sexual Transmission

Sexual transmission of HCV is uncommon. People who are in a stable long term monogamous relationship are at a low risk of getting HCV from their sexual partner. However, in some so-called high risk groups, including people who have unprotected sex with multiple partners or have sex with someone with a sexually transmitted disease, the risk of getting HCV is higher. Most government agencies do not recommend routine testing for someone who falls into a high risk sexual category or someone having unprotected sex with an HCV infected steady partner. If you are worried about sexual transmission and would like to get tested, talk with your medical provider.

Occupational Exposure

Health-care workers who come in contact with blood are at risk for getting HCV and should be tested. However, the general rate of transmission is very low with about a 2% prevalence of HCV in the healthcare industry. The most common cases of transmission occur in needle-sticks with hollow-bore needles. If you were exposed to any HCV infected blood you should be tested.

Getting Tattoos & Piercings

If you ever received a tattoo or piercing in an unsafe setting you should be tested for HCV. Most commercial tattoo parlors follow standard safety precautions and make sure that only new needles and a separate ink pot is used for each consumer. In other settings, such as in a prison or on the street, the chance of getting HCV is higher.

Acupuncture

If you get acupuncture, the same safety precautions apply. Only new acupuncture needles should be used for each client, and your acupuncture provider should take safety precautions against spreading HCV.

Sharing Personal Items

The transmission of HCV from personal hygiene items is uncommon. But there is a possibility of getting HCV from sharing toothbrushes, razors, clippers, and nail files. If you come in contact with a HCV infected personal hygiene item get tested to be safe.

If you want more details about these risk factors, or need more information about hepatitis C, visit www.hcvadvocate.org, HCV Advocate, March 2005

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*We must view young people
not as empty bottles to be
filled,
but as candles to be lit.*

-Robert H. Shaffer

