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Hepatitis C in Children – Not the Same as in Adults

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Hepatitis C (HCV) is an RNA virus of Flaviviridae family. There are 6 major HCV genotypes and more than 50 subtypes. The extensive genetic heterogeneity of HCV and the lack of a vigorous T-cell response has made this an elusive virus to treat. Furthermore, the lack of symptoms until many years after acquisition has allowed this virus to insidiously invade our society. Decompensated liver disease from HCV is now the most common indication for liver transplantation.

In childhood, the virus rarely causes symptoms and many cases probably go unrecognized. It is estimated that there are a quarter million cases in the US, but the number may actually be much greater. Prevalence studies (*Committee on Infectious Diseases. AAP. Pediatrics 1998*) have found a seroprevalence of:

- 0.2% for children less than 12 years and

- 0.4% for those between 12 and 19 years

A concerted effort to establish the natural history in the pediatric population and the indications for treatment is now underway.

Prior to 1990, the predominant mode of transmission was through contaminated blood products. Now, the most common mode is vertical transmission. The risk of transmission is estimated to be approximately 5%, but is increased by comorbid states such as HIV where there is a 20% risk. Spontaneous clearance of the virus occurs in the first year for 25-50% of children. Horizontal transmission may also occur among household contacts and between children, but the incidence is so rare there are no restrictions for school, day care or sports.

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Progression of liver disease may be influenced by the mode of acquisition and is also influenced by duration of disease. In general there is rare progression to decompensated liver disease in the pediatric population. Between 1995 and 2001 less than 1% of the pediatric liver transplants were for HCV. The histologic features are similar to those found in adult biopsies including lymphoid aggregates or follicles, sinusoidal lymphocytes and steatosis. However, children who have other underlying illnesses such as thalassemia may have more significant and rapid liver damage. Data analysis of 211 thalassemic subjects with a mean age of 8.7 years followed for at least 4 years demonstrated that hepatic iron content and HCV were independent risk factors for liver fibrosis progression. Their concomitant presence resulted in striking progressive liver damage. In a second study, a group of patients treated for cancer at St. Jude's Children's Research Hospital had an incidence of cirrhosis of 8.5%. However, in general, most studies examining children have showed minimal progression of liver disease during childhood including those acquiring HCV from transfusions for congenital heart disease and leukemia. In a histologic series from Italy and Spain examining 80 children followed for a mean of 3.5 years: ± 4.3 years, the frequency and severity of bile duct damage increased with patient age. However, the overall necroinflammatory score was low, grade 1 or 2, and only 1 child had cirrhosis.

Despite the generally benign course during childhood, treatment is still a strong consideration. Early acquisition of HCV implies potentially long duration of disease and eventual liver damage. Additionally, there are social concerns and public health concerns. Parents have to wrestle with issues of how to discuss this disease with their child. Difficult situations frequently arise with friends, babysitters and schools. Furthermore the additional risk of vertical transmission to the next generation concerns many families. The typical considerations involved in treat-

ment decisions include these social concerns, along with an understanding of the natural history of the disease balanced against the chance of successful therapy.

Interferon is better tolerated than in adults and may have better sustained virologic response (SVR). SVR with monotherapy in multiple studies range from 33-45% and is strongly influenced by genotype. SVR for individuals with type 1 is less than 30% while type 2 is 70%. Few studies have been completed using combination therapy. In the most recent, 70 children ages 3 to 16 years received 3 MU per meter squared of interferon alfa -2b three times weekly along with ribavirin at a dose of 15 mg/kg per day for a period of 1 year. Treatment in children:

- less than 12 years was 57% SVR;
- Only 30% SVR in those older than 12 years.
- Those infected with genotype 1 was 38% SVR and 82% SVR for those with types 2 and 3.
- Adverse events led to discontinuation in only 7% of subjects.
- No data regarding peginterferon and ribavirin have been collected to date.

Caring for children with hepatitis C is particularly challenging. The natural history in the pediatric population is unclear. We have yet to fully understand which children are at risk for severe liver disease and who will respond to therapy. Ideally, the next decades will bring information and therapies that will effectively treat this disease for those in need and prevent it from being transmitted to others.

Editor's Note:

Key points and comments:

- Household transmission is rare but not absent.
- Most cases of HBV in children progress slowly
- Female children progress more slowly than male children

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Treatment Interruption Shows No Benefit in Drug-Resistant HIV Infection

Prescribed interruptions in antiretroviral therapy—so-called “drug holidays”—may hasten disease progression in a subset of HIV-infected individuals, namely those whose treatment has been rendered significantly less effective by the development of resistance to multiple anti-HIV drugs (MDR-HIV). This was the finding in a study by researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH).

As reported in the August 28, 2003 issue of *The New England Journal of Medicine*, researchers found that study participants who underwent a four-month structured treatment interruption had more HIV-related complications and poorer immune response than did individuals who took antiretroviral drugs continuously throughout the study.

“Interruption of treatment has become increasingly common among HIV-infected individuals,” says NIAID Director Anthony S. Fauci, M.D. “This study helps to clarify the effects of treatment interruption in one group of patients and emphasizes how important it is for people to join clinical trials to help answer questions that will improve patient care.”

As used in this study, structured treatment interruption involves discontinuing all anti-HIV drugs for a defined period of time to allow the repopulating virus to regain susceptibility to anti-HIV drugs. Previous studies of individuals infected with MDR-HIV have shown that drug-sensitive variants of the virus re-emerge and become predominant after therapy is stopped. Treatment interruptions have also been used to give people time off from multiple medications that may be difficult to take and have toxic side effects.

“We had hoped that a structured treatment interruption would be beneficial for people experiencing treatment failure due to multidrug-resistant HIV,” says study chair Jody Lawrence, M.D., of the Department of Medicine at the University of California, San Francisco. “However, our results indicate that this strategy does not work and should be avoided by this group of HIV-infected individuals. Continuing therapy guided by HIV drug resistance testing proved to be a better approach.”

Conducted by NIAID’s Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA), the MDR-HIV study by Dr. Lawrence and colleagues is the

first randomized clinical endpoint study to examine the effectiveness of structured treatment interruption in people with few remaining treatment options. The study enrolled 270 participants with MDR-HIV who had HIV levels of more than 5,000 copies per milliliter of plasma. About one-half of the participants were randomized to a four-month interruption of treatment before starting a new optimized anti-HIV treatment regimen. The other half (the control group) immediately started a new optimized regimen. Physicians were given the results of two types of HIV drug-resistance tests to help them choose the optimized regimen.

After an average follow-up of nearly 12 months, 22 of the 138 individuals in the treatment-interruption group had either died or experienced disease progression, defined by the occurrence of one or more AIDS-defining conditions. In contrast, 12 of the 132 people in the control group (those who received continuous therapy throughout the study) had died or had their disease worsen. Participants in the treatment-interruption group also had persistently fewer CD4+ T-cells—crucial immune cells typically depleted during HIV disease—and showed no benefit in HIV viral load response or quality of life relative to the control group.

“This trial was conducted because community and healthcare providers were interested in finding better treatment strategies for people with treatment failure and multidrug-resistant HIV,” says Sandra Lehrman, M.D., director of the Therapeutics Research Program in NIAID’s Division of AIDS. “The strengths of the study,” she notes, “are the number of volunteers who participated in the study, the length of follow-up and the fact that there was a randomized comparison with a control group. These features allowed the researchers to study the overall impact of structured treatment interruption, including the effects on AIDS-related illnesses, HIV viral load, CD4+ T-cell count and quality of life.”

“It is important to remember,” adds Dr. Fauci, “that the failure of treatment interruption seen in this study pertains only to individuals who had drug-resistant HIV and detectable virus in their blood when they entered the study. For individuals who

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FUZEON (Enfuvirtide, T-20)

Breaking Barriers or Breaking the Bank?

by Matt Sharp and Rob Camp

T-20 is the first drug of a new class of HIV inhibitors that perform entry inhibition. More specifically, T-20 is one of a subset of entry blockers called fusion inhibitors. It acts by preventing the envelope of HIV from fusing to its target's cellular membrane. For treatment-experienced individuals with multiple-drug resistant virus, adding a drug from a new inhibitor class in combination with drugs from previously used classes is thought to be the most effective strategy for achieving durable viral suppression. As with all other HIV therapies, T-20 must be used in a combination, preferably with other new agents, in order to have the biggest punch.

Overview of Issues

Although therapeutically promising, unfortunately T-20 is not an easy drug to use and may be difficult for some to access. Drawbacks include:

Twice daily injection: Because it is a complex protein peptide, T-20 has to be administered by subcutaneous (subQ) injection twice daily, a substantial issue for most people. Adherence to life-long oral HIV therapies is already inherently difficult and we expect the technical demands of self-administering twice-daily injections to be even more so. We find the Roche/Trimeris video of people effortlessly incorporating T-20 into their daily lives misleading. A specific educational program is needed to deal with the complexity of drug reconstitution and self-injection. Patient experience may be very helpful in elucidating some basic dos and don'ts. Fuzeon also elicits concern from many former injection drug users in recovery that the use of needles may act as a potential trigger for relapse.

Reconstitution: The need to reconstitute T-20 is a significant drawback to ease of use. After mixing sterile water with the drug powder, T-20 can take up 30 minutes or longer to dissolve completely. It is unclear whether total reconstitution is necessary for maximum efficacy. Often drug powder is drawn up into the syringe before the drug has completely dissolved. Does injection of unreconstituted substance contribute to PISRs?

Problematic Injection Site Reactions (PISRs): The Achilles heel of T-20 may be the injection site reactions. T-20 injections cause a local, painful skin reaction, somewhat like a wasp sting, and have happened to almost all (98%) people studied thus far. Fifty per-

cent of the reactions are reported as mild, while the other 50 percent range between moderate and severe. Redness at the site of injection (of more than 4") and pain have been reported in 80 percent of people and hardness around the injection site (2" or more) in 85 percent of people. Twenty percent of the PISR nodules do not go away even after 7 days. For some, there seems to be no improvement over time.

Supply: Producing enough T-20 for all the research, the expanded access program and expected market demand has been a major stumbling block in the development of this drug. Because of the production difficulties, and the fact that a drug of this complexity has never been produced before, there is no promise that enough drug can be produced in a timely manner to reliably supply all who need it.

Price: A price of over \$21,000 has been announced for the European market. Is this the drug that will break payers' backs? Will providers be unable to justify or afford the high cost and refuse to add T-20 to their formularies, despite patient need?

The Community Demands:

Commit to informed access

An aggressive commitment to patient and provider education will be needed as the number of people using T-20 swells from 2,000 to perhaps 15,000 by year's end. So far, the sponsor has not been ready, willing, or able to do this. Education, for both the user and provider, must be the top priority on the Roche/Trimeris agenda and the educational programs must be scaled up and made accessible to all providers, including those who primarily serve Medicaid beneficiaries.

Minimize barriers to adherence

Toxicity management issues need to be better studied. Health care providers and patients need to understand the time commitment required to use T-20 correctly and to obtain the best advantage from its use. Treatment fatigue is common even with oral HIV treatments. Simply skipping one dose per month may be risky with this drug's resistance profile. Adherence issues and PISRs must be dealt with aggressively by finding ways to make administering T-20 more user-friendly and through additional programs to counsel people on the

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best and safest methods of injection. The sponsor should create a patient/provider advisory board to work on these issues. It is important that T-20 not join a person's list of quickly "used up" therapies.

Get to the bottom of PISRs

In an analysis of the pathology of (P)ISRs presented at the 10th Annual Retrovirus Conference, one patient (out of seven studied) who did not experience (P)ISRs "had insulin-dependent diabetes and had self-injected insulin for many years using optimum injection techniques." Are PISRs nothing more than bad injections? If so, the sponsors' education plan has not worked. Some experienced insulin injectors have suggested warming the syringe before injection. If PISRs are caused by something else (allergy, etc.), then that needs to be clarified. Does the incomplete dissolution of T-20 have anything to do with the PISRs? Is there a point when, although not completely dissolved, the drug is safe and efficacious to use?

Many users of T-20 are frustrated with the lack of importance given to this issue by the sponsor. Because both the cause and the resolution of the injection site reactions may be a key to success with this drug, Roche/Trimeris needs to learn more about why PISRs occur and they must look into other delivery mechanisms for the compound.

Continue dosing research

Questions have been raised concerning the potency of the control regimen and the small sample size used in the Phase II dose-finding study T20-206. Trimeris never ascertained the maximum tolerated dose for T-20 and based its dosing decision solely on the tolerability of the number of injections. Roche/Trimeris should continue to look for the maximum tolerated dose, which will mean more investigation into delivery systems.

Help identify optimal background regimens

In multi-drug experienced people, therapy optimization should be ascertained via genotyping and phenotyping. The recent news that only 25 percent of practicing clinicians know how to use the results of these resistance tests is very disconcerting. Providers who offer T-20 must know they need to have a good understanding of resistance test results in order to optimize the background therapy and maximize response.

Availability for those who need it most

With only a 16 percent success rate for keeping viral load below 50 copies at 24 weeks in heavily pre-treated trial participants, and with drug supply expected to be limited, T-20 may need to be rationed to those most in need — people without other treatment options. Use in other populations has not yet been studied, and the risk-benefit ratio in a treatment-naïve

population has not been determined. Finally, it should be noted that there are no study results demonstrating the impact of T-20 on the clinical progression of HIV disease.

Assure equitable access

Roche/Trimeris must assure that scaled-up production will be able to meet demand with no further supply issues. Roche/Trimeris must ensure that there is an adequate supply of the drug for continued clinical trials, expanded access, and for sale throughout the world. Roche should move to register the drug and assure access in all countries that have participated in clinical trials for T-20. Sufficient drug to conduct Phase IV studies of treatment options and side effects should be assured.

Roche/Trimeris needs to come to reasonable terms over its price with all payers, whether they be insurance companies, Medicaid or ADAPs. Details of the sponsor's "Patient Assistance Plan" (PAP) need to be defined (Roche has verbally promised one-third of drug to those most medically needy). The entry criteria for the PAP may well be determined by those who are unable to enter state ADAP plans. Administration of PAP eligibility should be coordinated with the ADAPs.

Tell the truth

The FDA needs to take its role as monitor of pharmaceutical advertising very seriously and remember that the wording on the label and in advertising for this drug should not be ambiguous or misleading regarding target populations. The FDA should insist that those people most likely to benefit from T-20 have first access.

GMHC Treatment Issues, March 2003

Medical Websites

Government

AIDS Clinical Trials, Information Services
www.actis.org

CDC Division of HIV/AIDS Prevention
www.cdc.gov/nchstp/hiv_aids

FDA Office of Special Health Issues
www.fda.gov/oashi/aids/hiv.html

HIV/AIDS Treatment Information Service
www.hivatis.org

NIH HIV/AIDS Information Service
<http://sis.nlm.nih.gov/aids/index.html>

NIH Office of AIDS Research
www.nih.gov/od.oar

Organizations

American Academy of Family Physicians
www.aafp.org

American Council of Science and Health
www.acsh.org

American Federation for Medical Research
www.afmr.org

American Medical Association
www.ama-assn.org

Association of Nurses in AIDS Care
www.anacnet.org

Gay and Lesbian Medical Association
www.glma.org

HIV Dentistry
www.hivdent.org

International Association of Physicians in AIDS Care
www.iapac.org/index.html

UNAIDS
www.unaids.org

World Health Organization (WHO)
www.who.int/asd

Databases

AIDS.org
www.aids.org/immunet/home.nsf/page/homepage

AEGIS
www.aegis.com

CDC National AIDS Clearinghouse
www.cdcnpin.org

Critical Path
www.critpath.org

Doctor's Guide AIDS Information Resources
www.pslgroup.com/aids/htm

HIV Database at Las Alamos
<http://hiv-web.lanl.gov>

HIV Medication Guide
www.jag.on.ca/hiv

Medline Plus
www.nlm.nih.gov

National Center for Health Statistics
www.cdc.gov/nchswww/default.htm

The Grateful Med
<http://igm.nlm.nih.gov>

The Body
www.thebody.com

The Combined Health Info. Database (CHID)
<http://chid.nih.gov>

Glossary (Definitions)

General Health Medical Glossary
www.ama-assn.org/insight/gen_hlth/glossary/index.htm

Multimedia

Animation of HIV Lifecycle
www.roche-hiv.com/search/section_frame.html

Nonalcoholic Fatty Liver

*By Janus P. Ong, M.D. and Zobair Younossi, MD, MPH
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Nonalcoholic fatty liver (NAFL) is a group of conditions which are characterized by significant fat (lipid) deposition in the hepatocytes of the liver parenchyma (steatosis or fatty liver) in individuals who have no history of excess alcohol ingestion. The term NAFL was coined to incorporate the full range of liver biopsy findings from steatosis alone to nonalcoholic steatohepatitis (NASH).

Individuals at the greatest risk for developing NAFL have conditions associated with insulin resistance syndrome such as obesity and type II diabetes, although NAFL has been found in individuals without risk factors.

The worldwide prevalence of NAFL has not yet been clearly determined. Estimates of its prevalence from North America, Japan, Northern and Southern Europe, South America, Australia, and the Middle East vary from 10-39%. Based on these studies, autopsy data and expert estimates, the prevalence of NAFL is thought to approach 20 percent.

NASH is part of the spectrum of NAFL that is characterized by fat deposition in the liver with liver cell injury and inflammation. The distinction of NASH from the other types of NAFL is important for prognosis as current evidence indicates that NASH is potentially progressive. Because a liver biopsy is necessary for confirmation of a diagnosis of NASH, the true prevalence of NASH may be underestimated. Nevertheless, the current data suggests that the prevalence of NASH ranges between 1.2 to 4.8 percent. This prevalence appears to be higher among those individuals who have persistent elevations of their liver enzymes or have type II diabetes. Due to its association with obesity and the increasing prevalence of obesity (especially in the U.S.), the prevalence of NAFL and NASH is likely to increase.

The clinical implications of these conditions are still under investigation, but liver-related deaths have been reported in patients with more severe types of NAFL, i.e., NASH. Several studies have demonstrated that individuals with steatosis alone do not demonstrate progressive liver disease over two decades of follow-up. Conversely, nearly 20% of individuals with NASH were shown to progress to advanced liver disease or cirrhosis.

As with the natural history, the pathogenesis of NAFL and NASH is still undergoing active investigation. At

the present time, most authorities believe that the progression from steatosis to fibrosis (or scarring of the liver) is the results of multiple "hits."

The initial "hit," deposition of fat in the liver parenchyma, results from increased uptake and synthesis of fatty acids in the liver. The second "hit" is generally attributed to an oxidative stress, which causes further injury to the liver cells and is responsible for fibrosis or scarring of the liver.

Diagnosis of NAFL and NASH

The diagnosis should be entertained in individuals with abnormal liver enzymes. The diagnosis requires thorough investigation to exclude other causes of liver disease. Patients, in general, are asymptomatic, and diagnosis is often made after evaluation for abnormal liver enzymes on routine laboratory testing. Radiological studies such as ultrasound are useful in detecting the presence of fat in the liver, but cannot accurately predict the presence of liver cell injury. Given the limitations of radiological investigations, the diagnosis of NASH requires a liver biopsy in most cases.

Treatment of NAFL and NASH

Numerous medications and approaches have been studied in an attempt to prevent the progression of NASH. Clinical trials of NASH have been limited by their small size, short duration and limited follow-up.

Weight reduction in overweight and obese individuals has been shown to improve steatosis, but has not been proven to prevent progression to fibrosis. On the other hand, rapid weight loss through very strict weight reduction programs may worsen liver inflammation and fibrosis or scarring. Long term studies of the impact of weight loss through bariatric surgery for morbid obesity are not available. In addition to weight reduction, a number of pharmacologic agents (i.e. ursodeoxycholic acid, vitamin E, clofibrate, betaine, trogliazone, rosigliatazone, etc.) have been evaluated in pilot trials for the treatment of NAFL. While the results of these trials have demonstrated encouraging results, their efficacy awaits confirmation in large randomized controlled trials.

For more information on Nonalcoholic Fatty Liver, please call 800-GO-LIVER. For a list of selected references, please call 202-882-5500.

Liverline, Spring 2003

Extrahepatic Manifestations of Hepatitis C

Part One: Essential Mixed Cryoglobulinemia

by Kara Wright, PA-C

There are several extrahepatic diseases (diseases of organs other than the liver) associated with chronic hepatitis C infection. Although rare, about 38% of patients with hepatitis C experience at least one extrahepatic manifestation of the virus. Most of these diseases appear to be directly related to the viral infection. In this series, we will discuss the different disorders by starting with the blood disorder, essential mixed cryoglobulinemia (EMC).

Cryoglobulinemia is a medical condition that is caused by proteins called cryoglobulins present in the blood. Cryoglobulins are abnormal proteins that precipitate (clump together to form a solid) from the blood when it is chilled and redissolve into the blood upon rewarming. These proteins can be deposited in the small and medium sized blood vessels, which restricts blood flow and leads to further problems. These cryoglobulins can affect many different bodily systems, causing pain and dysfunction.

It is unclear why cryoglobulins are produced. The exact cause of essential mixed cryoglobulinemia is not known, which is why it is called "essential". However, it is considered to be an autoimmune disorder. (Autoimmune disorders are caused when the body's immune system, which is meant to defend the body against bacteria, viruses, and any other foreign product, malfunctions and produces antibodies against healthy tissue, cells and organs.) The hepatitis C virus has the ability to bind to certain cells called B lymphocytes, which promotes production of autoantibodies.

Several studies of patients with essential mixed cryoglobulinemia found that 95% of patients had signs of HCV infection including HCV antibodies or virus. This suggests a strong association between HCV and cryoglobulinemia. The prevalence of cryoglobulinemia is particularly high in hepatitis C (54.3 %) as compared to other forms of viral hepatitis (hepatitis B: 15 % other liver disorders 32 %). It correlates with longer duration of disease and the presence of cirrhosis as scarring of the liver appears to be higher in patients with cryoglobulinemia. Patients with chronic HCV infection and EMC are more frequently females, cirrhotics and have a longer duration of HCV infection. Only a minority (approximately 10%) are associated with actual signs and symptoms of cryoglobulinemia disease. The other 90% have no symptoms or organ dysfunction.

The symptoms of EMC are caused by the deposition of cryoglobulins into the small blood vessels. This results in an abnormal thickness of the blood, which can lead to many problems such as stroke or blood clots in the eyes leading to blindness. It also causes red or purple blotchy skin suggesting some form of vasculitis (inflammation of the vessels). Vasculitis of arteries can result in blockage of arteries leading to damage to the organ(s) supplied by the affected blood vessels, such as in the skin, kidneys, or elsewhere. This can also lead to pain in the joints (arthralgias), enlargement of the lymph nodes, and peripheral neuropathy (numbness or weakness in feet and hands due to nerve damage from decreased blood flow). Other common symptoms are recurrent pain in the abdomen, heart attack, and bleeding in the lungs. Weight loss can occur as well as poor appetite.

EMC can cause renal disease in up to 60% of patients due to the deposition of proteins in the kidney. Symptoms of this include blood in the urine, and protein in the urine found by a simple urine test.

The diagnosis of EMC is first suspected due to the history the patient provides. Most patients first notice the characteristic blotchy skin rash. A simple blood test can be done to assess for cryoglobulins by drawing blood, then cooling it to see if precipitation occurs. Blood tests can also be done to determine the exact type of abnormal protein in the blood. A biopsy of a skin lesion can often confirm that cryoglobulins are responsible for the patient's signs and symptoms.

Treatment is indicated in patients with progressive systemic disease affecting the small blood vessels, kidneys, liver or peripheral nerves. Essential mixed cryoglobulinemia is treated with combinations of medications, which reduce inflammation and suppress the immune system. Medications used include nonsteroidal anti-inflammatory drugs (ibuprofen, aspirin, and others), cortisone preparations (prednisone, prednisolone), as well as medications that suppress the immune system.

Plasmapheresis (removing plasma from the body and replacing it with a saline solution to remove the circulating cryoglobulins) in conjunction with steroids and cyclophosphamide (chemotherapy) to prevent new antibody formation is used in severe cases.

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HCV/HIV Bits

Clinical Trials of Hepatitis C – Specific Antiviral Drugs Begin

(From The New York Times, 3-11-03)

When tests of a patient infected with Hepatitis C (HCV) indicate that treatment is needed, the standard approach is a combination of injected alpha-interferon (an immune system protein) and a pill, ribavirin. Neither drug was specifically designed to attack hepatitis C: each appears to help it attack the virus. This treatment, which has severe side-effects, is said to virtually eliminate the virus in about half of those treated.

In a study reported at the World Federation of Hemophilia's 25th International Congress these combination therapies were shown to have significant success in treating people with hemophilia and HCV, even those who are HIV infected, especially for HCV genotypes 1 and 2. The result are comparable to those in people without hemophilia.

Looking for a more effective and less toxic treatment, drug companies are finally testing HCV-specific antiviral drugs whose actions is similar to that of HIV-specific drugs. The new drugs entering clinical trials are designed to interfere with enzymes that HCV needs to make copies of itself, like protease and polymerase.

One of these experimental drugs, a protease inhibitor made by the German drug company Boehringer Ingelheim, was reported, at a November 2002 liver diseases conference, to have reduced viral levels dramatically. Other companies are now entering the race to create antivirals.

ViroPharma, a biotech company, announced in January that it had begun a clinical trial of a polymerase inhibitor (in partnership with the Wyeth drug company). So did the biotech company Idenix Pharmaceuticals. Japan Tobacco reports having a polymerase inhibitor in phase two clinical trials. Vertex Pharmaceuticals has said it will start a trial later this year of a hepatitis C protease inhibitor and Rigel Pharmaceuticals plans to start a polymerase inhibitor trial this year. Isis Pharmaceuticals is in phase two trials with a drug that tries to interfere with a different part of hepatitis C replication.

These drugs are still in the early stages of development. It will be years before their value is determined, but as clinical trials proceed there will be an opportunity for patients to participate. Since HCV, like HIV,

mutates rapidly and is likely to develop resistance to drugs, combinations of drugs will probably be needed. But because (unlike HIV) the DNA of HCV does not become incorporated into infected cells chromosomes, the virus can potentially be totally eliminated, giving the possibility of a real cure. *Hemophilia Outlook, Spring 2003*

FDA Approval Granted for Hepatitis C Viral Load Assay

Bayer HealthCare LLC announced recently that it has received premarket approval after expedited review from the U.S. Food and Drug Administration (FDA) for its Versant HCV RNA 3.0 Assay (bDNA), a predictive test that directly measures hepatitis C virus RNA levels in serum or plasma.

The Versant HCV viral load assay is the first and only FDA-approved quantitative test to measure HCV viral load levels, and will aid physicians by guiding therapeutic decisions early in treatment. The level of viral load, or HCV RNA, in patient's blood can identify, early in treatment, patients who may not respond to further therapy. Utilizing an accurate HCV RNA quantitative assay such as the Versant HCV viral load assay can help clinicians decide if therapy should be discontinued, thereby avoiding the unnecessary side effects of prolonged treatment.

FDA granted Bayer an expedited review of its premarket approval application on July 26, 2002. The FDA grants such reviews for products that provide treatment or diagnosis of life-threatening or irretrievably debilitating diseases or conditions and for which no approved alternative exists. *Medical Letter on the CDC & FDA*

Epidemiology: Hepatitis C Virus Presents Risk for Liver Cancer in

Adults with AIDS *By Sonia Nichols, Senior Medical Writer*

Government researchers have established a connection between hepatitis C virus (HCV) infection and liver cancer but not HCV infection and non-Hodgkin lymphoma (NHL) in people with AIDS.

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"HCV is linked to hepatocellular carcinoma (HCC) and possibly NHL, but the impact of AIDS on these associations is uncertain," said Eric A. Engels of the Viral Epidemiology Branch at the National Cancer Institute in Rockville, MD.

Engels and NCI colleagues reviewed information from a U.S. database to assess the etiology of HCC and NHL in more than 300,000 adults with AIDS. "The ratio of observed to expected cancer cases (standardized incidence ratio SIR) measured risk relative to the general population," said Engels and coauthors.

There was a higher risk for HCC among groups of AIDS patients where HCV infection rates were higher, such as those with hemophilia or who used injection drugs, than among groups with lower rates of HCV, including homosexual men and heterosexual men (Prevalence of hepatitis C virus infection and risk for hepatocellular carcinoma and non-Hodgkin lymphoma in AIDS 1 *Journal of Acquired Deficiency Syndromes*, 2002;31(5):536-541).

Although HCC was higher among patients with high risk for HCV, the incidence of NHL was lower.

"These data suggest an effect of HCV infection on HCC risk among adults with AIDS. On the other hand, NHL risk was not higher for groups in whom HCV infection was prevalent," Engels and colleagues stated.

The corresponding author for this study is Eric A. Engels, Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 8010, Rockville, MD 20892, USA.

Key Points reported in this study include:

- Scientists have been uncertain about linkage between certain cancers and hepatitis C virus infection (HCV) in AIDS patients.
- High risk for HCV infection associated with an elevated risk for liver cancer in AIDS patients.
- High risk for HCV infection did not associate with a risk for non-Hodgkin lymphoma in AIDS patients.

Hepatitis Weekly, 1/6/03

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Extrahepatic Manifestations (continued)

This regimen may lead to a reduction in the plasma concentration in 55-87% of patients. Renal function can usually be stabilized by this regimen. The two major concerns are: possible enhancement of HCV replication due to immunosuppression and possible exacerbation of low-grade non-Hodgkin's lymphoma. Some facilities can filter the cryoglobulins out of the patient's plasma and reinfuse the patient's own plasma.

In patients with hepatitis C, as a reduction in the HCV virus in patients responding to interferon treatment occurs, cryoglobulin levels decrease and skin lesions and symptoms improve. Recent studies have demonstrated some benefit of using interferon- alfa for those patients with evidence of hepatitis C virus. Approximately 50% of patients with hepatitis C associated cryoglobulinemia appear to respond to interferon-alfa, 3-5 MUs given three times weekly, for 12-18 months. Since decreasing the viral load leads to EMC disease improvement, pegylated interferon with ribavirin would be the best option since it has significantly improved hepatitis C viral response. If the patient has renal impairment, pegylated products are not advised. After therapy discontinuation, patients often experience a rebound of signs and symptoms of EMC. Antiviral therapy should be delayed for 2-4 months in patients with severe disease who are initially treated with plasmapheresis and immunosuppressive therapy.

The prognosis and natural history of the illness is not predictable. Kidney damage can be serious, and recent reports state that permanent failure of the kidney occurs in approximately 10% of patients. Death can occur, usually from serious heart disease, infection, or brain hemorrhage. Approximately 1/3 of patients undergo partial or complete remission, while most have a slowly progressive course that may be complicated by periodic acute exacerbations.

In conclusion, EMC associated with chronic HCV infection should no longer be referred to as "essential" but rather as hepatitis C associated cryoglobulinemia. Many patients with chronic HCV infection may have cryoglobulinemia, but most do not suffer from complications of the disease. If you have any of these symptoms, you should discuss them with your health care provider.

HCV Advocate Newsletter, July 2003

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Progenics Pharmaceuticals Discovers the First Liver-Specific Receptor for Hepatitis C Virus

Progenics Pharmaceuticals (Nasdaq:PGNX)

Receptor may reveal how HCV infects the liver and provide a new therapeutic drug target.

Scientists from Progenics Pharmaceuticals (Nasdaq:PGNX) may have solved a longstanding riddle concerning hepatitis C disease: How does the virus target the liver for infection? Researchers today reported discovering the first-ever liver-specific receptor, called L-SIGN, for hepatitis C virus (HCV). The Company also reported the identification of specific inhibitors, including a monoclonal antibody, that blocked HCV from binding to the L-SIGN receptor. Preventing HCV from binding L-SIGN on liver cells represents a new and targeted strategy for treating this serious disease. The studies are reported in a paper published today in the Proceedings of the National Academy of Sciences USA. The publication is scheduled to be available online this week in the PNAS Early Edition at <http://www.pnas.org>.

"In recent years, various cellular receptors for HCV have been proposed, but until now, none had been found that occurred specifically in the liver and was capable of binding with HCV," said the paper's senior author Williams C. Olson, PH.D., Progenics' Vice President of Research and Development. "As we reported in today's PNA's article, L-SIGN efficiently binds and captures naturally occurring hepatitis C virus particles. We further demonstrated that L-SIGN binds to a viral protein called E2 that is present on the surface of the HCV particle. L-SIGN is found on specialized liver cells that form a barrier between the bloodstream and the surrounding liver tissue. These cells are the first to contact HCV as it enters the liver via the bloodstream. Thus, L-SIGN is uniquely positioned to capture blood-borne virus and concentrate it in the liver, thereby potentially facilitating initial and subsequent rounds of infection."

HCV infection afflicts nearly 3% of the world's population and causes serious liver disease, including cirrhosis and cancer. No vaccine is available to prevent new infections. Current therapies are largely non-specific, effective in only about half of all cases, and have a high relapse rate. New treatment strategies are urgently needed to combat this debilitating disease.

"The L-SIGN receptor is abundantly expressed on endothelial cells of the liver and binds to the envelope of glycoprotein E2 of HCV," explained Tatjana Dragic, PH.D., Assistant Professor of Microbiology and Immunology, Albert Einstein College of Medicine and co-author of the manuscript. "Viruses often make use of cellular receptors

to target a specific tissue for infection. For example, the human immunodeficiency virus (HIV) targets the CD4 receptor on immune system cells. As the first step of viral entry, the HIV glycoprotein gp120 attaches to cellular CD4. HCV's E2 glycoprotein may serve as the functional equivalent of HIV gp120. Our paper shows that E2 bound to the L-SIGN receptor as a potential means of targeting the liver. The research further demonstrated that HCV bound to a related receptor, known as DC-SIGN, that is expressed on dendritic cells, which are specialized cells of the immune system. L-SIGN and DC-SIGN are also expressed in placental tissue, and thus the findings may also explain why HCV is readily passed from mothers to their newborn children.

"Our previous discoveries of the cellular receptors utilized by HIV have translated directly into novel therapeutic agents, and we are eager to leverage this expertise for HCV therapy," added Dr. Olson. "We have shown that HCV binding to L-SIGN can be blocked in the laboratory using specific inhibitors, including monoclonal antibodies. In addition, HCV appears to bind L-SIGN at a site different from that of its natural ligand (ICAM-3), which is a protein that mediates adhesion between cells. Thus, it may be possible to block HCV without blocking the natural activity of L-SIGN. These findings provide proof-of-concept for targeted therapy. Our current goals are to develop increasingly potent and drug-like inhibitors while concurrently exploring the role of L-SIGN in natural infection."

Company Profile

Progenics Pharmaceuticals, Inc. of Tarrytown, NY, is a biopharmaceutical company focusing on the development and commercialization of innovative therapeutic products to treat the unmet medical needs of patients with debilitating conditions and life-threatening diseases. The Company applies its expertise in immunology and molecular biology to develop biopharmaceuticals to fight viral diseases, such as human immunodeficiency virus (HIV) infection, and cancers, including malignant melanoma and prostate cancer. In symptom management and supportive care, therapies are being developed to provide patients with an improved quality of life. Progenics' most clinically advanced product is methylnaltrexone, a compound in phase-3 clinical testing that is designed to block the debilitating side effects of opioid analgesics without

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HCV Treatment

2nd International AIDS Society IAS Conference on HIV Pathogenesis and Treatment held July 13-16 in Paris as reported by Liz Highleyman in the September 2003 issues of the HCV Advocate Newsletter.

Two studies at the IAS conference looked at response to treatment with pegylated interferon in HCV/HIV coinfecting patients. E. Voight and colleagues from Germany found that 15 out of 58 patients (26%) treated with Peg-Intron plus ribavirin experienced a sustained response with undetectable HCV RNA after 24 weeks of follow up. Sustained response rates were higher in patients with HCV genotype 2 or 3 (50%) than in those with genotypes 1 or 4 (17%). As is the case with non-HIV-infected hepatitis C patients, those showing an early treatment response at 12 weeks were more likely to achieve a sustained virological response.

Martin Pols from the National Institutes of Health and colleagues reported data from a small pilot study indicating that HCV/HIV coinfecting patients may respond more slowly to HCV treatment. In hepatitis C patients without HIV, it is increasingly accepted that if a person does not achieve at least a 2-log decrease in HCV RNA viral load 12 weeks after starting therapy with Peg-Intron plus ribavirin, they are unlikely to achieve a sustained viral response with longer treatment. But Pols' results so far (from about 20 patients) suggest

that in coinfecting people, the rate of viral load decline may be the best predictor of eventual sustained response—even if the time period exceeds 12 weeks—and that the 12-week cutoff may not be appropriate for these patients.

Finally, in the June 1, 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes*, C. Uberti-Foppa and colleagues from Italy reported that taking anti-HCV therapy for six months prior to starting anti-HIV treatment reduces the chances that coinfecting patients will discontinue anti-HIV therapy due to drug-related liver toxicity. Out of 105 HCV/HIV coinfecting patients at a Milan hospital, 36 chose to receive HCV therapy (interferon monotherapy or interferon plus ribavirin) before starting anti-HIV drugs, while 39 opted to forgo HCV therapy and immediately start anti-HIV treatment. After beginning anti-HIV therapy, 6 out of 39 (15.4%) patients who immediately started HAART dropped out of the study due to severe liver-related side effects, compared to 4 out of 66 (6.1%) of those who received prior HCV therapy. The researchers estimated that pre-treatment for HCV may reduce the risk of severe drug-related liver toxicity by 10%. "Our data allow us to suggest that anti-HCV therapy should be given before starting antiretroviral therapy [for HIV], because this may reduce the risk of severe antiretroviral therapy-related liver toxicity and probably reduces the risk of progressing to liver failure," the researchers concluded. *HCV Advocate*, Sept. 2003

(Continued from page 11) **Progenics** (continued)

interfering with pain palliation. The Company is conducting multi-dose phase-2 clinical trials with its lead HIV product, PRO 542, a viral-entry inhibitor and is in preclinical development with PRO 140 and other follow-on product candidates in HIV infection. The Company is developing cancer immunotherapies based on PSMA (prostate-specific membrane antigen) technology and currently is conducting phase-1 clinical studies of a therapeutic prostate cancer vaccine. GMK is a cancer vaccine in phase-3 clinical trials for the treatment of malignant melanoma.

The press release contains forward-looking statements. Any statements contained herein that are not statements of historical fact may be forward-looking statements. When the Company uses the words 'anticipates,' 'plans,' 'expects,' and similar expressions they are identifying forward-looking statements. Such forward-looking statements involve risks and uncertainties which may cause the Company's actual results, performance or achievements to be materially different from those expressed or implied by forward-looking statements. Such factors include, among others, the uncertainties associated with product development, the risk that clinical trials will not commence when or proceed as planned, the risks and uncertainties associated with dependence upon the actions of the Company's corporate, academic and other collaborators and of government regulatory agencies, the risk that products that appear promising in early clinical trials do not demonstrate efficacy in larger-scale clinical trials, the uncertainty of future profitability and other factors set forth more fully in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2002 and other periodic filings with the Securities and Exchange Commission to which investors are referred for further information. In particular, the Company cannot assure you that any of their programs will result in a forward-looking statements, and thus it should not be assumed that the Company's silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

Editor's Note: Additional information on Progenics is available at <http://www.progenics.com>
Contact Progenics Pharmaceuticals, Inc., Richard W. Krawiec, Ph.D. 914-789-2800, rkrawiec@progenics.com

Alcohol Increases Hepatitis C Virus in Human Cells

Drinking May Compromise Treatment Success

A team of NIH-supported researchers today report that alcohol increases replication of the hepatitis C virus (HCV) in human cells and, by so doing, may contribute to the rapid course of HCV infection. The researchers tested the actions of alcohol in HCV replicon — viral HCV-ribonucleic acid or HCV-RNAs that, when introduced into human liver cell lines, replicate to high levels. In separate laboratory experiments they showed that

- alcohol increases HCV replication at least in part by upregulating a key cellular regulator of immune pathways and function known as nuclear factor kappa B (NF- κ B);
- alcohol inhibits the anti-HCV effect of interferon-alpha (INF- α) therapy; and
- treatment with the opioid antagonist naltrexone abolishes alcohol actions.

Wenzhe Ho, M.D., and Steven D. Douglas, M.D., Department of Pediatrics, University of Pennsylvania, and the Joseph Stokes, Jr. Research Institute at The Children's Hospital of Philadelphia, and colleagues in the Department of Psychiatry, University of Pennsylvania School of Medicine report their results in the July 2003 issue of *Hepatology* (Volume 38, Number 1, pages 57-65).

Speculating that alcohol somehow promotes HCV expression, the researchers relied on a recently available cellular system for studying the dynamics of virus replication (developed and provided to the investigators by Drs. C. M. Rice, The Rockefeller University, and Christoph Seeger, Fox Chase Cancer Center) to demonstrate for the first time that alcohol enhances HCV replicon expression at both the messenger RNA and protein levels. In the cell lines used for the study, the research team also showed that alcohol activation of NF- κ B was responsible for increasing HCV expression. "Although the replicon system mimics only some aspects of HCV replication, we have identified at least a likely mechanism whereby alcohol increases viral load and thus may become an important cofactor in HCV severity," Dr. Douglas said.

"These findings are immediately useful to clinicians for counseling HCV-positive patients about alcohol use," said Ting-Kai Li, M.D., Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA). "For clinical and basic scientists, they raise new research questions, many of which no doubt will be explored using the model and methods introduced today." NIAAA supported the experiments through a grant to Dr. Douglas, whose work also was supported by the National Insti-

tute of Mental Health and the National Institute on Drug Abuse (NIDA). The NIAAA and NIDA supported Dr. Ho's work on the study.

HCV is an RNA virus of the flavivirus family that infects about 4 million U.S. residents and produces some 30,000 new infections each year. HCV typically escapes clearance by the immune system and leads to persistent, chronic infection in 70 to 85 percent of infected individuals, of whom fewer than 50 percent respond to INF- α , the HCV therapy of choice. Over the long term, HCV infection can lead to cirrhosis, liver failure, and liver cancer. As a group, HCV-infected individuals are the major recipients of liver transplantation.

Clinicians have long observed a high incidence of HCV infection in heavy drinkers, including those without other risk factors such as intravenous drug abuse or history of blood transfusions. In addition, the virus is more likely to persist in heavy drinkers and to lead to such complications as cirrhosis and liver cancer. Suspected mechanisms for the latter effects include alcohol's capacity to compromise immune function and enhance oxidative stress. The role of alcohol use in HCV acquisition has been more of a mystery.

During the 1990s, several studies reported higher blood levels of HCV in drinkers than abstainers and in habitual than infrequent drinkers. Further, drinking reduction was shown to diminish the number of virus particles in the blood. These observations led Dr. Douglas and his colleagues to pursue the role of alcohol in HCV replication.

Using the same replicon, Drs. Ho, Douglas and their colleagues also demonstrated that alcohol compromises INF- α action against HCV and explored a plausible mechanism for alcohol's role in HCV expression. Alcohol interferes with endogenous opiates, which have a key role in its addictive properties. The researchers found that the opiate receptor antagonist naltrexone, better known for its utility in helping alcoholism treatment patients to avoid relapse, not only blocked the promoting effect of alcohol on HCV expression but also diminished alcohol activation of NF- κ B in these cells. "These data strongly suggest that activation of the endogenous opioid system is implicated in alcohol-induced HCV expression," the authors conclude.

For an interview with Dr. Douglas, (215) 590-1978; for an interview with Dr. Ho, (215) 590-4462. For an interview with NIAAA staff members, please contact the NIAAA Press Office. Publications and additional alcohol research information are available at www.niaaa.nih.gov. *NIH News, June 26, 2003*

HealthWise

Depression

by Lucinda K. Porter, RN, CCRC
and Eric Dieperink, MD

This three-part series has been excerpted from the Hepatitis C Support Project's newest publication, Coping with Depression and Hepatitis C.

Living with a chronic disease can be challenging. None of us ever think we will develop a chronic condition, so naturally it is not a situation for which we prepare. A diagnosis of chronic hepatitis C virus (HCV) infection can invoke a huge range of reactions. One common response is depression. This series will discuss various aspects of depression. Hopefully this information will provide you with tools to gain insight and control over depression. Life is indeed short, too short to spend it feeling depressed, especially since something can be done about this.

What is Depression?

Depression is the most common serious psychiatric illness. It is also one of the most treatable. Depression is a disorder that may affect our feelings and outlook on life. Persistent feelings of sadness, a loss of interest in life, hopelessness, and pessimism are common warning signs of depression. The symptoms can vary among people. All of us can feel blue from time to time. However, a persistent or unexplained bout of malaise (the "blues") is not normal and needs to be evaluated.

The following are some symptoms of depression:

- Feeling sad or "empty"
- Fits of crying with no reasonable explanation
- Feeling hopeless and pessimistic
- Feelings of guilt, worthlessness and helplessness
- Feeling anxious or irritable, or restless
- Loss of interest or enjoyment in hobbies, social activities and sex
- Fatigue or decreased energy
- Difficulty concentrating, sometimes accompanied by decision-making and memory problems
- Insomnia and other sleep-related problems
- Appetite loss and/or weight loss; overeating and weight gain
- Thoughts of death or suicide; suicide attempts

(Adapted from the National Institute of Mental Health: Depression. Available at: www.nimh.nih.gov/publicat/depression.cfm)

Depression can be accompanied by a number of other psychological as well as physical complaints. Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain may be related to depression. Other

physical complaints that may be related to depression are:

- Panic attacks and phobias
- Tight chest or throat
- Dizziness
- Shaking or tremors
- Gastrointestinal complaints such as nausea, diarrhea, gas, and stomach pain
- Muscle aches and pains

Depression and Hepatitis C

Depression is a common occurrence in people with HCV. Various research studies support the notion that depression is more common in those with HCV than in the general population. This seems to be true regardless of how a person contracted hepatitis C or the severity of the disease. Additionally, those coping with chronic illness are more likely to report depression as compared to the general population. A hepatitis C diagnosis can carry with it a number of issues and reactions. This article explores some of these common concerns.

The Hepatitis C Diagnosis

Any medical diagnosis can be a jolt. If you were feeling well at the time of your diagnosis, this new information can be especially shocking. An array of questions may be swimming around in your head, such as, what does this mean? Will I die from hepatitis C? What about my family? Is this contagious? If so, how?

Your questions will be answered over time. However, the period following initial diagnosis can be very stressful, emotional, and confusing. Fear, anxiety, anger, and denial are common reactions as well.

Isolation

Feeling isolated is a complicated problem because it can come from both internal and external factors. The part that comes from within can stem from "feeling infectious." Invisible, pervasive, and hideous, this feeling of having the potential to infect another human being can be an incredible burden. Isolation can result from a preoccupation with potential infectiousness.

Society can reinforce this isolation. Sometimes people are ignorant of how to prevent transmission of HCV in particular, as well as viruses in general. Patients have

reported stories of friends and family who would not let them in to their homes out of fear that their children would become infected. Hugs and kisses cease. Sexual relationships stop or are never initiated. In the extreme, marriages and partnerships have suffered.

It is tragic to witness this unnecessary and avoidable exclusion. Those struggling to live with a chronic disease need more support, not less. For some people with HCV, the isolation is worse than the virus. Just like other aspects of chronic hepatitis C, finding ways to manage these complexities is a key to learning how to live with HCV infection.

Note: The hepatitis C virus is a blood-borne virus. It is not passed casually or easily. For information about HCV transmission, click on the "About Hepatitis" button on the top left of this page.

Death

No one needs to be told that death is unavoidable. At the same time, none of us likes to be reminded of this fact. Sometimes a change in our health can be an unexpected reminder of our temporary existence on this planet. A common response upon hearing a diagnosis of HCV is "am I going to die from this?" This begs the question as to whether a person has mild disease or more advanced liver damage.

Thoughts and fears are common and normal. It is essential that we address these concerns so they do not become persistent. Most of our deepest fears can be soothed with facts. The majority of HCV-positive individuals will die with HCV, not of HCV.

Consider these suggestions if you find yourself wrestling with issues related to death:

Talk about it. Tell someone your fears and thoughts. Sometimes the act of saying the unspoken can be very powerful.

Get the facts. Talk to your doctor about your particular situation. Be specific with your questions. What are my chances of dying from this? How much time do I have? Should I be concerned about the fact that I cannot remember things like I used to? Your physician may not know the answers to these questions, but should take your questions seriously. You have the right to not be dismissed or made to feel uncomfortable about your concerns.

Compare notes. The key here is to talk to other people without HCV. Choose people close to your age and lifestyle. Ask them how they feel. You might be surprised to learn that many people your age are feeling tired, achy, and find their memories slipping.

Get support. Talk to people with hepatitis C. People with HCV have more health complaints than those not infected with the virus. Many have also developed ways to cope with these problems. They know the best and the worst doctors. They can recommend web sites and literature. Best of all, when you attend a support group you do not have to try to look or act your best.

Control what you can. Although you do not have control over the fact that the virus has taken up residence in your liver, you do have control over facts such as alcohol use. Alcohol and HCV do not mix. Look at your lifestyle. Do you smoke, drive without a seatbelt, or misuse drugs? Do you exercise and are you careful about what you eat? These are areas that can be controlled. One caution: permanent change does not happen instantly. Success is more likely to occur if you are gentle with yourself while maintaining your commitment.

Grieve. Grief is a part of chronic illness. Sometimes grieving is the only way to move on.

Live while you are alive. Focus on the present, not the future. Until breathing stops, you are still alive. How are you going to spend today and the rest of your life?

HCV Advocate Newsletter, September 2003

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Americans with Disabilities Act

When the Americans with Disabilities Act was passed by Congress in 1990 and formally took effect in 1992, it was intended to be a civil rights law for disabled people—preventing discrimination, establishing workplace rights, and guaranteeing equal access to public accommodations.

Although the law does not enumerate ailments and conditions considered to be legally protected disabilities, people with HIV disease were from the start assumed to be among those protected, says Ronda Goldfein, executive director of the AIDS Law Project of Pennsylvania.

But during recent months, federal courts—the U.S. Supreme Court in particular—have chipped away at the scope of the ADA. The result is a narrowing definition of who is considered disabled, which leaves some HIV-positive people fearful that they are not safeguarded after all, according to Catherine Hanssens, director of Lambda Legal Defense and Education Fund's AIDS Project.

"HIV-positive people's protection from stigma and discrimination hinges more and more on a narrow and moving target," Hanssens says. "There's a growing fear among people with HIV that they have less and less recourse under the ADA to even get into the courts."

The only specifically HIV-related ADA case to be reviewed by the Supreme Court came in 1998. *Bragdon vs Abbott* focused on an HIV-positive Florida woman who was denied in-office treatment by her dentist. She sued, claiming her rights under the ADA had been violated. The justices, in a 5-4 decision, ruled that in this situation HIV disease did qualify as a disability.

The ADA prescribes a three-pronged approach for determining precisely who is covered by its protections, Goldfein says. The first requirement is to show that a claimant's condition substantially limits one or more major life activities. A second is if there is a widespread perception that the condition is disabling. And the last is to show a long-term record of being disabled, regardless of whether the conditions of that disability are currently present.

The plaintiff in *Bragdon*, Sidney Abbott, argued that a major life activity, in her case being able to reproduce, was severely limited because of her HIV disease. The court agreed. While some of the justices hinted that

they were willing to always consider HIV infection a disability, the final ruling focused only on a reproduction issue, leaving claims relating to other major life activities to be determined case by case. It also remains unclear how having limited reproductive options might apply in future ADA cases to HIV-positive people with no plans to have children, such as gay men and seniors. "Whatever shot we had at having HIV considered always to be a disability passed, and the court won't go there at this point," Hanssens says.

Instead, the direction in which the Supreme Court seems to be heading is troubling for many AIDS activists. Two recent cases heard by the court could have significant consequences for HIV-positive workers and even for those simply seeking public services.

The first, *Toyota Manufacturing Kentucky, Inc. v. Williams*, focused on a woman with carpal tunnel syndrome who was denied a change in job tasks. The court ruled unanimously in January that the assembly-line worker was not considered disabled under the ADA because her ailment affected her only at work and only in one particular type of job. Some activists worry that this might be seen to apply to HIV-positive workers who also seek on-the-job accommodations related to their illness.

But because HIV disease extends beyond on-the-job complications, the *Toyota* ruling may actually help HIV-positive people by requiring proof of more substantial limitations on daily activities, notes Peter Petesch, a partner at the Washington, D.C. law firm Ford & Harrison and a cochair of Business Responds to AIDS/Labor Responds to AIDS, a partnership sponsored by the Centers for Disease Control and Prevention. "This case forces you to look deeper with every individual claiming to be protected under the ADA to see in what ways they're truly substantially limited." That was precisely what occurred in *Bragdon*.

Potentially damaging to people with HIV, however, is the second case, *Echazabal v. Chevron USA, Inc.*, according to Joel L. Lazarine, senior staff attorney for Dallas Legal Hospice in Texas. This case centers on a man with asymptomatic hepatitis C who had a job offer rescinded because his would-be employers determined that the chemicals used in the company's refinery could worsen his disease.

A prior decision by the U.S. ninth circuit court in the matter stated that the language of the ADA does not “permit employers to shut disabled individuals out of jobs on the ground that, by working in the jobs at issue, they may put their own health or safety at risk.” But Hanssens sat in as oral arguments were presented to the Supreme Court, and she is not optimistic that the high court will support the lower court’s view when it issues its own ruling, likely by the end of June.

If the justices do rule that a company has the right to keep chronically ill employees out of “hazardous” environments, the decision could be seen by some to also apply to HIV-positive workers. “All you need is some bad science to say that there’s a threat to the person, and you can essentially tell them, ‘You don’t have enough sense to protect yourself, so we’re going to do it for you,’” Goldfein says.

That kind of scenario is not unprecedented. It has happened since the beginning of the epidemic, Hanssens says. “People with HIV have been turned away for years when they needed liver transplants under the argument that their compromised immune system makes it not likely for them to survive,” she explains. “They’ve been denied cosmetic surgery under the claims that it wouldn’t be good for them. HIV-positive women are discouraged from getting pregnant. There’s a whole range of things that HIV-positive people are regularly denied because it’s supposed to be for their own good.”

And it is not just industrial workplaces, such as Chevron’s El Segundo, Calif. Refinery at the heart of the *Echazabal* case, that could seize upon a court decision in favor of the employer, Hanssens adds. HIV-positive workers in the health care industry, particularly at hospitals, could be denied employment because pathogens they may be exposed to could cause them to become ill. Teachers could be similarly denied work under the same argument because of the types of diseases that are passed around in grade schools.

“It’s a very, very thin line in these kinds of cases that separates a genuine paternalistic concern for the workers and outright discrimination,” Hanssens says.

But attorneys Petesch and Rob Ghio, who is head of the employment section in the Dallas office of Arter & Had-den, believe that employers should have a right to keep workers from endangering their health. Ghio, who exclusively represents employers in employment-related issues, says he does not anticipate companies will suddenly begin offering up unsubstantiated claims that their workplaces are hazardous for some of their workers or applicants. “The courts,” he says, “are never going to get to a point where they let employers guess as to a

person’s medical condition and what is and isn’t a threat to them.”

Another possible—but yet unaddressed-legal issue that could crop up in ADA cases, Ghio says, is how HIV should be treated in today’s age of highly active antiretroviral therapy, which has helped transform HIV disease into a chronic but manageable condition.

“When the ADA was passed, the medical view on HIV was that it was a death sentence,” Ghio explains. “We’ve come a long way since then. The fact that the conditions isn’t as immediately debilitating may mean that it won’t always be treated as a disability.”

With HIV-positive people facing such conundrums related to if, how, and when they are protected by the ADA, why are federal jurists making it more and more difficult to establish a disability? According to James Walsh, a workplace diversity expert and the author of the book *Mastering Diversity*, the root of the matter is that congress deliberately passed the buck on defining the law’s scope to the nation’s judiciary, which is still deciding how wide a net the law’s protections should cast.

Ghio agrees: “The courts are saying, ‘We’ve got to find a way to preserve the heart of the statute but discourage every injured employee or ones with minor maladies from coming in and claiming they’re disabled.’”

As flawed as it may be, in most states the ADA provides the only legal protections for disabled workers and residents. In states with strong anti-discrimination laws, such as California, New York, and Illinois, federal ADA rulings are troubling but are often unrelated to the stronger protections, contained in state statutes. However, in states with limited or no protections, federal rulings can have an immediate and profound impact.

Lazarine sees that every day in Texas. “Texas has really bad laws in terms of protecting employees in any area, so the ADA is actually the best thing we have,” he says. “The only protections we get are from federal legislation, so the federal court cases can be devastating to us.

A table with ADA Information Services is continued on page 21

HIV Plus

Taking Care of Business

Taking on the System

If You Find You Are Not Well Enough to Work, Do Not Expect the Disability Benefits to Just Fall in Your Lap

While antiretroviral cocktails have helped many men and women return to the workplace, they have also had an unfortunate effect on those whose health may not be improving—they have made qualifying for disability more difficult.

“Social Security examiners have begun to realize that even someone with a severe opportunistic infection might in six months be ready to go back to work,” says Rice Russell, senior work services specialist at AIDS Project Los Angeles. “The definition of a person with a permanent disability is someone who is unable to support himself or herself for 12 months or more. It’s more difficult for people with HIV to prove that now.”

The best initial steps to take to determine if you are medically qualified to launch a disability claim is to talk directly with your primary care provider and then meet with a benefits coordinator, case manager or advocacy specialist, says Ralph Horton, director of access and assessment services at New York’s Gay Men’s Health Crisis. Most major AIDS service organizations have specialists on-site to guide clients through the process.

But Russell says that before you even consider opening a disability claim, you should be sure that the reason you are seeking to stop work is because you are no longer healthy enough to continue your employment. “Some people testing positive today are seeing HIV-positive people on disability, receiving housing supplements and food from a food bank, and thinking that because they’re positive they’re also automatically eligible for those benefits,” he says. “They’re not. The reality is that you have to be really sick and unable to work.”

“The whole idea of having to budget and live on a smaller income becomes very real,” Horton adds. “You may even need to consider such things as food stamps or getting a subsidy to help pay your rent. It’s a difficult transition, even if you’re coming into a long-term disability program through your job but even more so if you’re seeking government benefits.”

Many companies do offer their employees the kind of

long-term disability insurance Horton mentions. Qualifying for this type of benefit is similar to applying for government-backed disability programs, he says, in that the applicant must show that one is no longer healthy enough to continue working and is likely to remain in that condition.

Social Security Disability income is a federal program that provides continuing income. Qualification varies depending on the age of the applicant and the amount of time worked. The amount of the monthly benefit payment is based on the applicant’s lifetime average earnings, and Social Security contributions, but Horton says that most middle-income earners with a documented work history of five years or more generally receive about \$1,000 a month. SSDI recipients become eligible for Medicare health coverage after the disability claim has been open for 24 months. Benefits continue as long as you are disabled.

Supplemental Security Income is available for disabled people with few assets and a limited income or work history. SSI provides the same basic payment to each person receiving the benefit (\$531 per month for an individual, \$796 for a couple), but many states add money to the basic benefit. SSI recipients also are eligible for Medicaid. Benefits continue as long as you are disabled.

The application process for SSDI and SSI claims is complex, says Russell, who himself was on SSDI from 1996 through 1999. “You can end up with a file a half inch thick,” he notes. “There’s a large application your doctor has to fill out—or your psychologist or psychiatrist if you’re seeking benefits for mental health reasons. There’s a questionnaire. Basically, you fill out any kind of report, form or questionnaire that you can to support your claim.”

But simply submitting what appears to be a well-documented claim is not a guarantee that benefits will be approved. It is possible that the application will be rejected, in which case you should file an appeal to have the claim reexamined. You also should seek help in carrying out the appeal process if you have not already talked with a benefits specialist, Horton says, “Most definitely have an advocate go through your claim. It has become an art of knowing what to put on your form, making sure you’ve got all the right paperwork in, and just navigating the whole bureaucracy.”

Dollars and Sense

That Almighty Dollar has to be a Primary Consideration in Disability Plans

Until a few years ago, financial planning for HIV-positive people may have been as simple as selling a life insurance policy to a viatical company or just making sure that wills and estate plans were in order to provide for heirs. But the arrival of protease inhibitors in the mid 1990's changed the rules—both for HIV disease itself and for HIV-positive people planning for their futures.

"Years ago, you didn't have to do long-term planning because the future really wasn't seen as long-term," says Barbara Freeman Wand of the Boston law firm Hill & Barlow. "You can't assume anymore that that is the case."

For HIV-positive people returning to work, it is imperative to examine insurance options and work regulations in advance, says Nancy Breuer, a partner in West Hollywood, CA-based Work Positive, a firm that specializes in HIV-related workplace issues. Social Security Disability Income coverage includes both a nine-month trial work period and an additional three-month grace period that allows a person to maintain federally funded health insurance while easing back into work. Private disability programs operate differently, and benefits may end immediately. "Working this out all in advance is the only way to go," Breuer says.

Privately obtained medical insurance is another option, says Eva Rosenberg, who operates a tax-related Web site called TaxMama.com. "If there's a way to get that inexpensively, then you may as well do it and get the medical deduction for it if you itemize," she says. "Having that kind of coverage is extremely important."

Preparing a budget that will allow you to live comfortably within your means while also setting aside money for the future is another viral step, Freedman says. In some cases this may mean "cutting down your lifestyle" to make the budget work, he explains. An effective budget also should reduce credit card and other debt to manageable levels or eliminate it altogether.

Retirement planning is also a back-burner issue that has become important for many. The easiest way to build up a nest egg if you are working or returning to the workforce is to divert part of your pay into a 401(k) program, according to both Rosenberg and Freedman. Investing in a 401(k) provides financial benefits in both the short and long term. "You get to invest pretax dollars and defer paying tax on the money in the fund which is impor-

tant," Freedman explains. "In many cases, there's also an employer matching of funds of some sort, and so you get the most bang for your buck that way."

Whereas 401(k) investors build up accounts through pretax dollars, it is also possible for those with lower incomes to invest in a Roth IRA—a type of individual retirement account that uses posttax money. For individuals making less than \$95,000 or married couples earning less than \$150,000 per year, a \$2,000 annual contribution to such a fund is allowed. Withdrawals from the fund after age 59 1/2 are tax free. Best yet, Freedman says, it is possible to take certain early distributions from a Roth IRA.

Selling a life insurance policy to a viatical company remains an effective option to raise cash for those whose health is rapidly deteriorating., Rosenberg says. Any money you get from selling your policy—usually about 30 cents for each dollar of coverage—is typically tax-free. But Rosenberg warns, that if you are thinking of selling a life insurance policy, you should "do some soul-searching" before taking this irreversible step. "If you're not absolutely sure, don't do it," she says. "If you have a family or loved ones you're responsible for, they're still going to need help after you're gone, and you need to be sure that selling your policy won't affect them. Think hard and even get some financial counseling before you make this decision."

Even in the midst of planning ahead, it is important to not overlook the present, Rosenberg says. Focusing all your attention on the future could rob you of today's pleasures. "When you don't have a crystal ball," she says, "financially you should try to achieve some balance in your life. Leave enough money currently to enjoy today and also try to put enough aside so you don't have to worry about tomorrow."

An approach Rosenberg might recommend to some of her HIV-positive clients is to invest about half as much for their retirement as they would if they did not have a chronic disease and use the other half for travel, recreation, and other pleasurable activities." Get some of the great lush luxuries out of life," she advises.

HIV Plus, February/March 2002

(Continued from page 3)

Treatment Interruption (continued)

are being successfully treated with anti-HIV medications, other studies have shown that cycles of treatment interruptions for shorter periods may be of potential benefit to conserve medications and reduce drug-related toxicities."

The CPCRA is a national community-based clinical trials network whose main goal is to inform health-care providers and diverse populations of people living with HIV about the most appropriate use of HIV therapies.

NIAID is a component of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma and allergies.

Reference: J Lawrence *et al.* Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *The New England Journal of Medicine* 349(9):837-46 (2003).

Press releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at <http://www.niaid.nih.gov>

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National Institutes of Health, August 27, 2003

(Continued from page 2)

- This is the same in adult patients

Hepatitis C in Children (continued)

- Younger children respond better than older children to HCV medications
- Why treat children?:
 - Prevention of a chronic disease
 - Prevent HCC
 - Improves general well being
 - Social issues (school, peer relationships, dating, sex) may outweigh all other considerations

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HCV Advocate, 2003

ADA Information Services

This list contains phone numbers/internet addresses of federal agencies and other organizations that provide information about ADA and informal guidance in understanding and complying with different provisions of the ADA.

The Department of Justice which administers the ADA. It provides information on how to file ADA complaints.
Info Line for Publications, Questions, & Referrals
800-514-0301; 800-514-0383 (TTY)
www.usdoj.gov/crt/ada/adahom1.htm

The Equal Employment Opportunity Commission offers technical assistance on ADA provisions applying to employment, it also provides information on how to file complaints.
Questions: 800-669-4000; 800-669-6820 (TTY)
Publications: 800-669-3362; 800-800-3302 (TTY)
www.eeoc.gov

Dept. of Transportation, Federal Transit Administration. ADA Assistance line for regulations & complaints
888-446-4511; TTY use relay service
www.fta.dot.gov/office/civ.htm or email: ada.assistance@fta.dot.gov

Federal Communications Commission, technical assistance on ADA phone relay service requirements.
TRS Publications & Questions
888-225-5322; 888-835-5322 (TTY)
www.fcc.gov/cgb/dro

The Access Board (or Architectural and Transportation Barriers Compliance Board), offers tech. assistance on ADA accessibility guidelines.
Publications & Questions
800-872-2253; 993-2822 (TTY)
www.access-board.gov

The IRS, provides info about tax code provisions, including tax credits/deductions that assist businesses in complying with ADA.
Tax Code Info 800-829-1040; 800-829-4059 (TTY)
Tax Code Legal Questions 202-622-3110, TTY use relay
www.irs.gov

Dept. of Education funds 10 regional centers to provide technical assistance on the ADA
800-949-4232 (voice and TTY)
www.adata.org

The Job Accommodation Network is funded by the Dept. of Labor to provide advice on accommodating employees with disabilities.
800-526-7234 (voice and TTY)
www.jan.wvu.edu

Project ACTION is funded by Dept. of Transportation to provide ADA info & publications on making transportation accessible.
800-659-6428; TTY use relay service
202-347-3066; 202-347-7385 (TTY)
www.projectaction.org

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**Those who cannot forgive others
break the bridge
over which they themselves must pass.**

*Confucius
Chinese Philosopher*