

## **The Best in the News on HCV, HBV and HIV/HCV Coinfection from July 15th, 2003 to August 13th, 2003**

Alan Franciscus  
Editor-in-Chief

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July 15th, 2003

**Millions Unaware They Have Hepatitis C**

Millions of people have been unknowingly infected with hepatitis C, some of them from contaminated blood during transfusions, according to health officials.

"We know that many people are infected with hepatitis C and are unaware that they have the disease," said newly appointed US Surgeon General Dr. David Satcher.

"Unfortunately, many of them cannot be readily identified because the disease does not cause symptoms until it is far advanced."

"Many with hepatitis C virus have no reason to believe they are infected," researchers say. "Many of those at high risk are average people -- middle-aged housewives who had a cesarean section delivery, young adults who had transfusions as high-risk babies or middle-aged men who served in Vietnam."

It is believed that millions are infected with hepatitis C by transfusions.

Hepatitis C is a potentially deadly disease that infects the liver, causing extreme fatigue, nausea, loss of appetite and abdominal pain. It can eventually cause cirrhosis of the liver and death.

It is considered a silent epidemic because many people don't develop symptoms for decades. The Centers for Disease Control and Prevention (CDC) in Atlanta estimates that 40 to 70 percent of those exposed to tainted blood become infected with hepatitis C. Symptoms of Hepatitis C are nausea and vomiting, weakness, fever, muscle and joint pain, yellowing of eyes and skin, dark urine and tenderness in upper abdomen.

It is spread most commonly through intravenous drug use, blood transfusions and organ transplants. It can also be spread through sexual contact, although it is a less likely means of transmission.

Satcher said that those who were infected from contaminated blood transfusions could be tracked through hospital and blood bank records.

An estimated 8,000 to 10,000 people die from hepatitis C each year.

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## **Prevention of Hepatitis B Recurrence after Liver Transplantation**

by [gastrohep.com](http://gastrohep.com)

Combined lamivudine and HBIg is effective in preventing recurrence of HBV infection in patients who are HBsAg-positive/HBV DNA negative before liver transplantation, find doctors in the August issue of the American Journal of Transplantation (Am J Transpl 2003; 3(8): 999-1002).

Hepatitis B immunoglobulin (HBIg) has been shown to be effective in preventing recurrent hepatitis B virus (HBV) infection after liver transplantation (LT).

In this study, researchers from France determined whether the addition of lamivudine to HBIg would be more effective in the prevention of HBV recurrence after LT.

The team assessed 60 HBsAg-positive/HBV DNA-negative patients who underwent LT between 1990 and 2001.

All 60 patients received intravenous HBIg to maintain serum anti-HB levels above 500 IU/L, indefinitely.

However, 17 patients received combined oral lamivudine (150 mg/day) and HBIg. These patients were compared with the historical cohort of 43 patients.

None of the 17 patients in the combined treatment group had HBV recurrence.

The physicians found that in the historical control group, the recurrence rate was 23%, after a median follow-up of 98 months.

They found that 5 patients died from HBV-related liver disease.

However, the team found that after a median follow-up of 30 months, none of the 17 patients in the combined treatment group had HBV recurrence. HBV DNA was undetectable by PCR in at least 3 serum samples per patient.

The team determined that HBV recurrence was significantly lower in the combined group, when compared with the historical control group.

Dr. Jerome Dumortiera's team concluded, "Our results suggest that combined lamivudine and HBIg can avoid the recurrence of HBV infection in patients who are HBsAg-positive/HBV DNA negative before LT".

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July 16th, 2003

## **Nelfinavir Has Least Liver Risk in HIV-Hepatitis Co-Infected Patients**

by Michael Smith

Antiretroviral medications can be toxic to the liver, which creates a dilemma for physicians whose patients are co-infected with HIV and hepatitis -- which drugs to choose?

Using a large Canadian database, Elizabeth Phillips, MD, of Sunnybrook and Women's College Health Sciences Centre, in Toronto, Ontario, Canada, attempted to tease out some answers. The analysis showed that ritonavir, boosted protease-inhibitor regimens, and high cumulative exposure to stavudine (d4T) are associated with a significantly higher risk of severe liver toxicity.

However, patients on nelfinavir-based regimens -- without other protease inhibitors, didanosine, or stavudine -- appeared to be at lesser risk, Dr. Phillips said.

"Nelfinavir is not an important risk factor for liver toxicity," she said. She presented the findings here at the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment.

Dr. Phillips used the HIV Ontario Observational Database to study the histories of 404 patients with both HIV and hepatitis B or C, as well as 1,653 HIV-positive patients without hepatitis. The patients who were not co-infected acted as controls in the retrospective study, she said.

Just over 60% of co-infected patients had ever had severe liver toxicity, compared with 41% of patients without hepatitis, she said. Liver toxicity was defined as grade 3 or 4 elevations in transaminase enzymes.

The biggest risk factor for severe liver toxicity was just the hepatitis co-infection, Dr. Phillips said, while both male gender and age were also significant.

But also significant were the extent of exposure to antiretroviral drugs, number of nucleoside analogues, number of non-nucleoside reverse transcriptase inhibitors, and number of protease inhibitors.

"Nelfinavir overall -- without accounting for drugs given with nelfinavir -- has about a 70% risk of these patients ever having had a grade 3 or 4 toxicity," Dr. Phillips said.

Even that level of risk for nelfinavir, however, "may be the company it keeps," she said: When the effect of other drugs is removed statistically, the risk drops to about 61%.

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July 21st, 2003

## **Surgery-Related Morbidity in Living Donors of Right-lobe Liver Graft**

Complications occur in a significant proportion of right-lobe liver graft donors, find investigators in the latest issue of Transplantation (Transplantation 2003; 76(1): 158-63).

Living-donor liver transplantation (LDLT) using the left lateral segment or left-lobe graft is widely accepted. However, right-lobe grafts are commonly used in many LDLT programs.

The risks for the donors of right-lobe grafts are unknown. 75 complications were identified in 69 donors.

In this study, researchers from Japan assessed 200 donors of right-lobe grafts. They focused on the incidence and variety of surgery-related morbidity.

The team evaluated changes in liver function tests to clarify the relation with donor age, steatosis of the liver, and residual liver volume (RLV).

Complications were surveyed for a median period of 28.7 months.

The physicians found that liver enzymes and bilirubin normalized within 1 month in all donors.

However, enzymes in older donors, those with macrovesicular steatosis, or with larger RLV, were significantly higher on day 1.

The team also determined that bilirubin on day 1 was significantly higher in donors with smaller RLV.

In addition, they found that biliary enzyme was not normalized in the majority at 1 month after donation.

Overall, the team identified 75 complications in 69 donors.

Of these, they found that biliary complications were the most common. These consisted of bile leakages (13%) and biliary strictures (2%), in 27 donors.

However, no complications led to mortality or to long-term sequelae.

Dr Takashi Ito's team concluded, "Complications occurred in a significant proportion of right-lobe donors irrespective of donor age, BMI, estimated RLV, and medical history".

"Living-liver donor surgery requires more care in right-lobe transplants".

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## **FeRx Receives Phase II SBIR Grant to Develop Targeted Radioactive Particles for Treatment of Liver Tumors**

Delivery of Radionuclides Using FeRx Magnetic Targeted Carriers (MTCs) Could Result in Localization of Radiation Dose In Tumor Sites, Eliminating Exposure to Healthy Tissue or Organs

FeRx Incorporated, a targeted drug delivery company, today announced that it has been awarded a \$640,000 Phase II Small Business Innovation Research (SBIR) grant from the National Cancer Institute of The National Institutes of Health (NIH). The grant, entitled "Targeted Radioactive Particles for Liver Tumor Therapy", supports research to continue the development of an intra-tumoral radiation therapy of liver lesions using FeRx's proprietary MagneTarg(tm) drug delivery system. Receipt of the entire grant award

is contingent upon the achievement of certain research and development milestones.

The ultimate goal of the program is to fund pre-clinical and clinical development of an MTC-radionuclide product.

"This continuing grant award recognizes the need to develop an innovative product that could overcome the dosing limitations of current external and internal radiotherapies," said Jacqueline Johnson, Ph.D., President and CEO of FeRx. "While our initial clinical indication under investigation is the treatment of both primary and metastatic liver cancers, the characteristics of the MagneTarg system could also allow for other solid tumor types to be studied as well."

The NIH SBIR program is a competitive, peer-reviewed grant program that provides research support to small businesses to discover and develop innovative biomedical products for the treatment of serious unmet medical needs. FeRx previously received a \$100,000 Phase I SBIR grant award from the National Cancer Institute to prepare and characterize in vitro radiolabeled Magnetic Targeted Carriers(tm) (MTCs) and then investigate in vivo the binding stability, targeting and retention of these radioactive particles. The Principal Investigator on the grant is Gilles Tapolsky, Ph.D., MBA, Senior Director of Research at FeRx.

Results from preclinical studies investigating the use of MTCs in the local delivery of the radionuclide <sup>90</sup>Y to the livers of rabbits implanted with VX2 tumors were presented at the SIR meeting in March 2003 by Jeff Geschwind, MD, Associate Professor of Radiology, Oncology, and Surgery at The Johns Hopkins University School of Medicine, and Director of Interventional Radiology at The Johns Hopkins Hospital. In these studies, radioactivity measured in organs on various days post-dosing showed that the majority of the <sup>90</sup>Y was localized in the liver. MRI performed 7 days after treatment showed the presence of MTCs in the tumors and microscopic examination of tissue showed that these particles were confined to the liver. Importantly, liver necrosis was greater in treated animals (> 70% necrosis) when compared to controls (50% necrosis), with complete tumor destruction seen at the highest dose administered. The study suggested the feasibility of intra-tumoral radiotherapy using magnetic targeting and provides the foundation for the additional investigations being conducted under the Phase II SBIR grant.

Existing data from clinical studies in humans indicate that MTCs can be efficiently targeted to and distributed within the tumor while remaining at the site of localization without redistribution. Thus, the MagneTarg drug delivery system may achieve the selective targeting needed to deliver radiation therapy to the desired site, while minimizing the radiation dose to the untargeted organs. An additional advantage to using MTCs is that larger doses of radiation could be delivered to the tumor site if radioactivity does not readily escape the magnetic targeting mechanism.

FeRx Incorporated is a privately held drug delivery company pursuing the development and commercialization of its proprietary MagneTarg™ system. MagneTarg offers a unique and simple method for localized delivery of a variety of pharmaceutical agents. FeRx believes the proprietary MagneTarg drug delivery system can efficiently deliver an increased concentration of drug to the desired site in the body while reducing the total amount of drug administered and limiting the toxic

side effects commonly found in association with chemotherapy and other nonspecific systemic therapies. The MagneTarg System has applications across a range of therapeutic areas and provides a broad technology platform for targeted delivery of small molecules, radionuclides, biologics and genetic vectors.

Current clinical studies conducted by FeRx are designed to demonstrate the intra-arterial delivery of magnetically targeted pharmaceuticals to specific areas of the body while reducing systemic toxicity and increasing the local concentration of drug at the target site. These trials are focused on the delivery of FeRx's lead product, MTC-DOX (doxorubicin), to primary liver tumors (hepatocellular carcinoma -- HCC) and to tumors that have metastasized to the liver.

The Company strategy is to initially focus on the use of MagneTarg drug delivery for the treatment of certain solid tumors for which there are few, if any, effective therapies today. FeRx will use potent anti-cancer drugs whose mechanism of action is well understood, but whose efficacy and use are often limited by the debilitating side effects of systemic circulation. In addition to the tumors treated in our ongoing clinical trials, other solid tumors such as those found in the lung, pancreas, kidney, bladder, head and neck and limb can also be treated with the MagneTarg system. The Company believes that future applications beyond oncology could include targeted drug delivery in infectious disease, transplantation surgery and gene therapy.

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July 22nd, 2003

## **Alcohol Ups Hepatitis C Virus Replication**

Alcohol increases the replication of hepatitis C virus (HCV), and it interferes with the effectiveness of interferon used to treat hepatitis C.

That warning comes from an article in the medical journal *Hepatology*. The authors—Dr. Wen-Zhe Ho from The Children’s Hospital of Philadelphia, Pennsylvania and associates—examined the effects of alcohol on HCV-infected cells in lab dishes.

“As demonstrated in our study, alcohol not only induced HCV replicon expression but also compromised anti-HCV effect of interferon alfa,” Dr. Ho told Reuters Health. “These findings provide practical guidance toward the reduction of risk factors that interfere with interferon-based therapy and promote HCV disease progression.”

Other experiments showed that naltrexone, a drug used to treat opiate addiction, blocked the enhancing effect of alcohol on HCV. This suggests that “there might be an additional benefit for treating HCV-infected alcohol abusers with naltrexone,” Dr. Ho added.

However, Dr. Ho stressed that all this was determined in laboratory research, not patients. Whether it is meaningful in clinical practice “needs to be confirmed by epidemiological investigations, which is what we would like to do in the future.”

SOURCE: Hepatology, July 2003.

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July 23rd, 2003

## **The Impact of Hepatitis C Virus Coinfection on HIV Disease Progression Before and After HAART**

As the nature of the HIV epidemic changes, there is increasingly an overlap between the populations at risk for acquiring HIV and hepatitis C virus (HCV) infections because of shared routes of transmission.

Injection drug use is the fastest growing risk for both infections, accounting for 26% of new HIV infections in Canada in 1999.

The results of several studies have suggested that HCV disease progression is enhanced by coinfection with HIV. Whether HCV is a co-factor for HIV disease progression remains unclear. Most studies, conducted in the era before HAART, suggest that HCV has a limited effect on the progression or severity of HIV disease.

The two studies conducted in the post-HAART era have conflicting results. The Swiss Cohort found that HCV coinfection was associated with HIV progression, whereas the Johns Hopkins Cohort found no such association.

To compare the impact of hepatitis C virus (HCV) coinfection on progression of HIV infection in the eras before and after the introduction of highly active antiretroviral therapy (HAART), researchers at the Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada conducted a retrospective cohort study.

Results of the study appear in the July 1, 2003 issue of JAIDS.

### **Abstract**

One hundred twenty-five HCV+ patients and 1076 HCV- patients were studied; 83% of HCV+ patients were injection drug users.

HCV+ subjects experienced no clear benefit from HAART. The adjusted hazard ratios (HRs) of opportunistic infection, death, and hospitalization were 0.74, 1.78, and 2.1, respectively, comparing the post-HAART era with the pre-HAART era.

In contrast, HCV- subjects experienced rate reductions for all outcomes. Comparable HRs for opportunistic infection, death, and hospitalization were 0.49, 0.28, and 0.51, respectively.

HCV+ subjects remained at increased risk for death and hospitalization post-HAART even after additional adjustment for antiretroviral use and time-updated CD4 cell and viral load measures.

Deaths and hospitalizations in HCV+ patients were primarily for non-AIDS-defining infections and complications of injection drug use.

The authors conclude “HCV coinfection and comorbidity associated with injection drug use are preventing the realization of substantial health benefits associated with HAART.”

#### Commentary

In the pre-HAART era, the unadjusted rates were consistently lower for HCV+ subjects compared with HCV- subjects for all outcomes. The rates were 11.0 versus 22.9 per 100 person-years for opportunistic infection, 6.9 versus 14.9 per 100 person-years for death, and 9.7 versus 21.0 per 100 person-years for hospitalization, respectively, and are illustrated in crude survival analyses. After adjustment, rate ratios remained below 1, but confidence bounds included 1.

In the post-HAART era, there was no difference in the rate of opportunistic infection observed between HCV+ and HCV- subjects (unadjusted rate: 12.8 vs. 13.1 per 100 person-years).

A reversal occurred with respect to the other outcomes, however. HCV+ subjects in the post-HAART era experienced greater rates of both death (unadjusted rate: 9.5 vs. 5.3 per 100 person-years) and hospitalization (unadjusted rate: 25.9 vs. 12.6 per 100 person-years). The adjusted risks of death and hospitalization remained significantly higher among HCV+ subjects.

In both the pre- and post-HAART eras, baseline CD4 cell count was an independent protective factor against opportunistic infection, death, and hospitalization (i.e., in the post-HAART era, for each additional 100 cells, the HR of opportunistic infection was 0.50, 95% CI: 0.39-0.65,  $p = .001$ ). History of prior AIDS-defining illness increased risks of death and hospitalization, and longer duration of HIV infection increased risk of death. Calendar year of cohort entry was strongly associated with primary outcomes. For example, after HAART, the risk of death diminished substantially in each additional year (i.e., HR = 0.046, 95% CI: 0.013-0.165 for 1999 compared with 1996). Adjustment for calendar year did not change risk estimates associated with HCV status, however. The following factors were not associated with primary outcomes: age, gender, birthplace, and baseline CD8+ cell count.

In the pre-HAART era, both HCV+ subjects and HCV- subjects died predominantly from AIDS-related complications. Despite chart review, the exact cause of death could not be determined for a number of subjects who died at home or in a hospice (likely AIDS related). In the post-HAART era, deaths and hospitalizations among HCV+ subjects were primarily attributable to non-AIDS-defining infections (i.e., bacteremia, pneumonia) and complications of injection drug use.

Hepatitis C virus infection is fast becoming one of the greatest challenges facing an increasing number of HIV-infected individuals and their care providers.

Understanding the impact of coinfection on morbidity and mortality in HIV infection is essential to optimizing the management of the epidemic in developed countries.

The impact of HCV infection on the progression of HIV infection in the era prior to widespread use of HAART has been debated. The majority of older studies have shown no association between HCV infection and survival from HIV disease. In

contrast, more recent studies have reported that immunologic progression, development of AIDS, and shorter survival after AIDS were associated with HCV coinfection.

Recently, the Swiss HIV Cohort Study reported that HCV infection was independently associated with the combined outcome development of a new AIDS-defining condition or death (HR = 1.7, 95% CI: 1.26-2.30) in individuals beginning HAART. In contrast, the Johns Hopkins Cohort, which included both treated and untreated individuals, detected no increased risk in HCV-coinfected persons of a first opportunistic infection, CD4 cell decline, or death once adjustments were made for use of HAART and failure to suppress HIV replication. The reason for these discrepant findings is unclear but may be related to demographic differences in the populations studied and the inclusion criteria employed, primarily the receipt of HAART. By examining both the pre-HAART and post-HAART eras, this study attempted to assess the impact of HCV on HIV progression directly while accounting for HAART exposure.

In the post-HAART era, we found that HCV status was clearly associated with an increased risk of both death and hospitalization but not of opportunistic infection. The lack of an observed effect of HCV status on the risk of opportunistic infection raises the possibility that HCV status does not influence HIV-related outcomes so much as other health events (i.e., other infections, liver disease).

Undoubtedly, one of the major factors contributing additional increased risk of morbidity and mortality associated with HCV infection is the high prevalence of active injection drug use in this population.

This lifestyle has been shown to be associated with violent and accidental deaths, suicide, and overdose, which were also seen in our cohort.

This is the only study to have examined the morbidity and mortality associated with HCV coinfection in both the pre-HAART and post-HAART eras and regardless of antiretroviral treatment. As stated earlier, the study findings suggest that HCV infection, and comorbidity associated with injection drug use, are preventing the realization of improved health outcomes in this population.

07/23/03

Source

MB Klein. The Impact of Hepatitis C Virus Coinfection on HIV Progression Before and After Highly Active Antiretroviral Therapy. *Journal of Acquired Immune Deficiency Syndromes* 33(3): 365-372. July 1, 2003.

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## **Association of HCV Prevalence, RNA, Genotype, and Drug Use with HIV Infection in a Cohort of New York City Drug Users**

by [hivandhepatitis.com](http://hivandhepatitis.com)

Nearly 4 million persons in the United States and an estimated 170 million worldwide have been infected with hepatitis C virus (HCV). Transmission occurs primarily via injection, and injection drug users (IDUs) are at particularly high risk for HCV infection.

It has been reported that 40-85% of IDUs are HCV seropositive, and injection drug use (IDU) accounts for approximately 60% of HCV transmission in the United States. Although acute HCV infection is usually mild, 70-80% of those infected develop chronic hepatitis, with substantial long-term morbidity and mortality due to HCV-related chronic liver disease.

Among HIV-infected IDUs, rates of HCV co-infection range from 52-93%. As potent antiretroviral therapy for HIV has decreased AIDS-associated morbidity and mortality, chronic HCV has become a significant cause of morbidity and mortality in this population.

End-stage liver disease has become a leading cause of death in HIV-infected persons. HIV co-infection may accelerate progression of HCV infection, with more severe liver fibrosis and a higher frequency of decompensated liver disease and cirrhosis. HIV infection is also associated with a higher level of HCV RNA.

The purpose of the current study, published in JAIDS (July 1, 2003), was to identify prevalence of and factors associated with HCV seropositivity, detectability and level of serum HCV RNA, and HCV genotype in a cohort of current and former opiate-addicted drug users in the Bronx, New York City.

Factors associated with serum HCV antibody, HCV RNA level, and HCV genotype were assessed in 557 current and former drug users. Additional assays included HIV antibody, CD4+ lymphocyte counts, HIV viral loads, and hepatitis B markers.

Seventy-five percent of subjects were anti-HCV positive, of whom 75% had detectable HCV RNA.

On multivariate analysis HCV seropositivity was associated with history of drug injection, HIV seropositivity, and increased age and inversely with drug snorting.

Among anti-HCV-positive persons, detectable HCV RNA was independently associated with HIV seropositivity, male gender, and history of injection and inversely associated with hepatitis B surface antigen positivity.

Among persons with detectable HCV RNA, higher levels were independently associated with higher HIV viral load, increased age, and genotypes 2a and 2b.

Genotype could be determined in 303 (96.8%) of the 313 individuals with detectable HCV RNA. Most common were genotypes 1a and 1b, found in 180 (59.4%) and 59 (19.5%) participants, respectively. Other genotypes included 3 (1.0%) type 2a, 38 (12.5%) type 2b, 15 (5.0%) type 3a, and 8 (2.6%) type 4a.

The distribution of HCV genotypes did not differ significantly by gender, whether persons had ever injected drugs, HIV status, or age. However, blacks were

significantly more likely than others to have genotype 1a or 1b. Multivariate analysis confirmed an independent association of genotype with race, but with no other variables.

These findings demonstrate an association of HCV RNA level with HIV viral load, independent of the level of immunosuppression.

However, a substantial degree of the person-to-person variability in the prevalence and level of detectable HCV RNA remains unexplained.

#### Commentary

This study confirms that there is an alarmingly high prevalence of HCV infection among drug users and that persistent HCV infection is especially common among those co-infected with HIV.

HCV RNA levels showed a trend toward being higher in HIV seropositives, among whom levels were significantly higher in those with higher HIV viral load, independent of CD4+ lymphocyte count. These findings are consistent with increasing evidence that HCV infection is more severe when HIV co-infection is present.

Persons with genotypes 2a or 2b had significantly higher HCV RNA levels than those with other genotypes. While some studies have observed no relationship between genotype and HCV RNA levels, others have reported increased RNA levels in association with HCV genotype 1.

The authors conclude, "In summary, this study of New York City drug users shows that the risk of having acquired HCV infection was independently associated with HIV seropositivity, increased age, and having ever injected drugs and was inversely associated with drug snorting.

False-negative HCV antibody results were not found, even among those with HIV infection."

"Among persons anti-HCV positive, detectable serum HCV RNA was independently associated with HIV co-infection, male gender, and IDU and was inversely associated with HBsAg positivity. Higher HCV RNA levels were seen with HIV seropositivity and were significantly associated with higher HIV viral loads, genotype 2a or 2b, and increased age.

Despite these findings, the substantial degree of interperson variability in rates of detectable HCV RNA and in HCV RNA levels remains unresolved."

07/23/03

#### Source

L Strasfeld and others. The Association of Hepatitis C Prevalence, Activity, and Genotype with HIV Infection in a Cohort of New York City Drug Users. *Journal of Acquired Immune Deficiency Syndromes* 33(3): 356-364. July 1, 2003.

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## **Effects of Heparin on Liver Fibrosis in Patients with Chronic Hepatitis B**

By hivandhepatitis.com

The aim of this study, conducted at the Shandong Provincial Hospital in Shandong Province, China, was to evaluate the effects of heparin on liver fibrosis in patients with chronic hepatitis B.

Fifty-two cases under study were divided into two groups, group A and group B. The two groups were given regular treatment and heparin/low molecular weight heparin (LMWH) treatment respectively. Hepatic functions, serum hyaluronic acid (HA) and type IV collagen levels were measured before and after the treatment, and six cases had liver biopsy done twice.

After treatment, hepatic functions became significantly better in both groups. Serum HA and type IV collagen levels in group B compared with group A decreased significantly after treatment. Collagen proliferation also decreased in group B after treatment.

The authors conclude Heparin/LMWH can inhibit collagen proliferation in liver tissues with hepatitis B.

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July 24th, 2003

## **Prisons to Reduce Hepatitis Treatment: Fewer Pa. Inmates will be Eligible, Due to Budget Issues. Officials Say The Candidates Will Be Better Targeted**

by Mark Fazlollah, Inquirer Staff Writer

Faced with looming state budget problems, Pennsylvania prisons this fall will begin reducing by about 75 percent the number of inmates being treated for the potentially deadly hepatitis C virus.

Pennsylvania now has 8,030 state inmates infected with hepatitis C and is treating 550, said Fred Maue, chief of medical services for the Department of Corrections. He said those 550 would get their medicines, which cost \$16,000 per patient for a 48-week course of treatment.

But beginning in September, he said, prisons will apply stricter rules for treating infected inmates. He estimated that 130 a year would receive medicines and that that number eventually might be cut to fewer than 100. He said the number of infected inmates is likely to remain constant-about 23 percent of the prison population.

“We were facing medical cutbacks. We were faced with having to live with a limited budget,” he said. “We felt that we needed to prioritize our budget.”

Maue said much of the treatment would be focused on prisoners with a highly curable form of hepatitis C - about 15 percent of those infected.

He stressed that the reduction in treatment was justified because the state was doing better at targeting patients who could benefit from the medicine.

Thomas Shaw-Stiffel, a specialist at Pittsburgh’s Center for Liver Diseases, said that approach might get more bang for the buck.

“It’s to the patients’ benefit to be more focused,” said Shaw-Stiffel, who worked with the University of Rochester’s hospital when it was treating New York inmates with hepatitis C. “On the surface, [the reduction] may look ominous, but it may be beneficial.”

The new guidelines are in line with national prison standards.

More than three million Americans are infected with hepatitis C, with a huge portion rotating through the correctional system. An estimated one million infected inmates leave jails and prisons each year, the U.S. Centers for Disease Control and Prevention says.

Nationally, hepatitis C is the leading reason for liver transplants. It has become one of the leading causes of death among Pennsylvania inmates.

The reduction in treatment comes at a time when the medications are more successful in effectively curing the disease - prompting some criticism that the state is going in the wrong direction.

“It’s disappointing,” said lawyer Angus Love, director of the Pennsylvania Institutional Law Project, when told of the state’s new rules. “It’s not surprising, given the budgetary constraints.”

Despite the reductions in treatment, Pennsylvania will still be providing more care than many states. New Jersey, for example, is treating 33 inmates - a dramatic change from last year, when it was treating one. Officials do not know how many inmates are infected because New Jersey prisons do not conduct widespread testing.

Under Govs. Tom Ridge and Mark Schweiker, Pennsylvania developed one of the nation’s most aggressive treatment programs. In the past, the state’s secretary of corrections had boasted that his department was saving lives of inmates. The secretary, Jeffrey A. Beard, also said that treating the disease in prisons made inmates less likely to spread it after their release.

Maue said his department last year was “over our budget,” spending about \$8.8 million for treating hepatitis C.

He estimated that for this year, “top dollar would be \$6 million,” with treatment costs even lower next year.

Maue said prisons would require that inmates have at least 18 months remaining on their sentences before consideration for medication. In the past, inmates were required to have a year left on their sentences.

Inmates also will be required to undergo liver biopsies before being considered for treatment.

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## **Quebec to Offer Free Injection Kits to Addicts**

Drug addicts in Quebec will be offered free injection kits to try to cut transmission of the hepatitis C virus, the provincial government said on Wednesday.

A Quebec government official said the Canadian province will spend C\$600,000 (\$430,000) a year to buy about 150,000 kits.

The kits consist of syringes, utensils to heat drugs, filters, sterile water phials and dry wads to be used after injection.

The kits will be available at Quebec’s 680 so-called syringe replacement centers. About 23,000 hard-drug addicts are targeted.

“We want to prevent new contamination. Most young drug users are infected with hepatitis C after six months. We have to target those people,” said Richard Cloutier, a civil servant in charge of the program at the provincial health department.

He said the sharing of utensils, filters or liquids such as saliva and urine contribute to the propagation of the hepatitis C virus, which affects the liver.

A total of one million syringes will be made available each year, but the number is low as some cocaine addicts inject themselves as many as 30 times a day.

“We are far behind places like British Columbia, a province that has three million syringes for the same number of drug users. We are urging community groups to help us out,” Cloutier said.

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## **HCV infection raises the risk for type 2 diabetes in predisposed individuals**

by Sonia Nichols, senior medical writer - NewsRx.com

A prospective study of individuals diagnosed with type 2 diabetes has shown that hepatitis C virus (HCV) infection heightens the risk for the disease in people who are already predisposed to developing it.

In the case-cohort analysis, researchers at Johns Hopkins University in Baltimore, Maryland looked at diabetes onset among more than 1000 men and women between the ages of 44 and 65.

“Among 1084 adults free of diabetes at baseline, 548 developed diabetes over 9 years of follow-up evaluation,” reported Shruti H. Mehta and colleagues in *Hepatology*.

Using common factors such as body mass index (BMI), investigators categorized study participants relative to their having a high or low risk for acquiring diabetes. “Among those at high risk for diabetes, persons with HCV infection were more than 11 times as likely as those without HCV infection to develop diabetes (relative hazard, 11.58; 95% CI, 1.39-96.6),” they said.

In contrast, the group with a low risk for diabetes didn’t show elevated diabetes rates in the face of HCV infection, investigators noted (*Hepatitis C virus infection and incident type 2 diabetes. Hepatology, 2003;38(1):50-56*).

Although larger studies are needed to confirm the results, Mehta’s team concluded that those with risk factors for type 2 diabetes face a heightened risk with HCV infection.

Key points reported in this study include:

- 1) Over half the more than 1000 individuals enrolled in a case-cohort study acquired type 2 diabetes over a 9-year follow-up period
- 2) People with a heightened risk for acquiring type 2 diabetes were more likely to develop the disease if they were infected with hepatitis C virus (HCV)
- 3) HCV infection encourages the development of type 2 diabetes in people with pre-existing risk factors.

This article was prepared by Biotech Week editors from staff and other reports.

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## **State Prisons Changing Way It Treats Inmates with Hepatitis C**

Pennsylvania’s state prison officials plan to treat far fewer inmates found to be infected with Hepatitis C, but those who are treated will get better care.

In fact, new guidelines that go into effect in September not to mention more effective drugs already being used to fight the chronic liver disease will mean not only better treatment for prisoners but better news for taxpayers, state prison officials, medical experts and prisoner advocates say.

About 8,000 of Pennsylvania’s roughly 40,000 state inmates or 20 percent are infected with Hepatitis C. Currently, about 5 to 7 percent of infected inmates are being treated, but new screening techniques mean only 1 to 2 percent of infected inmates will be treated, officials project.

What the Pennsylvania plan is designed to do is get better drugs to the prisoners who need them most, stop the treatment of inmates who may not need it, and ensure that inmates finish treatment before they leave prison, said Dr. Fred Maue, chief of clinical services for the Pennsylvania Department of Corrections.

As a result, inmates will also be refused treatment unless they have at least 18 months left on their sentence. That's because it will take about six months to screen the inmates to see if they're eligible for treatment plus up to a year to receive the treatments.

That's important because, unlike drugs for HIV another disease that affects prisoners at much higher rates than the general U.S. population Hepatitis C drugs aren't covered by the government assistance programs.

"The problem with Hepatitis C is there's nobody to pay for their meds after they're out of prison," said Dr. Richard Greifinger, a nationally known CDC consultant who last year authored a congressional report on the national state of correctional health care. "It's actually dangerous for the patient, I think, to have an incomplete treatment."

The new medicines, pegylated interferon combined with ribavirin, should cure roughly 50 to 60 percent of those infected and 80 to 90 percent of those with less aggressive strains of the disease, said Dr. Thomas Shaw-Stiffel, a specialist with the Center for Liver Diseases at UPMC Health System in Pittsburgh.

"That's very exciting because (those cure rates) are now the standard across the country for people on the outside" of prisons, said Shaw-Stiffel. The old medicines cured only 10 to 40 percent of those treated, medical researchers say. Pennsylvania's new plan "is absolutely consistent with current recommendations for correctional health care" put forth by the U.S. Centers for Disease Control and Prevention and the National Institutes of Health, Greifinger said.

Hepatitis C is spread by intravenous drug use and, in rare instances, transfusions or sex. The disease can cause jaundice, fatigue, pain and vomiting and gradually can cause cirrhosis and liver cancer. Only 20 percent of those infected exhibit symptoms, and those with the disease often don't have symptoms for decades after contracting it, experts say.

Nationally, about 18 percent of prison inmates are infected that's 10 times the 1.8 percent infection rate in the general U.S. population, which has 4 million people infected, according to the CDC.

Pennsylvania switched to the new medicines last fall. The old treatments cost about \$11,600 for a 48-week regimen the new meds cost nearly \$8,000 for a 24-week dose and \$16,000 for a full 48-week regimen. Inmates will be evaluated after 24 weeks to make sure the drugs are working because, otherwise, continued treatments have generally been found to be ineffective, Shaw-Stiffel said.

The state has treated about 550 inmates since its program began three years ago and currently has about 550 in treatment slightly more than the 5 percent treatment rate the state projected, Maue said.

Once the state gets caught up and has screened and treated all of inmates now in its care about 88 percent of inmates had been tested for the disease through April the state will essentially only have to worry about the 8,000 new inmates the state system takes in each year, Maue said.

If 20 percent of those, or 1,600, turn out to be infected, that means the state should only have to treat 16 to 32 new inmates each year if the 1-2 percent projection holds.  
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July 25th, 2003

## **Spontaneous Resolution of Chronic Hepatitis C after Withdrawal of Immunosuppression**

Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 32 Fruit Street, Boston, MA 02114, USA.

Approximately 85% of acute cases of hepatitis C infection result in chronic hepatitis.

Spontaneous clearance of hepatitis C virus has been thought to occur exclusively after acute infection and is associated with a robust cellular immune response.

In the June 2003 issue of Gastroenterology, researchers describe a case of a renal (kidney) transplant recipient who acquired post-transplant hepatitis C virus infection with rapid histological progression.

However, the patient subsequently experienced spontaneous viral clearance along with histological remission after removal of immunosuppression.

Immunologic studies showed persistently strong cellular immune responses. The authors conclude, "This case underscores the importance of restoration of the immune system in the control of hepatitis C virus viremia and disease progression and the need to minimize or obviate immunosuppression in organ transplant recipients."

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July 27th, 2003

## **Viral Protein Could Help Liver Therapy**

by Science News

Researchers experimenting with a protein from hepatitis B virus have developed a new technique for delivering therapeutic genes to the liver while minimizing the accidental introduction of genes to other tissues.

The ideal delivery system for a gene therapy would target only those organs or tissues that need genetic repairs. Live viruses that are altered to carry human genes meet that criterion, but they can trigger dangerous immune responses and cause other problems. Other delivery vectors tend to usher genes to tissues other than the intended ones, a flaw that can lead to side effects.

Shun'ichi Kuroda of Osaka University in Japan and his colleagues suggest a hybrid vehicle: hollow globules of fat covered with a protein isolated from hepatitis B virus. These so-called L particles selectively target liver cells, just as hepatitis B virus does, but are less likely than an intact virus to get out of hand, the researchers say.

Using L particles, the researchers introduced a test gene into clusters of human liver cells growing in laboratory dishes and into mice that had received injections of cancerous human liver cells. In both sets of experiments, the viral protein helped guide the particles to targeted cells, the researchers report in an upcoming *Nature Biotechnology*.

L particles are big enough to accommodate even relatively large medicinal parcels, which could include some conventional drug molecules in addition to therapeutic genes, the researchers note. Furthermore, they suggest, the particles could be engineered to have different surface proteins that would target organs and tissues other than the liver.

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July 28th, 2003

## **24 Weeks of Therapy with Peginterferon Alfa Plus Ribavirin Is Sufficient for HCV Genotypes 2 and 3**

Patients with chronic hepatitis C infected with HCV genotypes 2 and 3 can be successfully treated in more than 80% of cases. This is in sharp contrast to success rates for treatment of patients with genotype 1, which is about 60%.

It has been shown that a 24-week TIW [3 times weekly] treatment period with standard interferon alfa and ribavirin is sufficient for patients with genotypes 2 and 3. However, the recent multicenter studies investigating the effect of the pegylated interferons and ribavirin used a 48-week schedule for all patients irrespective of the HCV genotype.

In this German study, researchers prospectively investigated the efficacy of a 24-week treatment period with PEG-Intron (peginterferon alfa-2b), 1.0-1.5 microgram/kg once weekly and ribavirin (1-1.2 g daily) in 54 patients with HCV-genotype 2 and 3 at two different sites.

29 patients were included in Herne (private practice) and 25 patients were treated in Hannover (Medical School). After the end of follow-up, 46 (85%) patients showed a

virological sustained response in the intent to treat analysis. Only four patients demonstrated a virological treatment failure (3 relapses, 1 breakthrough), two patients were non-compliant, and at each center therapy was stopped in one patient due to adverse events.

There was no difference regarding treatment response between the two sites, even though the patients in Herne were treated only with 1.0 microg/kg PEG-IFN alfa-2b, while patients in Hannover received 1.5 microgram/kg PEG-IFN alpha-2b.

The authors conclude, “The response rates of this study do not differ from the results of the 48-week treatment period of the recently published multicentre trials. Thus, we suggest treating all patients with HCV-genotype 2 and 3 for only 24 weeks when PEG-IFN alfa-2b is used in combination with ribavirin.”

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## **FDA Approves New Hemophilia Therapy**

Healthcare products maker Baxter International Inc. said on Friday it won U.S. approval for a hemophilia drug that eliminates the risk of infection because it treats the bleeding disorder without using human or animal materials.

Unlike other hemophilia treatments, Baxter’s latest generation medicine, Advate, is genetically engineered without using human or animal plasma proteins, which may carry viruses or blood-borne diseases. It is injected directly into a vein.

Deerfield, Illinois-based Baxter, which also makes vaccines, intravenous drug delivery systems and renal therapy products, is pinning its recovery in the second half of the year on Advate sales. This third-generation treatment will be priced at a premium, the company has said.

Baxter said it expects to begin shipping Advate to distributors in three to six weeks. A spokeswoman for the company said it had not yet determined the exact price of the new product.

Hemophilia, a potentially deadly disorder, is caused by a deficiency of a particular blood protein called Factor VIII, one of a series of proteins essential to the blood clotting process.

Hemophiliacs, who are almost exclusively male, suffer recurrent bleeding, mostly into joints and muscles. They also have a high incidence of AIDS resulting from their treatment.

Baxter, which up until early last year could not make enough of its lucrative hemophilia treatment to meet demand, suddenly saw its fortunes turn, due in part to increased competition and price pressures in the market.

Advate is under regulatory review in Europe and Canada. European approval is expected in the second half of the year.

According to the World Health Organization, more than 400,000 people in the world may have hemophilia A, which affects 15 to 20 out of every 100,000 males born worldwide.

“The hemophilia community has indicated there will be a high demand for this innovative therapy because it removes concerns about unknown viruses and infectious proteins carried in protein additives,” Baxter said in a statement.

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## **Canadian Docs Develop Gene Therapy for Hepatitis**

by John C. Martin, [hepatitisneighborhood.com](http://hepatitisneighborhood.com)

A gene-based therapy may someday become the next promising treatment for hepatitis C (HCV) after it cleared a hurdle in a Canadian study this past spring. Doctors with the Ontario Cancer Institute, part of the University Health Network in Toronto, successfully treated HCV-infected mice using a form of gene therapy that forces hepatitis-infected cells to commit suicide through a process known as apoptosis (ap-uh-TOE-sis).

### **‘Genetic Smart Bomb’**

Christopher Richardson, Ph.D., and Eric Hsu, Ph.D., of the Ontario Cancer Institute and their colleagues inserted a gene into a harmless virus, then introduced the engineered virus into the livers of mice infected with HCV. Once the gene entered infected cells, it was only then that it was activated, causing apoptosis to occur. In turn, this cellular suicide halted the replication of the virus, a process by which the virus reproduces itself in an infected host.

This modified gene “acts as a ‘genetic smart bomb’ that targets hepatocytes [liver cells] and other cells that are infected with hepatitis C virus,” said Richardson, in an e-mail interview with Priority Healthcare.

The newly discovered therapeutic approach could theoretically reduce the amount of virus in the blood in humans, and potentially eliminate HCV at early stages of infection or prior to liver transplantation, experts contend.

The technique was tested in vitro in a laboratory setting before it was done with mice, Richardson explained.

Success with the mice translated to the amount of virus present, he said. “When the initial virus loads were low to medium, virus clearance was extremely efficient, and there did not appear to be any rebound over 28 days. Higher initial virus loads may require prolonged treatments to completely clear the virus, and further experiments are addressing this issue.”

### **History of Gene Therapy**

Gene therapy is a concept that is not new. Genes, which are carried on chromosomes, are the basic physical and functional units of heredity. They essentially carry

instructions for cells about how to make protein, the substances that make up most life functions and are the most common component of cells.

However, when genes are altered so that their corresponding proteins can't function properly, genetic disorders or disease results. So, medical scientists have developed a technique to replace the faulty gene with one that works correctly. There are several approaches used with this objective in mind:

- A normal gene may be inserted into a nonspecific location within the genome (the entire set of genes within a person) to replace a defective gene. This is the most common technique.
- An abnormal gene could be traded for a normal gene
- The defective gene could be repaired through a process known as selective reverse mutation, which returns the gene to its normal function.
- The regulation (the degree to which a gene can be turned on or off) of a particular gene could be altered.

#### Delivering a Therapeutic Gene

In most studies using gene therapy, a normally functioning gene is used to replace a disease causing gene by using a carrier molecule called a vector. The vector delivers the normal gene to the patient's target cells. Currently, the most common vector used is a virus that has been re-engineered so that it does not create disease; it only delivers the therapeutic gene to cells.

Target cells like those of the liver or lung are "infected" with the viral vector. The vector then unloads its genetic material containing the therapeutic human gene into the target cells. The gene, in turns, restores the target cell to a normal state.

#### Limitations of Gene Therapy

Yet despite what appears to be a valuable treatment for human disease, gene therapy does have its limitations and potential risks. Before gene therapy can be a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional for the long-term, and the cells containing the new DNA must also be long-lived and stable. So far, problems with integrating therapeutic DNA into the genome, and the rapidly dividing nature of many cells, is preventing gene therapy from providing any long-term benefits.

Additionally, the risk of stimulating the immune system when a virus even one that causes no harm is introduced into the body is ever present. Not only that, but the immune system becomes enhanced when it spots viruses it has seen before. This also limits gene therapy's effectiveness.

Viruses themselves also present a range of problems relative to gene therapy, including potential toxicity, immune and inflammatory responses, and gene control and targeting problems. Scientists are also concerned that the initially harmless virus may somehow recover its ability to cause disease.

Finally, more common diseases high blood pressure, Alzheimer's disease, arthritis, heart disease and diabetes are caused by abnormalities in many combinations of genes. That multi-faceted problem means these diseases are very difficult to treat using gene therapy.

### A Hopeful Finding

Meanwhile, the scientists who took part in the hepatitis study using this novel gene therapy approach are hopeful. Still, much research still needs to be accomplished before the therapy can be tested in a human clinical trial, Richardson explained. First, there are plans to attempt the technique in chimpanzees chronically infected with hepatitis C.

“Human trials with this protocol are probably premature at this time,” Richardson said. “Safety issues would have to first be addressed in the chimpanzee studies. However, we were pleasantly surprised as to how effective the approach was in our mouse model.”

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## **Specific Markers in the Body May Indicate Fibrosis Risk As Well as Liver Biopsy**

by John C. Martin, [hepatitisneighborhood.com](http://hepatitisneighborhood.com)

Five specific biomarkers in the body can predict whether patients co-infected with hepatitis C (HCV) infection and HIV will progress to fibrosis as well as liver biopsy. That's according to a group of Paris doctors who set out to determine ways to predict fibrosis non-invasively. Their findings are published in the March 2003 issue of the journal AIDS.

### Biomarkers That Predict Fibrosis

The biomarkers/biochemicals that serve as an indication of disease include proteins known as alpha2-macroglobulin, apolipoprotein A1, and haptoglobin; a pigment called bilirubin that is produced when the liver processes waste products; and an enzyme known as gamma-glutamyl-transpeptidase.

The researchers say the patient's age and sex also serve as key indicators of fibrosis development. Their study was led by Robert P. Myers, M.D., of the department of hepatology and gastroenterology at Hopital La Pitie-Salpetriere.

These biomarkers, taken together, accurately predict HCV-related lesions that appear on the liver in patients without HIV co-infection, but has never been tested in those who are also infected with the AIDS virus, the clinicians noted.

### Liver Biopsy Comparison

To make that determination, Myers and his colleagues compared the diagnostic value of the biomarkers with that of liver biopsy in a group of 130 co-infected patients at their hospital. Indicators of HIV infection, such as numbers of CD4 cells (targeted by HIV during onset of infection), and HIV-RNA (an indicator of HIV infection) were also included.

They found that higher levels of alpha2-macroglobulin and GGT, lower levels of apolipoprotein A2, and male sex were the “most informative” markers of liver

fibrosis. These markers were similar to the predictive value of liver biopsy, the researchers noted.

Using this biomarker combination as a diagnostic measurement” could reduce the necessity for liver biopsy by 55 percent, while maintaining an accuracy of 89 percent,” the French doctors noted.

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## **Is Liver Biopsy Needed in Co-Infected People?**

In an editorial accompanying the French study, Vincent Soriano, M.D., and his colleagues from Hospital Carlos III in Madrid, Spain, describe the need for routine liver biopsy in patients with chronic HCV without HIV co-infection as controversial. Such routine biopsy may be even less justifiable in co-infected patients, they write.

That’s because 95 percent of people with both HIV and hepatitis C have at least moderate fibrosis, compared to those with only hepatitis C. Plus, these patients face higher risks of biopsy-related complications, Soriano and his co-authors pointed out. Instead, most patients co-infected with HCV and HIV should be considered candidates for hepatitis C therapy, regardless of the health of their liver.

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## **Drugs, Words Battle Deadly Hepatitis C**

by Jason Felch, Denver Post

Mackie Faye Hill carried hepatitis C for 20 years before discovering she was infected with the “silent killer.”

When her doctor told her that she had the disease, the 50-year-old, who holds a doctorate in psychology, began preparing for death. There was no cure, she was told, and without a liver transplant the disease could be terminal.

She wrote a list of all the things she wanted to do before she died and began a book about her life.

Today, Hill, of Denver, laughs at the death plans she made. Thanks to new drug treatments, Hill says, “the virus disappeared, and they never saw it again. I think I’m cured.”

Her doctor agrees. The challenge now, says University of Colorado Hospital’s Dr. Gregory Everson, one of the nation’s top liver specialists, is to spread the word.

Despite being the most common blood-borne disease in the United States - four times more common than AIDS - most people are still confused about hepatitis C, a recent survey by the American Gastroenterological Association shows.

More than 2.7 million Americans are infected with the virus - perhaps as many as 5 million, Everson says - yet only 49 percent of the population is aware of the disease, as compared with the 81 percent familiar with HIV, the June survey found. The Colorado Department of Public Health and Environment estimates that 60,000 people in Colorado carried the virus in 2001.

And despite the new drug treatments available, which some doctors say cure half of those who receive it, fewer than half of people infected are receiving any prescription treatment.

Many have no idea they carry the virus. After 20 years, Hill only learned of her infection in 1993 after donating blood. She had never felt ill, and never heard of the disease. "I thought, what is that? I had heard of A and B, but not C," Hill said.

With the help of doctors, she discovered she had probably been exposed to the virus when she received a blood transfusion during a difficult pregnancy in 1973.

Between 1973 and 1984, Hill donated her infected blood regularly. "Probably somebody got my blood and is now carrying this virus," Hill said.

The virus wasn't identified until 1988, and an accurate test was not developed until the early 1990s.

Everson says those at risk of carrying the virus include people who received a transfusion of blood products before 1992; those who have used intravenous drugs, even once in their lives; those who have snorted cocaine; and those who have been tattooed in unsanitary tattoo parlors.

Myths about the disease are still common. "You can't get hepatitis C from hugging, eating, kissing, sitting on toilets," Everson said. Sexual transmission of the disease is "exceedingly rare," he said.

Symptoms are often subtle, and include chronic fatigue and nausea, which can be indicators of many other problems. Those who think they may have been exposed should see to a doctor about getting tested, Everson said.

But for many in Colorado - particularly the poor and uninsured - identifying hepatitis C is only half the problem.

Without health insurance, the combination drug therapy can cost more than \$20,000 per year, Everson and drug companies estimate. Some uninsured patients may be eligible for patient-assistance programs.

The Hispanic community has been particularly hard-hit by the virus. In Colorado, though the majority of those infected are white, 30 percent are Hispanic, though Hispanics make up only about 17 percent of the state's total population, according to a study by the Colorado Department of Public Health and Environment.

"Over a third of our community doesn't have health insurance," said Rosario C. de Baca, a health worker at Denver's Latin American Research and Service Agency.

Because of the cost, “when people have hepatitis C, they sometimes don’t have a choice but to live with it,” Baca said.

“There are thousands of people who can’t afford the treatment,” said Ann Jesse, founding director of Denver-based Hep C Connection, which runs 13 support groups in Colorado and mails newsletters to 7,000 people nationwide.

Jesse visited Congress in May for the introduction of the Hepatitis C Epidemic Control and Prevention Act. If passed, the legislation could help more people get the care they need, Jesse said.

Hill, who received the treatment for free by participating in one of the early trials, thinks more needs to be done to make information and the treatment available to everyone.

“We should encourage our elected officials to get more money for research and education,” she said.

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## **Ribavirin ANDAs Await Decision by FDA; Par, Roche Expect Launch In August**

by Pink Sheet

Par expects a final decision on the approvability of generic versions of ribavirin by Aug. 1.

FDA is resolving issues regarding the labeling of generics and the potential for shared exclusivity among the three pending ANDA applicants: Geneva, Teva and Three Rivers. Par will market the Three Rivers product.

“I would hope that by the time we get to late next week at the latest we will have an answer between labeling and the shared exclusivity issue,” Par CEO Scott Tarriff told a July 24 investor conference call.

The Los Angeles federal court ruled July 14 that the generics do not infringe ICN’s patents on Rebetol (ribavirin) (“The Pink Sheet” July 21, 2003, p. 12).

Par’s Tarriff declared that the company is ready to launch upon approval, despite the likelihood of an appeal by ICN.

FDA recognizes generics are ready to launch and “they want to have that happen,” Tarriff maintained.

ICN argues that generics should not be approved without language included in the Rebetol label referencing use in conjunction with Schering-Plough’s PEG-Intron; the labeling is still protected by exclusivity.

However, according to the L.A. court, FDA told Three Rivers that it can carve out the pegylated interferon labeling and reference only combination use with the older Intron formulation.

ICN and Hogan & Hartson have submitted citizen petitions to FDA raising concerns about potential generic approvals.

The determination of 180-day exclusivity could also be complicated. Three Rivers expects to receive shared exclusivity, but Tarriff acknowledged the possibility that it would not.

“The possible scenarios could be Geneva by themselves, it could be us having shared exclusivity with Geneva, or it could be all three of us going to market,” Tarriff said.

In any event, it is a “great victory for us,” Tarriff declared. “We won on non-infringement. That means...we are going to market ribavirin. We’re either going to start marketing it now or we’re going to market it in six months, and I think either scenario is wonderful.”

“Obviously, marketing it now is more wonderful,” Tarriff added.

Because the ruling was non-infringement and not invalidity of the patents, Tarriff noted, any additional generic competitors will be relatively slow in coming to market.

“I would think at the end of the exclusivity, the three parties -whichever way it shakes out - will wind up being on the market by themselves for another 12 months after that, give or take.”

Roche, which markets the ribavirin brand Copegus under a separate license with ICN, predicted that generics will come to market soon.

“We know that over the month to come, generic ribavirin will appear,” Pharmaceutical Division President William Burns told a July 23 conference call. “That is now pretty clear from ICN having lost the court case.”

However, Burns noted at an analysts conference later that day, there is another regulatory wrinkle for ribavirin ANDAs.

“There is still an open question whether Copegus can be substituted by a generic,” Burns said. Since Copegus and Rebetol were approved under separate NDAs, “why should generics that come in for Rebetol be substitutable for Copegus?”

“Its an open question,” Burns said. “It may be a nicety, but we have to see how this plays out.”

Burns maintained that the generic impact would be less significant for Roche in any event. He estimated that more than two-thirds of Roche hepatitis C sales are from the interferon ingredient Pegasys, rather than ribavirin.

“The other guy took a lot of their profit and sales through ribavirin,” Burns said.

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July 29th, 2003

## **New Clotting Factor for Hemophiliacs**

HealthDayNews

The U.S. Food and Drug Administration has approved a new clotting factor to treat people with hemophilia A. It's the first such treatment produced without using additives derived from human or animal blood, the agency says, eliminating the risk of viral and bacterial contamination with germs including hepatitis, HIV, and West Nile virus.

People with hemophilia are unable form blood clots, and risk life-threatening bleeding episodes. Advate (Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method) is approved to prevent and control bleeding or to prepare hemophilia patients for surgery.

Existing clotting factors derived from human or animal plasma are processed to kill any germs before they are administered to hemophiliacs. None of these products has transmitted HIV or hepatitis since 1987, the FDA says.

Advate, rAHF-PFM is manufactured by Baxter Healthcare Corp.

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## **Chicago Hospitals Accused of Transplant Fraud**

Three Chicago hospitals were accused of fraud by prosecutors on Monday for manipulating diagnoses of transplant patients to get them new livers.

Two of the institutions paid fines to settle the charges.

The University of Chicago Hospitals and Northwestern Memorial Hospital paid fines of \$115,000 and \$23,587, respectively, without admitting or denying guilt in the "whistle-blower" suits initiated by a transplant specialist.

The University of Illinois Hospital was sued for \$3 million.

"By falsely diagnosing patients and placing them in intensive care to make them appear more sick than they were, these three highly regarded medical centers made patients eligible for liver transplants ahead of others who were waiting for organs in the transplant region," said Patrick Fitzgerald, the U.S. attorney for the Northern District of Illinois.

“Organ donation can be a matter of life and death. There is no room for fraud when it comes to deciding which patient receives an organ,” Illinois Attorney General Lisa Madigan said in the joint statement.

Some patients were hospitalized in intensive care or given a more urgent transplant status to make them eligible for precious livers from organ donors.

The suit against the University of Illinois hospital said the improper diagnoses were used to meet the minimum number of liver transplants to qualify for government health insurance programs.

Donated livers are in short supply, with nearly 20,000 Americans awaiting new ones and roughly 5,000 transplants performed each year. The United Network for Organ Sharing draws up regional lists based on patient need and other factors.

The cases grew out of a 1999 lawsuit filed by transplant specialist Dr. Raymond Pollack, who will share in the fine proceeds.

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## **Maxim Announces Completion of Enrollment of Phase 2 Hepatitis C Clinical Trial**

Maxim Pharmaceuticals announced that it has completed enrollment of a Phase 2 trial of its drug candidate Ceplene™ (histamine dihydrochloride) for the treatment of hepatitis C nonresponder patients. The M0406 Phase 2 trial includes 302 hepatitis C patients who failed to respond to prior therapy with the combination of interferon-alpha and ribavirin. The randomized, controlled Phase 2 trial is designed to compare the treatment of nonresponder hepatitis C patients with a triple-drug combination of Ceplene, Peg-Intron® (peginterferon alfa-2b) and Rebetol® (ribavirin, USP) versus treatment with the Peg-Intron and Rebetol combination.

“Enrollment of this trial was one of our key corporate objectives for 2003, and we are pleased to have reached this milestone,” said Larry G. Stambaugh, Maxim’s Chairman and Chief Executive Officer. “Current treatments are ineffective for approximately half of the patients with hepatitis C, and in particular there are a lack of effective treatment options for patients that have failed prior treatment. The M0406 trial is one of the programs that we have underway to advance the potential use of histamine therapy in chronic liver disease, including the development of an oral form of histamine.”

In the M0406 trial, patients will be treated for up to 48 weeks and followed for an additional 24 weeks after completion of treatment. The primary measures of efficacy in the study are sustained complete viral response and sustained biochemical response (normalization of the liver enzyme ALT, a standard measure of liver function) at 72 weeks. The trial is being conducted in North America, Western Europe and Israel.

## Overview of Ceplene and Histamine Therapy

Research has shown that oxygen free radicals released by certain immune cells can suppress the immune system and damage normal tissue, a process commonly referred to as oxidative stress. Oxidative stress, implicated in numerous diseases, is most pronounced in the liver and can damage or destroy liver tissue in patients with hepatitis and other chronic liver diseases.

The naturally occurring molecule histamine has been shown in preclinical work to prevent the production and release of oxygen free radicals, thereby reducing oxidative stress. Accordingly, treatment with histamine has the potential to prevent or reverse damage induced by oxidative stress and to protect critical cells and tissues, including the liver. Research regarding histamine and related clinical results has been the subject of more than 80 presentations at major scientific and clinical meetings, and has been published in more than 300 scientific and clinical articles.

Phase 3 clinical trials of Ceplene, the injectable form of histamine dihydrochloride, have been conducted in Stage IV malignant melanoma and acute myeloid leukemia. Ceplene has also been tested in Phase 2 trials in advanced renal cell carcinoma. Nearly 2,000 patients have participated in the Company's completed and ongoing clinical trials.

Testing of histamine therapy has been expanded beyond oncology as it has shown the potential to prevent or inhibit oxidative stress, a condition associated with most acute and chronic liver diseases. Based upon the basic mechanism of action of histamine therapy, and the results seen in clinical and preclinical testing, Maxim intends to further explore the testing and development of histamine in chronic liver diseases such as hepatitis C and nonalcoholic steatohepatitis (NASH).

"Initial testing in hepatitis C has been conducted with the Ceplene injectable drug candidate," said Kurt R. Gehlsen, Ph.D., Maxim's Chief Scientific Officer. "We expect that an alternative formulation, such as the oral formulation of histamine currently under development, most likely will be integrated into further testing of histamine in chronic liver disease."

## Maxim Overview

Maxim Pharmaceuticals is a global biopharmaceutical company with a diverse pipeline of therapeutic candidates for life-threatening cancers and liver diseases. Maxim's research and development programs are designed to offer hope to patients by developing safe and effective therapeutic candidates that have the potential to extend survival while maintaining quality of life.

In addition to Ceplene, Maxim is developing small-molecule inhibitors and activators of programmed cell death, also known as apoptosis, which may serve as drug candidates for cancer, cardiovascular disease and other degenerative diseases. The Company's third technology platform, the MX8899 topical gel, is being tested in an attempt to help patients who suffer from oral mucositis and radiation dermatitis, both of which are debilitating side effects of certain cancer therapies. Ceplene, the apoptosis inducers, and MX8899 are investigational drugs and have not been approved by the U.S. Food and Drug Administration (FDA) or any international regulatory agency.

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## **Maxygen Reports Second Quarter 2003 Financial Results Company Updates 2003**

Maxygen, Inc. today reported financial results for the second quarter ended June 30, 2003.

For the second quarter of 2003, Maxygen reported a non-GAAP (formerly pro forma) net loss of \$9.0 million, or \$0.26 per share, compared to the company's non-GAAP net loss of \$6.5 million, or \$0.19 per share, in the comparable period in 2002(A). In both cases, these results are exclusive of stock compensation expense, amortization of intangible assets and subsidiary preferred stock accretion. Including such charges, Maxygen reported a net loss applicable to common stockholders on a GAAP basis of \$10.3 million, or \$0.30 per share, for the second quarter of 2003 compared to a net loss applicable to common stockholders of \$8.7 million, or \$0.26 per share, in the second quarter of 2002(A).

Revenue in the second quarter of 2003 was \$7.3 million compared to \$10.5 million in the same period in 2002. The decrease in revenue is primarily attributed to an expected decrease in partner funding as the research terms of the Company's collaborations with Lundbeck and InterMune wind down on schedule. Expenses relating to research and development decreased in the second quarter of 2003 to \$13.8 million, compared to \$15.4 million for the same period in 2002. The decrease in expenses was due to reduced activities related to the Lundbeck and InterMune-funded programs and Maxygen's continued cost control measures.

At June 30, 2003, cash, cash equivalents and marketable securities totaled \$217.1 million. This includes \$29.6 million held by Maxygen's subsidiaries Verdia and Codexis.

"Maxygen continued to make strong progress this quarter towards achieving our strategic, operational and financial goals for 2003," said Russell Howard, Ph.D., Chief Executive Officer of Maxygen. "The highlight of the quarter was the establishment of our broad collaboration with Roche to develop next-generation interferon therapies. Roche is a world leader in interferon therapies and in protein pharmaceuticals; this collaboration clearly validates Maxygen's ability to create novel and improved next-generation protein pharmaceuticals. Importantly, the structure of this collaboration provides Maxygen the option to co-fund development of products after clinical proof of concept in exchange for profit share or higher royalty rates. This is a great opportunity as it minimizes financial risk to Maxygen while providing a clear route to substantial potential financial reward."

"Maxygen continues to advance its products while controlling cash utilization. This has enabled us to lower our 2003 guidance for expected consolidated cash utilization to approximately \$35 million, compared to our original guidance of \$38 to \$43 million(B). Excluding Codexis and Verdia, our cash utilization is anticipated to be approximately \$25 million, compared to our earlier guidance of approximately \$30

million(B). Maxygen's current cash position of over \$217 million is an important strategic asset, and we will continue to make focused investments in key product opportunities while endeavoring to maintain a strong cash position relative to cash utilization."

## COMPANY HIGHLIGHTS

Broad product development alliance established with Roche.

In May 2003, Maxygen established a broad collaboration with Roche, an established leader in interferon therapies. Roche licensed from Maxygen worldwide commercialization rights to specific novel interferon product candidates for the treatment of hepatitis C and B virus infections. Maxygen receives an initial payment, full research and development funding for the first two years of the collaboration and option fees. In addition, Maxygen is eligible to receive milestone payments and royalties based on product sales.

The Roche agreement also provides the companies with the option to expand the collaboration to develop other novel interferon alpha and beta products specifically tailored for indications outside of HBV and HCV, including oncology, autoimmune diseases, inflammatory diseases, and other infectious diseases such as HIV. Maxygen retains the right to develop such products while Roche may elect to acquire worldwide license and commercialization rights to these product candidates.

Maxygen has the option to co-fund the development in the United States of any product to which Roche acquires a license in exchange for profit sharing or an increased royalty rate.

Payments to Maxygen could exceed \$230 million plus royalties on product sales if there is successful development of the novel interferon product candidates.

## Non-GAAP Financial Measures

To supplement our consolidated financial statements presented in accordance with GAAP, we use non-GAAP financial measures of cash utilization and non-GAAP net loss, which are adjusted from results based on GAAP to exclude certain expenses. These non-GAAP financial measures are provided to enhance the user's overall understanding of our current financial performance and our prospects for the future. Specifically, we believe the non-GAAP financial measures provide useful information to both management and investors by excluding certain expenses that may not be indicative of our core operating results. Our management uses non-GAAP net loss and cash utilization in analyzing the performance of each of our operating business segments and in analyzing the performance of Maxygen as a whole. In addition, because we have historically reported certain non-GAAP financial measures to investors, we believe the inclusion of non-GAAP financial measures provides consistency in our financial reporting. These measures should be considered in addition to results prepared in accordance with GAAP, but should not be considered a substitute for or superior to GAAP results. The non-GAAP financial measures included in this press release have been reconciled to the nearest GAAP measure.

## About Maxygen

Maxygen, Inc. headquartered in Redwood City, California, is focused on creating novel products using its integrated proprietary technologies for human therapeutics and industrial applications. Maxygen's technologies bring together advances in molecular biology and protein modification to create novel biotechnology products. Maxygen has strategic collaborations with leading companies including Roche, Aventis, InterMune, Lundbeck, ALK-Abello and the International AIDS Vaccine Initiative (IAVI). Additionally, Maxygen has a range of other strategic alliances in industrial applications, as well as funding from U.S.A. government organizations including USAID, NIST-ATP and U.S. Army Medical Research and Material Command.

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## **ALT Levels May Show Response to HCV Care: Small Viral Kinetics Study**

by Patrice G.W. Norton, Internal Medicine News

A strong correlation between alanine transaminase levels and hepatitis C viral load changes during the first 4 weeks of high-dose interferon treatment suggests that ALT levels could serve as a surrogate marker for response.

This is one of the early findings of a viral kinetics study performed at the University of Illinois, Chicago, led by Dr. Thomas J. Layden and reported by Alan S. Perelson, Ph.D., at a meeting sponsored by the American Association for the Study of Liver Diseases.

ALT levels generally are monitored only at the start and end of therapy in patients with hepatitis C virus (HCV). By monitoring ALT levels throughout treatment, physicians could individualize therapy Dr. Perelson suggested.

The researchers randomly assigned 35 treatment-naive chronic HCV patients to receive 10 million IU of interferon alfa-2b daily or the same interferon regimen plus 1,000 mg/day of ribavirin (those weighing more than 75 kg received 1,200 mg/day) for 28 days. All participants subsequently received 3 million IU of interferon three times a week plus ribavirin for 48 weeks.

Patients were monitored intensively for the first month (9-10 viral load measurements in the first week and 1 each in weeks 2 and 4) and then at 12 and 48 weeks, said Dr. Perelson of the Los Alamos National Laboratory's Theoretical Biology and Biophysics Group in New Mexico.

ALT levels were unchanged in nine patients, four of whom cleared the virus by 48 weeks. ALT levels decreased in five patients, and increased in three patients. For 14 patients, ALT levels rose on day 2 and 3 of treatment, then decreased to pretreatment or normal levels. Four patients were lost to follow-up after less than 1 week.

Among the 17 patients whose ALT levels increased, those with smaller initial increases in the first 48 hours were more likely to clear the virus by week 48. Those who cleared the virus had less than a 10% initial increase in ALT; those not clearing the virus had more than a 35% initial increase in ALT.

The decline in HCV viral load at 4 weeks correlated significantly with the drop in ALT levels during the first 4 weeks of treatment, Dr. Perelson said.

The efficacy of treatment in blocking viral production differed by almost 10% between whites (98.2% with or without ribavirin) and African Americans (88.6% with ribavirin and 87.0% without ribavirin). No patient who blocked less than 90% of viral production cleared the virus at 48 weeks.

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July 30th, 2003

## **Quality of Life and Cognitive Function in Hepatitis C at Different Stages of Liver Disease**

Hepatitis C has been associated with a decrease in quality of life and with neurological abnormalities. The aim of the present study, conducted at multiple sites in Spain, was to investigate the relationship between quality of life and cognitive (mental) function.

Quality of life, clinical variables and neuropsychological function were evaluated in 120 patients with hepatitis C (mild chronic hepatitis, compensated cirrhosis and decompensated cirrhosis) and in healthy controls (n@, in each group).

Patients with chronic hepatitis or compensated cirrhosis showed a decrease in quality of life, in spite of unimpaired neuropsychological tests. Patients with decompensated cirrhosis exhibited a further decrease in quality of life and neuropsychological abnormalities.

The decrease in quality of life was associated with the severity of liver failure, neuropsychological abnormalities and treatment with beta-blockers or diuretics.

However, in the multivariable analysis, only treatment with beta-blockers or diuretics (which was limited to decompensated cirrhosis) was independently associated with quality of life.

The authors conclude, "Hepatitis C causes a decrease in quality of life even in the absence of major cognitive impairment. The mechanisms that worsen quality of life are unknown. However, in cirrhotic outpatients with prior decompensations, treatment with beta-blockers or diuretics appears to have an important effect on quality of life."

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## **Cytokines Participate in Pathogenesis of HCV and Help to Predict Efficacy of Interferon**

by [hivandhepatitis.com](http://hivandhepatitis.com)

The purpose of the current study, conducted at the Hospital of Zhejiang University in Hangzhou, China, was to evaluate the roles of serum interleukin-18 (IL-18), interleukin-10 (IL-10) and soluble interleukin-2R (sIL-2R) in the pathogenesis of chronic hepatitis C and to observe the effects of interferon (IFN) on these serum cytokines.

The levels of IL-18, IL-10 and sIL-2 were detected in 10 healthy individuals, 24 asymptomatic hepatitis virus C (HCV) carriers and 27 patients with chronic hepatitis C (before and after interferon/IFN treatment) using enzyme linked immunosorbent assay (ELISA).

The levels of the cytokines in patients with chronic hepatitis C are higher than in healthy people ( $P < 0.05$ ) and in asymptomatic HCV carriers ( $P < 0.05$ ). The values of the cytokines show a significant positive correlation to ALT ( $P < 0.05$ ).

Levels of tested cytokines decreased observably after IFN treatment ( $P < 0.05$ ). The grades of the serum levels for sIL-2R and IL-10 before IFN treatment (from high to low) were categorized accordingly: non-response group > partial- response group > complete- response group ( $P < 0.05$ ).

The authors of the study conclude, "The tested cytokines co-participate in the pathogenesis of chronic hepatitis C, and can be used to evaluate the effect of IFN on the immune state of organisms. Furthermore, sIL-2R and IL-10 are important for predicting the anti-viral efficacy of IFN."

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## **Favorable Prognosis of Hepatitis C after Interferon Therapy**

by [www.gastrohep.com](http://www.gastrohep.com)

A cohort study published in the August edition of *Hepatology* (*Hepatology* 2003; 38: 493-502) concludes that interferon therapy is of long-term clinical benefit for patients with chronic hepatitis C.

At present the prognosis of chronic hepatitis C after interferon therapy is poorly defined.

Dr Fumio Imazeki and his team at Chiba University in Japan examined the effect of interferon therapy on survival in 459 patients with hepatitis C.

Mortality rates were estimated from medical records and patient questionnaires.

Of the 104 patients who were not treated with interferon, 14% died during follow-up, compared to only 9% of the 355 patients who had received interferon therapy.

The standardized mortality ratio for liver related death was reduced from 19.7 to 7.9 in patients treated with interferon.

Interferon therapy was particularly effective in patients with a sustained virologic response to treatment.

Interferon treatment reduced the risk ratio of liver-related death to 0.208 compared with untreated patients.

Interferon treatment was not associated with liver unrelated death.

Dr Imazeki concludes that interferon therapy has a long-term clinical benefit for hepatitis C patients.

However, Dr Rafael Esteban, writing in an editorial in the same journal, adds a note of caution, "The study was retrospective and non-randomized, so the interpretation of the results is difficult."

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## **Hepatitis C Coinfection Hampers Benefits of HAART in HIV Patients**

by David Douglas

Despite undergoing highly active antiretroviral therapy (HAART), patients infected with both hepatitis C virus (HCV) and HIV are at increased risk of hospitalization and death, Canadian researchers report in the July 1st issue of the *Journal of Acquired Immune Deficiency Syndromes* (J Acquir Immune Defic Syndr 2003;33:365-372).

As lead investigator Dr. Marina B. Klein told Reuters Health, "Hepatitis C coinfection, along with other associated factors such as injection drug use, have prevented such individuals from realizing the substantial health gains brought about by HAART."

Dr. Klein and colleagues at McGill University Health Centre, Montreal, initially hypothesized that "it is quite likely that HCV-coinfected patients may not have derived equal benefit from the revolution brought about by HAART."

To investigate, the researchers conducted a retrospective cohort study covering the eras before and after the introduction of HAART. In total, 125 HCV-positive patients, 83% of whom were injection drug users, were involved, as were 1076 HCV-negative patients.

Altogether, say the investigators, the HCV-coinfected patients "experienced no clear benefit from HAART." Compared to the pre-HAART era, post-HAART adjusted hazard ratios for opportunistic infections were 0.74, for hospitalization 2.1, and for death 1.78.

In contrast, corresponding figures for HCV negative patients were 0.49, 0.51 and 0.28.

The researchers also note that deaths and hospitalizations in HCV-positive patients “were primarily for non-AIDS-defining infections and complications of injection drug use.”

Summing up, Dr. Klein said, “The main conclusion that we drew from our research is that unless hepatitis C infection and associated behaviors are directly dealt with, coinfecting patients will continue to suffer significant rates of illness and death that might be otherwise preventable.”

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## **Immune System Drug May Reduce Transplant Risk in Fatty Livers**

by DataMonitor Healthcare Newswire

Studying rats with fatty livers, the researchers discovered that bathing the livers in a human immune system protein called interleukin-6 (IL-6) rescues them from failure when transplanted into other rats. The findings appear in the July issue of *Gastroenterology*.

Roughly 40% of adults in the US have so-called “fatty” livers, which frequently fail to function at all or fail quickly when transplanted, and it is hoped that IL-6 may be used to ‘rescue’ some of the lost organs. However, the technique needs to be tested in larger animals, such as pigs, before human studies are undertaken.

“IL-6 is already approved for use in humans, but it has many negative effects when injected,” said Dr Zhaoli Sun, a scientist in the department of surgery at Johns Hopkins. “Fortunately, our technique stores the liver in IL-6 before it’s transplanted, rather than giving IL-6 to the organ recipient, so side effects should be minimized.”

For his experiments, Dr Sun developed two special rat colonies. In humans, fatty livers generally stem from either diet or alcohol consumption, and the two rat models developed fatty livers under equivalent conditions.

After removing a fatty liver from one animal, and before transplanting it into another, Dr Sun bathed the liver in a soup of nutrients that either did or did not include IL-6. Livers soaked in IL-6 had better blood flow, better function and allowed recipients to live, while fatty livers never exposed to IL-6 succumbed quickly to damage and never worked well enough to save their new hosts.

Dr Sun said it is not yet known how IL-6 protects the fatty livers from damage or how it improves so-called “microcirculation,” which helps prevent large chunks of the liver from dying. But while those questions are interesting scientifically, Dr Andrew Klein, who as director of the Johns Hopkins Comprehensive Transplant Center collaborated on the trial, said clinical trials will not have to wait for those answers.

“Eventual clinical trials, if approved, would probably begin by looking for reduced damage or improved function in organs we would already use for transplant,” said Dr Klein, who notes that a generally acceptable cutoff is a liver with no more than 30% of cells containing big droplets of fat. “Moving toward livers that currently would be borderline would be a gradual process.”

Roughly 17,500 people are awaiting liver transplants in the US, and 5,327 liver transplantations were performed last year across the country, according to statistics kept by the United Network for Organ Sharing. IL-6 has been administered to people as part of early phase clinical trials in adults and children with various cancers, but was limited by its toxicity.

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## **Prophylaxis and Treatment of Hepatitis B Recurrence after Liver Transplantation**

by [hivandhepatitis.com](http://hivandhepatitis.com)

A serious complication after liver transplantation for hepatitis B-related liver disease is the redistribution of virions from extra-hepatic reservoirs with resultant reinfection of the graft. Prophylaxis of hepatitis B virus recurrence is a major issue in these patients.

With the introduction of passive immunoprophylaxis and the development of antiviral drugs, liver transplantation has evolved as an established therapy for hepatitis B-induced end-stage liver failure.

However, even under indefinite monoprophyllaxis, a significant percentage of patients develop reinfection due to the high mutation rate of the hepatitis B virus.

Progress, especially in the field of antiviral therapy, has opened up new strategies, including combination prophylaxis and therapy, which has further improved outcome.

On the other hand, the broad use of antiviral drugs brings about new problems, such as the development of resistance prior to liver transplantation. In addition, due to the high costs of hepatitis B immunoglobulin, alternatives such as prophylaxis with nucleoside analogs or vaccination are increasingly being investigated.

### **Key Issue**

The major issue in hepatitis B virus (HBV) patients after liver transplantation is the prevention of reinfection with HBV. Today, hepatitis B recurrence is preventable in more than 90% of patients by using hepatitis B immunoglobulin (HBIg) and low-dose lamivudine combination prophylaxis.

Combination prophylaxis reduces recurrence rates from 35% (low dose HBIg or lamivudine monoprophyllaxis) and 20% (high dose HBIg prophylaxis) to less than 10% (lamivudine plus HBIg).

Conversion to lamivudine monophylaxis is feasible in low-risk patients 12 to 18 months post-transplantation with minimal recurrence rates (but significant reduction of costs).

As a consequence of intensified prophylaxis, antiviral therapy of reinfection becomes a domain of new drugs with activity against lamivudine resistant strains.

Since the introduction of antiviral therapy, results of liver transplantation for hepatitis B-induced liver failure compare well with other indications for liver transplantation, even in patients with active viral replication prior to transplantation.

However, high-risk patients produce higher costs due to the need of indefinite combination prophylaxis.

In the case of lamivudine resistance with elevation of liver enzymes after transplantation, new antiviral agents such as adefovir, entecavir or tenofovir are highly effective and should be used in this setting.

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## **Efficacy of Intron A (interferon alfa-2b) and Eпивir-HBV (lamivudine) Combination Therapy for Chronic Hepatitis B in Children**

by hivandhepatitis.com

The aim of this Turkish study was to evaluate the efficacy of interferon (IFN) alfa-2b (Intron A) and lamivudine (Eпивir-HBV) combination therapy in children with chronic hepatitis B virus (HBV) infection.

Ten children who developed chronic hepatitis B infection received IFN alfa-2b 10 million international units (IU)/m<sup>2</sup> body surface area, subcutaneously three times a week for six months. IFN + lamivudine therapy began to be used in patients who were unresponsive to IFN treatment.

Among 27 HBsAg (+) subjects in this study, interferon treatment was given to 11 subjects who developed chronic hepatitis. One case was excluded from the study due to detection of herpes type 1 encephalitis.

At the end of six months of follow-up, complete response was obtained in three (30%) patients and partial response in four (40%) patients, whereas no response was detected in three (30%) patients.

Fifty percent of the cases experienced serological response, 70% biochemical response, and all (100%) had histological response. In three patients who started concomitant IFN + lamivudine therapy, HBV-DNA became negative in the second month of treatment.

The authors conclude that interferon alfa-2b plus lamivudine can be used safely and effectively for the treatment of chronic hepatitis B infection in children.

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## **Noninvasive Index to Predict Fibrosis and Cirrhosis in Hepatitis C**

A simple index using readily available laboratory results can identify chronic hepatitis C patients with significant fibrosis and cirrhosis with a high degree of accuracy, finds a team of investigators in the August issue of *Hepatology* (*Hepatology* 2003; 38: 518-26).

Information on the stage of liver fibrosis is essential in managing chronic hepatitis C (CHC) patients.

However, most models for predicting liver fibrosis are complicated and separate formulas are needed to predict significant fibrosis and cirrhosis.

In this study, investigators from the United States designed a simple model, consisting of routine laboratory data, to predict both significant fibrosis and cirrhosis in patients with CHC. Cirrhosis could be predicted in 81%.

They evaluated 200 consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period.

The researchers divided the patients into 2 sequential cohorts, a training set of 192 patients and a validation set of 78 patients.

The team found that the best model for predicting both significant fibrosis and cirrhosis in the training set of patients included platelets, aspartate aminotransferase (AST), and alkaline phosphatase. They developed a novel index (AST to platelet ratio index (APRI)) to amplify the opposing effects of liver fibrosis on AST and platelet count.

The physicians determined that the area under receiver operating curves (AUC) of APRI for predicting significant fibrosis and cirrhosis were 0.80 and 0.89, respectively, in the training set.

When they used optimized cut-off values, significant fibrosis could be predicted accurately in 51% of patients, and cirrhosis could be predicted in 81%.

The team found that the AUC of APRI for predicting significant fibrosis and cirrhosis in the validation set were 0.88 and 0.94, respectively.

Dr Chun-Tao Wai's team concluded, "A simple index using readily available laboratory results can identify CHC patients with significant fibrosis and cirrhosis with a high degree of accuracy".

“Application of this index may decrease the need for staging liver biopsy specimens among CHC patients”.

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July 31st, 2003

## **Japanese Delicacy Shown to Raise Hepatitis Risk**

Eating the meat of Sika deer, a Japanese delicacy, can increase the risk of infection with hepatitis E, doctors said on Friday.

The infection, which is caused by the hepatitis E virus (HEV), is rare in developed countries. It usually affects young adults but is not normally life-threatening.

In a letter to The Lancet medical journal, scientists from the Toshiba General Hospital in Tokyo said they traced the infection of four members of two Japanese families to Sika deer.

“Our patients became infected with HEV by eating the raw meat of an infected deer,” Dr Shunji Mishiro said.

“We know of no report that has described the presence of HEV RNA or antibodies in deer, whereas many have described its presence in swine, cow, goats and rodents,” he added.

The doctors tested frozen portions of the left-over deer meat and found traces of the virus that were identical to those in the patients.

“We suggest Sika deer and consumption of its raw meat be added to the list of food with a risk of transmitting HEV,” Mishiro said.

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## **Outcome of Liver Transplantation for Patients Infected by Hepatitis C**

by gastrohep.com

More severe fibrosis and rapid fibrosis progression occurs following transplantation in patients infected with hepatitis C virus genotype 4, determine researchers in the August issue of Liver Transplantation (Liver Transpl 2003; 9: 796-804).

The predictors of post-transplantation hepatitis C virus (HCV)-related liver disease remain unclear.

In addition, the impact of HCV genotype on the outcome of transplantation has not been established.

In this study, a team of physicians from Birmingham, England, examined the outcome of liver transplantation in patients with infected with HCV genotype 4.

The team assessed 128 patients who underwent transplantation for HCV infection. Of these, 28 patients were infected with genotype 1, 11 with genotype 2, 19 with genotype 3, and 32 with genotype 4.

The team determined that the median interval from transplantation to biopsy was 1.92 years.

5-year survival rates were similar for the different genotypes.

They found that 26% of HCV genotype 4 patients developed either severe fibrosis or cirrhosis, compared with 7% of patients with other genotypes.

Furthermore, a greater fibrosis progression rate was observed in patients with genotype 4.

Univariate and multivariate analysis found that rapid liver fibrosis was associated with the presence of HCV genotype 4 infection.

Donor and recipient age, and graft warm ischemic time also were associated with the rate of fibrosis progression.

The investigators established that the 5-year cumulative rate for the development of cirrhosis or severe fibrosis was 84% in genotype 4 patients, and 24% in other genotypes.

In addition, the 5-year survival rates for patients with genotypes 1, 2 and 3, and 4 were 72%, 80%, and 79%, respectively.

Dr Mohamed Wali's team concluded, "5-year survival for patients who underwent transplantation for HCV genotype-4 infection was similar to that of genotype non-4 patients".

"However, more severe fibrosis and rapid fibrosis progression was observed after transplantation in patients with genotype-4 infection".

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August 01, 2003

## **Guidelines for the Screening and Follow-up of Infants Born to Anti-HCV Positive Mothers**

by [hivandhepatitis.com](http://hivandhepatitis.com)

Hepatitis C virus infection in infancy largely depends on vertical transmission. The transfer of hepatitis C virus from mother to child is almost invariably restricted to children whose mother is viremic, and the rate of transmission seems to be influenced

by maternal virus load, although, in the single patient, the levels of viremia cannot be used as predictors of pediatric infection.

In fact, the flow chart for screening children at risk for vertically transmitted hepatitis C virus infection takes into account maternal viremia. In children born to anti-hepatitis C virus antibody positive, hepatitis C virus-RNA negative mothers, alanine aminotransferase and anti-hepatitis C virus should be investigated at 18-24 months of life.

If alanine aminotransferase values are normal and anti-hepatitis C virus is undetectable, follow-up should be interrupted. In children born to hepatitis C virus-RNA positive mothers, alanine aminotransferase and hepatitis C virus RNA should be investigated at 3 months of age:

- (1) Hepatitis C virus-RNA positive children should be considered infected if viremia is confirmed by a second assay performed within the 12th month;
- (2) Hepatitis C virus-RNA negative children with abnormal alanine aminotransferase should be tested again for viremia at 6-12 months, and for anti-hepatitis C virus at 18 months;
- (3) Hepatitis C virus-RNA negative children with normal alanine aminotransferase should be tested for anti-hepatitis C virus and alanine aminotransferase at 18-24 months, and should be considered non-infected if alanine aminotransferase is normal and anti-hepatitis C virus undetectable;
- (4) Anti-hepatitis C virus seropositivity beyond the 18th month in a never-viremic child with normal alanine aminotransferase is likely consistent with past hepatitis C virus infection.

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## **Hepatitis C Drug for Children**

The U.S. Food and Drug Administration has approved the Schering-Plough drug Rebetol for treating the hepatitis C virus in children, the manufacturer says.

Used in combination with a type of interferon called Intron A, Rebetol is the only approved pediatric hepatitis C therapy, the company says.

The FDA granted Rebetol its so-called “orphan-drug” designation for rarely diagnosed conditions, since the virus is believed to affect fewer than 200,000 children in the United States.

By contrast, some 4 million American adults have been diagnosed with the infection, and 70 percent are expected to develop chronic liver disease. The virus contributes to the deaths of as many as 10,000 Americans annually—a number that could triple by the year 2010, according to Centers for Disease Control and Prevention statistics cited by the drug maker.

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## **ICN Pharmaceuticals Resolves Arbitration with Schering-Plough on Indigent Royalty Payments - Company Expects No Material Current or Future Financial Benefit**

ICN Pharmaceuticals, Inc. announced that it received a decision in its arbitration case between ICN and its 80-percent owned subsidiary, Ribapharm Inc. (NYSE: RNA) and Schering-Plough Corporation. The arbitration dispute was related to royalties on ribavirin sales that were part of Schering's indigent care program.

In the ruling, the arbitrator said that ICN and Ribapharm were entitled to receive past royalties for sales of ribavirin under the Schering indigent care program prior to 2002. In addition, the arbitrator ruled that neither ICN nor Ribapharm would be entitled to receive future royalty payments under the Schering indigent care program as currently structured. The amount awarded is approximately equal to the receivable ICN and Ribapharm have recorded for such payments. Thus, ICN expects that the royalty will have little impact on its or Ribapharm's financial results or condition.

ICN is an innovative, research-based global pharmaceutical company that manufactures, markets and distributes a broad range of prescription and non-prescription pharmaceuticals under the ICN brand name. Its research and new product development focuses on innovative treatments for dermatology, infectious diseases and cancer.

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## **Use of Hepatitis B Core Antibody-positive Liver Donors in Recipients without Evidence of Hepatitis B Infection: A Survey of Current Practice in the US**

by [hivandhepatitis.com](http://hivandhepatitis.com)

Because of the current organ shortage, some liver transplant programs have begun to accept marginal organs that previously would have been rejected. An example is the use of donors with evidence of past hepatitis B virus (HBV) infection.

To gain insight into the use of hepatitis B core antibody-positive (anti-HBc(+)) donor livers in recipients without evidence of HBV infection, Drs. Burton and Shaw-Stiffel conducted a survey of current practice in the US.

Surveys consisting of 12 multiple-choice questions were sent to all 110 liver transplant programs across the United States in mid-2001, and 56 of 110 surveys (51%) could be evaluated.

Overall, 32 of 56 programs (57%) indicated they would transplant an anti-HBc(+) liver into a recipient without serological evidence of HBV infection. Of those who would accept an anti-HBc(+) liver, 16 of 27 respondents (59%) indicated knowledge of HBV DNA status would change their protocol.

Forty-six (46) percent of these respondents would decrease prophylaxis if HBV DNA was negative, 27% would increase prophylaxis if HBV DNA was positive, and 27% would not accept the liver if HBV DNA was positive.

Conversely, 9 of 28 respondents (32%) who would not accept an anti-HBc(+) liver stated that knowing HBV DNA status would change their protocol in that they might consider accepting livers if HBV DNA was negative.

The authors conclude “As of mid-2001, of transplant medical directors in the United States who responded to our survey, 57% would accept an anti-HBc(+) donor liver for an HBV-naive recipient. Treatment protocols for using these organs varied. Knowledge about HBV DNA status of the donor and/or liver would greatly influence prophylaxis for those accepting anti-HBc(+) donor livers.”

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## **Role of Hepatitis B Immunoglobulin in Infants Born to Hepatitis B “e” Antigen-negative Carrier Mothers in Taiwan**

by [hivandhepatitis.com](http://hivandhepatitis.com)

Department of Pediatrics, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University and Hospital, Tainan, Taiwan.

The effectiveness of hepatitis B immunoglobulin (HBIG) in infants of hepatitis B e antigen (HBeAg)-negative hepatitis B surface antigen (HBsAg) carrier mothers in Taiwan is not clear.

The aim of the current study was to describe the responses of infants born to HBeAg-negative carrier mothers receiving HBIG combined with hepatitis B vaccine.

Term babies born to HBeAg-negative carrier mothers were assigned based on chart number to 1 of the 2 treatment groups:

Group A infants (n = 94) received 0.5 ml (145 IU) of HBIG within 24 h of birth and 3 subsequent doses of recombinant hepatitis B virus (HBV) vaccine at 3 to 5 days, 1 month and 6 months of age.

Group B infants (n = 122) received 3 doses of vaccines only.

Infants (n = 19) born to HBeAg-positive carrier mothers were treated like those in Group A and are referred to as Group C.

Sera obtained from infants at 2 and 7 months of age were tested for hepatitis B virus (HBV) markers.

There were 2 (1%; one in Group A and one in Group B) subclinical breakthrough hepatitis B infections among studied infants. One (5%) child of Group C had asymptomatic HBV infection at the age of 7 months and became a chronic carrier. The rate of protective anti-hepatitis B surface antibody (anti-HBs) titers achieved (>10 mIU/ml) by 2 months of age was significantly higher in Group A than that in Group B (98% vs. 57%,  $P < 0.001$ ). However, it was not different by 7 months of age.

Infants (Group A) immunized with HBIG and vaccine had a significantly higher geometric mean titer (GMT, milli-International Units/ml) of anti-HBs than those (Group B) with vaccines only at 2 months of age ( $P < 0.001$ ).

Conversely at 7 months of age, the GMT of anti-HBs was significantly higher in infants who received vaccine only ( $P = 0.001$ ).

The authors conclude, "A protective level of antibodies was achieved earlier in those infants receiving both passive and active immunizations. However, infants receiving active immunizations alone achieved a higher GMT at 7 months of age. There was no clear benefit of passive-active vs. active immunization alone for chronic HBV infection in infants of HBsAg-positive, HBeAg-negative mothers."

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August 08, 2003

## **Hepatitis C Virus and HIV Coinfection in Spain**

by [hivandhepatitis.com](http://hivandhepatitis.com)

In this cross-sectional study conducted by the Hospital General in Castellon, Spain, researchers compared the characteristics of patients with or without hepatitis C coinfection and assessed the possible association of hepatitis C virus coinfection with socioeconomic, HIV-related, and hepatitis B-related variables.

The study population was drawn from a cohort comprised of HIV-infected patients of fifteen tertiary level institutions in Spain.

A total of 4709 patients were studied. Median age was 37 years, 78.3% were male. HIV risk behaviors were: parenteral drug use in 63.8% of patients, heterosexual in 22.3%, and homosexual in 10.8%.

Serology of hepatitis C was positive in 69.2% of participants. The following variables were associated with increased prevalence of hepatitis C coinfection, both in univariate and in multivariate analysis: HIV risk behavior, positive anti-HBs, longer time elapsed since HIV infection diagnosis, younger age, lower social status, lower CD4 cell count increase between nadir and last available result, and lower educational level (all  $P < 0.001$ ).

Patients with heterosexual behavior were more frequently coinfecting than patients with homosexual behavior ( $P < 0.001$ ).

The authors note "This study highlights that, in Spain, more than two thirds of patients with HIV infection are coinfecting with hepatitis C virus."

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August 11th, 2003

## **Progression of Fibrosis in Hepatitis C Is Most Influenced by Age, Date of Infection, Alcohol Consumption, and Genotype**

by hivandhepatitis.com

The objective of this study was to assess the influence of age and date of acquisition of hepatitis C virus (HCV) infection on the distribution of genotypes and the progression of fibrosis in HCV-infected patients who were born in Spain and had their habitual place of residence in this country.

Genotypic analysis was performed in 375 patients in whom it was possible to establish the year of HCV infection because the mode of transmission was known (transfusion, injection drug use, blood donor, or epidemic outbreak).

In 298 patients with liver biopsy, fibrosis stage was related to age at infection, duration of infection, alcohol consumption, and HCV genotype.

HCV subtype 1b was almost exclusively detected among transfusion recipients, but the onset of intravenous drug addiction was associated with the introduction of HCV genotypes other than 1b among injecting users with subsequent spread to other exposure risk groups.

Fibrosis progression was influenced by alcohol consumption, increased duration of infection, and older age at infection.

The authors conclude, "Spread of intravenous drug use determined HCV infection by genotypes other than 1b. The risk of fibrosis progression was influenced more by age at viral acquisition and alcohol consumption than by the infecting genotype."

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## **Retreatment with Daily High Dose Interferon Alfa plus Ribavirin Produces Significantly Higher SVR Rates Among HCV Genotype 1 Non Responders than in Genotype Non-1 Patients**

by hivandhepatitis.com

A randomized trial was conducted to assess the efficacy of daily (QD) or thrice weekly (TIW) administration of interferon-alfa (IFN) in high doses in combination with ribavirin (1.0-1.2 g/day) in patients with chronic hepatitis C (CHC) who were nonresponders to previous IFN monotherapy.

Interferon was administered as 10 MU IFN (QD or TIW) for 4 weeks, followed by 5 MU IFN (QD or TIW) for 20 weeks, and then by 3 MU IFN (QD or TIW) for 24 weeks.

Sustained virological response (SVR) was evaluated in 142 patients who received at least one dose of medication. One-fourth of the patients achieved SVR, 26% of those treated with IFN QD and 25% of those treated with IFN TIW (P = 0.85).

For genotype 1 patients, SVR rates were 32.4 and 15.8% for IFN QD and IFN TIW, respectively, whereas for genotype non-1 patients the corresponding SVR rates were 20.6 and 36.4%, respectively (test of homogeneity:  $P = 0.031$ ).

This finding was further confirmed by multivariate logistic regression analysis where a statistically significant interaction ( $P = 0.012$ ) was found between treatment and HCV genotype indicating that the IFN QD regimen was superior to IFN TIW among genotype 1 patients whereas, among genotype non-1 patients, the two treatments were similar.

In conclusion, re-treatment of patients not responding to previous IFN monotherapy with a combination of high daily dose of IFN with ribavirin may be beneficial for genotype 1 infected patients.

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## **Artists to Play for Escovedo in Gotham Trilogy**

by Barry A. Jeckell

NEW YORK (Billboard) - Levon Helm, Ian Hunter, Lenny Kaye, Mary Lee's Corvette and Garland Jeffreys are among the artists who will perform at a trio of New York benefit concerts for singer/songwriter Alejandro Escovedo, who is recovering from the effects of Hepatitis C, and is not expected to perform again until spring 2004.

The first With These Bands event will be held Sept. 2 at Brooklyn, N.Y.'s Southpaw, and will feature Mary Lee's Corvette, the Roscoe Trio with Eric Ambel, Paige Wood, Stephen Clair, Milton and Mary McBride.

The next night, Manhattan's Mercury Lounge will host Hunter, the Last Hombres with Helm, Los Lonely Boys, Cindy Bullens, Willie Nile and the Worry Dolls and Tammy Faye Starlite. The final show, Sept. 4 at the Knitting Factory, also in Manhattan, will boast Jeffreys and Kaye, along with Ivan Julian, Jon Langford with Ship and Pilot, Chip Taylor and Carrie Rodriguez and the Star Spangles.

Similar events have been staged or are being planned in Austin, Texas; Chicago; San Diego; Seattle; Raleigh/Durham, N.C.; and Toronto.

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## **Hemispherx Biopharma Enters into Agreement with the Johann Wolfgang Goethe University, Institute of Virology. Independent US Scientific Panel Recommends Further Evaluation of Ampligen(R) for SARS**

Hemispherx Biopharma, Inc. (AMEX: HEB) announced today that it has entered into a Research Project Agreement with the Institute for Medical Virology, Johann

Wolfgang Goethe University Hospital, Frankfurt am Main, Germany ([www.klinik.uni-frankfurt.de](http://www.klinik.uni-frankfurt.de)). The Institute is one of the largest molecular biological centers for virus diagnostic in the world with emphasis on research in SARS, HIV/AIDS, Hepatitis, Chlamydia infections and cancer therapy and has requested the Company to use its lead compounds for research.

#### Parameters of Collaboration

The Research Project will consist of work conducted utilizing the experimental Phase 3 immunotherapeutic Ampligen(R) and Alferon(R), a natural high purity alpha interferon approved by the FDA and various non-US regulatory authorities for the treatment of genital HPV, Condylomata Acuminata. The studies will evaluate the antiviral activity of Ampligen(R) and Alferon(R) alone and in combination against the SARS virus. Recently, the Institute has evaluated the antiviral effect of the three other interferon types against SARS coronavirus in vero cells. Research will also be conducted in the field of anti-cancer therapy with Alferon(R). In recent studies, the Institute for Medical Virology showed that interferon-alpha in combination with Valproic yield strong synergistic effects against human neuroectodermal (brain) tumors. Furthermore, different studies will compare the effects of Ampligen in anti-tumor assays.

#### NIH Panel Formally Recommends Further Ampligen/SARS Testing

The Company also received a report of the National Institutes of Health (NIH), dated July 18, 2003, concerning therapeutic Ampligen activity against Human Coronavirus OC-43. In the report, an independent panel of virology experts recommended to NIH further antiviral testing of the experimental agent Ampligen against the SARS virus.

#### About SARS and Seasonal Outbreaks of Infection

In the last several months, Severe Acute Respiratory Syndrome (SARS) has impacted thousands of people worldwide, especially in China and Hong Kong. Although the epidemic seems to be under control, several organizations are still searching for a potential treatment in the event of a future outbreak. SARS, being a different class of coronavirus infection is very likely to be a seasonal virus. Coronavirus infection accounts for approximately 30 % of all common colds in humans. Most colds occur during the fall and winter seasons. Beginning early September, the incidence of common colds typically escalates and remains high until late spring. This period is known as the "cold season" and is believed to be the result of a broad range of causes.

#### About Hemispherx

Hemispherx Biopharma, based in Philadelphia, is a biopharmaceutical company engaged in the manufacture and clinical development of new drug entities for treatment of viral and immune-based chronic disorders. Its flagship products include Alferon and the experimental immunotherapeutics/antivirals Ampligen and Oragens. These novel proteins, approved for a category of STD infection, and experimental nucleic acids are being developed for globally important chronic viral diseases and disorders of the immune system including HPV, HIV, CFS, Hepatitis and SARS. Its platform technology includes large and small agent components for potential treatment of various chronic viral infections. Hemispherx has approximately 400 patents comprising its core intellectual property estate, a fully commercialized product (Alferon N) and GMP certified manufacturing facilities for its novel pharma products. For more information please visit [www.hemispherx.net](http://www.hemispherx.net)

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## **Interferon Alfa Combined with Ketoprofen in Treatment-naive HCV Patients Is Significantly More Effective Than Interferon Alfa Monotherapy**

by [hivandhepatitis.com](http://hivandhepatitis.com)

In this randomized controlled study, researchers evaluated the efficacy and safety of interferon alfa-2a (Roferon) combined with ketoprofen to that of interferon alfa alone in naive patients with chronic hepatitis C.

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) that is primarily used to treat pain, tenderness, inflammation (swelling), and stiffness caused by arthritis. It also is used to relieve pain associated with other conditions including muscle and menstrual pain and pain after surgery, dental work, or childbirth.

In this randomized, controlled trial, 40 patients received interferon alfa-2a (3 million units three times a week) and ketoprofen (150 mg twice a day) and 40 received only interferon alfa-2a at the same dose. Patients were treated for 6 months and followed up for 6 months.

Response was defined by undetectable HCV-RNA in serum at the end-of-treatment and after 6 months from the completion of therapy (long term response). At the end of treatment, the response was similar in the two groups.

However, combination treatment showed significantly higher efficacy than monotherapy in achieving long-term response (10% vs 32.5%;  $P = 0.014$ ). Overall adverse events were similar in the two groups. 'Flu-like syndrome was significantly less common in the ketoprofen plus interferon group which experienced a significantly higher incidence of epigastric pain'.

Our results indicate that the combination of ketoprofen plus interferon is significantly more effective than interferon alone in the treatment of naive patients with chronic hepatitis C and is well tolerated.

However this combined treatment appears to be less effective than the association of pegylated IFN and ribavirin, which represent the current standard treatment. Thus, the role of ketoprofen in the treatment of chronic hepatitis C needs to be further evaluated against this new standard of care.

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## **Hepatitis B Severity May Be Based on a Clotting Protein, Claim Scientists**

by John C. Martin, [Hepatitisneighborhood.com](http://Hepatitisneighborhood.com)

How severe your hepatitis B may become may depend on the action of a protein in your body. It's been discovered by a group of Canadian scientists who claim the molecule, known by its scientific name Fgl2/fibroleukin prothrombinase (fye-broh-LEW-kin pro-THOMB-in-aze), causes blood to clot in livers infected by hepatitis.(1) In trials with animals, the same protein causes blood to clot in the livers of mice exposed to the corona virus; a mutant form is believed to be responsible for the infamous SARS infection that has spread around the world.(2)

Blood or fibrin clots are the clumps that form when blood coagulates, and may partially or fully block a blood vessel. This deprives the tissue of normal blood flow and oxygen, resulting in tissue damage or death.

#### A Protein's Role in Hepatitis Severity

Scientists at the University of Toronto found that the clotting protein molecule fgl2 plays a key role in chronic hepatitis. It also raises the question, they point out, of whether the same protein molecule has some purpose in the spread of SARS.

"This offers new hope to patients by paving the way for future therapies that will change the course of hepatitis," said Philip Marsden, M.D., a professor of medicine at the University of Toronto and a nephrology specialist at St. Michael's Hospital, who took part in the study. "Our work represents an innovative new approach to combating viral disease."

"Therapies to date have focused on getting rid of the virus, but this work points the way to blocking the damage the virus does," Marsden said.

#### Hepatitis B Prevalence

Chronic hepatitis B affects approximately 1.25 million Americans, of whom 20 to 30 percent acquired the infection in childhood. Symptoms range from jaundice and fatigue to loss of appetite and joint pain.(2)

#### Eliciting a Clotting Effect

The study was done originally in the lab of Gary Levy, M.D., who is also a professor of medicine at the University of Toronto. Levy's team isolated the protein molecule from the livers of corona virus-infected mice, and found that it has unique and novel-clotting aspects.

More specifically, the protein is expressed by immune cells only triggered by the presence of the corona virus. Once it is produced, it causes a clot at the site of the acute viral infection, whether it be the liver or some other organ, the researchers reported.

This same protein is reportedly triggered by the hepatitis B virus, creating liver damage. Interestingly, Marsden, Levy and the rest of their team found the protein is produced only in patients with "marked chronic" hepatitis B, defined as disease that includes evidence of advanced liver damage, as opposed to those with "minimal chronic" HBV.

"These studies confirm previous studies in mice of the importance of fgl2, or the clotting protein, in viral disease," explained Levy, who is also director of the Multi-Organ Transplant Program at Toronto General Hospital. "Antibodies are now being

generated to neutralize fgl2 activity, which we hope will be useful in treating patients with viral hepatitis, and may be of value to patients with SARS.”

Levy and his colleagues are currently examining SARS patients to determine if the fgl2 protein is present, and whether neutralizing antibodies can be designed to treat them.

#### Hunting for a Clotting Protein

To confirm the presence of the clotting protein in mice, the researchers first removed the gene that produces it from the rodents. The animals were then infected with the corona virus, and compared to corona virus-infected mice that did have the gene.

They found that only the mice that carried the gene became ill, and ultimately succumbed to the infection four to seven days after being infected. Subsequent blood tests showed evidence of liver inflammation and cell death.

Mice without the gene failed to generate blood clots, and 40 percent of them were still alive two weeks after being infected.

#### Fgl2 in Severe Hepatitis B.

In addition to rodent tests, the scientists performed liver biopsies on 23 patients with severe hepatitis B, and 13 people with minimal chronic hepatitis. They were searching for a possible link between severe HBV infection and the presence of the clotting protein.

They found that, indeed, patients with severe chronic HBV had the fgl2 protein in their livers, and it was directly involved with blood clots that resulted in liver cell death. By contrast, patients with mild chronic hepatitis B had no evidence of the protein or blood clots in their livers.

Based on their discovery, the Canadian researchers hope that the clotting protein can become a logical target for developing newer treatment options for people with chronic hepatitis.

They say it's the first time that blocking a clotting protein has been thought of as a possible treatment option for HBV. Typically, treatments are designed to either kill the virus, or block it from replicating; that is, making copies of itself.

“Our results provide compelling evidence for a role of the Fgl2/fibroleukin prothrombinase in viral hepatitis,” the team of researchers wrote. “Collectively, these data argue that the Fgl2/fibroleukin prothrombinase is a logical target for molecular manipulation, and offers the hope for the development of new treatment approaches for patients with fulminant and marked chronic viral hepatitis.”

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## **High Rate of Long-term Virological Response After a 1 Year Course of Interferon and Ribavirin in Chronic Hepatitis C Relapsers**

by gastrohep.com

One-year retreatment of chronic hepatitis C relapsers with the combination of interferon and ribavirin led to a sustained virological response in 61% of patients, according to research published in the August issue of *Liver International* (*Liver International* 2003; 23: 255-61).

Chronic hepatitis C is often responsive to therapy with interferon alone. However, relapse after interferon monotherapy is common.

For those who relapse after interferon treatment, the benefit of another course of interferon has been evaluated by a number of studies, though its efficacy remains unclear.

In 1996 Dr Eveline Boucher and colleagues initiated a study comparing the efficacy and the safety of a 12-month retreatment with interferon alone to treatment with interferon plus ribavirin in patients with chronic hepatitis C relapse.

191 relapsers were randomized to receive 3 million units three times a week of interferon alpha with or without 1-1.2g/day ribavirin.

Sustained virological response was seen in 61% of patients taking interferon and ribavirin and only 8% of patients receiving interferon alone.

The results of the study were published in the August issue of *Liver International*.

A sustained virological response to treatment was seen in 61% of patients who received combined interferon and ribavirin. Only 8% of patients who received interferon alone had a sustained virological response.

A significant histological improvement was observed in both treatment groups.

The Metavir activity score became significantly lower in patients treated with interferon plus ribavirin compared to those receiving interferon alone.

Dr Boucher concludes "The therapeutic schedule of interferon combined with ribavirin can be considered of considerable interest for the treatment of chronic hepatitis C relapsers."

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## **Husband's Liver Donation a Success**

by Associated Press

Teddy Mocibob gave up smoking and drinking, then he did a little gambling. He surrendered 60 percent of his liver to his wife, Elena, despite doctors' warnings of the possible risks to his health and even his life—and having to cast aside his longtime vices.

“THEY SAID WE were a 100 percent match and I said ‘Set up the date and let’s go,’” Mocibob recalled Friday. “I love her. If I had to do it again next week, I would do it.”

There won't be any need for that, since doctors have declared the July 29 procedure a success.

“The surgery went extremely well and they’re doing extremely well,” said Dr. Patricia Sheiner, Westchester Medical Center’s director of liver transplants. “There’s no evidence of any rejection.”

In three months, she said, the transplanted piece of liver that Elena Mocibob received will regenerate to 90 percent of normal size.

Elena, 43, who suffered from a liver disease, would have lived only a few years without a transplant, doctors said.

Before her husband could be a donor, he had to be in good enough health to withstand the surgery and recovery. That meant a cold turkey approach to alcohol and tobacco, habits he picked up in his native Croatia.

Teddy Mocibob, 50, who speaks with a heavy accent, said he knew he could give it all up for her.

Sheiner said it was clear that Teddy Mocibob was willing to do anything for his wife, but that wasn't enough.

“We have to make sure they know the risks,” she said.

Potential donors undergo significant screening for more than just physical readiness. Criteria such as how they will handle the emotional and psychological impact of the procedure, and basics like whether they can afford to be out of work for months and if children depend on them also are evaluated.

The intensive screening process was put in place statewide after the death last year of a donor who gave part of his liver to his brother at a New York City hospital.

The Mocibobs have been married less than four years and their four children, all teenage or older, are from previous marriages.

Mocibob, who now has a large Y-shaped scar on his chest, walked slowly into a news conference and sat gingerly. He was released from the hospital August 4.

“I don't think I'll go back to smoking,” Mocibob said. “Drinking, I might have a beer or two.”

His wife, her skin still slightly yellow, was in a wheelchair and hooked up to an intravenous tube. She will leave the hospital on Monday.

She said she was most looking forward to holding her granddaughter. “Before, I wasn’t able to do anything with them,” she said of her grandkids, ages 5 and 2.

Her daughter, Helen Curtin, said she was deeply grateful to her stepfather. Her children “have never seen my mother healthy,” she said.

More than 90 percent of all liver transplants are done from cadavers. Of live donations, there’s only about one case a year nationwide involving husband and wife.

Elena said she worried about accepting her husband’s gift, but said she joked that a main concern was waking up with an accent like his.

In the end, though, Teddy’s decision didn’t surprise her. “We’re husband and wife,” she said. “We’re one.”

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## **Report from the 2nd IAS Conference on Pathogenesis and Treatment**

by Sean R. Hosein

The average HIV positive person who uses highly active antiretroviral therapy (HAART) usually has increased CD4+ cell counts as a result. But the size of this increase may be affected by several factors, including the ability to take medications as prescribed and directed -adherence. Now researchers in Vancouver, British Columbia, have found that co-infection with hepatitis C virus (HCV) may somehow weaken the immune system’s ability to rebuild itself despite the use of HAART.

Paula Braitstein and colleagues at the B.C. Centre for Excellence in HIV/AIDS studied the effect of HCV on CD4+ cell count changes among HAART users by reviewing records in the centre’s database, collected between August 1996 and July 2000. Information was analysed on 1,416 people with HIV/AIDS (PHAs) who had never previously taken HAART but began to do so during the study period. The research team also found results of blood tests for antibodies against HCV in a subset of 552 subjects as follows:

- 235 people who were positive for HIV and HCV
- 317 people who were positive for HIV only

A factor the researchers took into account when later analysing the data was adherence. The research team assessed adherence in an indirect way. They checked pharmacy databases to determine whether subjects had their prescriptions filled on a regular basis. According to previous studies, the ability to fill prescriptions on a regular basis is linked to a high degree of adherence.

Before starting therapy, the profile of the 235 PHAs who were also HCV positive was as follows:

22% female, 78% male  
average age 37 years  
average CD4+ cell count 290 cells  
average viral load more than 100,000 copies  
10% had symptoms of AIDS  
43% were judged to be more than 95% adherent  
Results -HIV positive only

Among subjects positive only for HIV and whom researchers judged to be at least 95% adherent, the average increase in the CD4+ cell count after the first 1= years of treatment was 230 extra cells. Among subjects who were less than 95% adherent, the increase was 190 extra cells.

#### Results - Positive for HIV and HCV

Among co-infected subjects, results of treatment were not as promising. After 1= years of treatment, in the group whose adherence was at least 95% there was an increase of 120 extra CD4+ cells. In subjects whose adherence was less than 95%, there was an increase of only 50 extra cells.

According to the research team, these results show that after adjusting for adherence, HCV has a powerful effect on the ability of HAART to affect the immune system. It is not clear why HCV infection might have this effect. One possibility is that HCV affects the liver's ability to properly process drugs (such as protease inhibitors and non-nukes), and so levels of these drugs in the blood are not as high as they should be. But this theory needs to be tested and confirmed. The fact that the response to HAART was worse in co-infected people raises questions about the timing for initiating HIV therapy in this population. Perhaps HAART would be more effective in HCV co-infected people if taken earlier in the course of HIV disease, when their CD4+ counts are higher? Again, this is another idea that requires further study.

Overall, the Vancouver study confirms results by research teams in the European Union and lays the foundation for future studies in the area of HIV/HCV co-infection.

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August 12th, 2003

## **Schering-Plough Business Won't Fund Costs**

Schering-Plough Corp. on Tuesday said income from operations would not cover its expenses for the rest of the year, which analysts said could lead the drug maker to cut or eliminate its dividend.

The company, which made a similar statement in May, said it could cover its expenses with its investments, debt and \$3.63 billion in cash.

However, some analysts said the company is likely to cut the dividend, which costs it \$250 million per quarter, to help preserve cash for strategic moves such as acquiring or developing new drugs.

“It is my belief that the company does not have the cash flow to a sufficient level to pay a dividend and make important investments in new products,” said Richard Lawrence, an analyst at Parker Hunter Inc.

Shares of Schering-Plough slipped to \$15.90 in pre-market trading on Instinet from a close at \$16.25 on Monday.

The company, under federal investigation for its manufacturing and marketing practices, has seen sales of its allergy drug Claritin nearly evaporate after the expiration of its patent last year. The expiration prompted Schering-Plough to move the drug to over-the-counter status.

Also, sales of its other lucrative franchise, its line of hepatitis C drugs, is suffering in the face of competition from Roche Holding AG (ROCZg.VX).

Schering-Plough’s second-quarter earnings dropped 71 percent from a year earlier to just \$182 million.

The company hired Fred Hassan, a turnaround specialist from Pharmacia Corp., as its new chief executive in April.

In a Securities and Exchange Commission filing addressing investor questions and concerns, the company said its ongoing business might not be enough to fund many of its expenses.

“For the remainder of 2003 and possibly beyond, cash provided by operating activities will not be sufficient to fund working capital, capital expenditures and dividends if these items remain at levels comparable to that in the first and second quarters,” it said.

In May, the company made the same statement, referring to the level of first-quarter spending.

Schering-Plough said on Tuesday it believes cash on hand, short-term investments, committed lines of credit and access to capital markets would be sufficient to meet its financial requirements.

Schering-Plough, based in Kenilworth, New Jersey, has said it is evaluating all of its financial expenditures, including its quarterly dividend of 17 cents per share.

An additional drain on Schering-Plough’s reserves has been a \$500 million fine, or consent decree, levied by the U.S. government last year in connection with shoddy manufacturing practices at four plants in New Jersey and Puerto Rico.

The company said on July 7 that earnings for the second half of 2003 could be lower than earnings for the first half, which were 24 cents per share. (Additional reporting by Toni Clarke.)

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## **Schering-Plough Warns on Cash**

by Jed Seltzer and Toni Clarke

NEW YORK (Reuters) - Schering-Plough Corp. said on Tuesday cash from operations would not cover major expenses for the rest of the year, and analysts said the drugmaker might cut or eliminate its dividend.

The company, which faces federal investigations into its manufacturing and marketing practices, made a similar statement in May. Its shares fell as much as 4 percent on Tuesday before recovering.

It reiterated that while cash from operations would not cover the costs of working capital, capital expenditures and its dividend, these costs could be covered by investments, debt and \$3.63 billion in cash.

However, some analysts said Schering-Plough was likely to cut the dividend, which costs it \$250 million per quarter, to help preserve cash for strategic moves, such as acquiring or developing new drugs.

“It is my belief that the company does not have the cash flow to a sufficient level to pay a dividend and make important investments in new products,” said Richard Lawrence, an analyst at Parker Hunter Inc.

With Schering-Plough’s stock down about 70 percent over the past 2.5 years, the dividend has become expensive. The annual yield for stockholders is now among the top 10 percent of companies in the Standard & Poor’s 500 index.

The company has seen sales of its allergy drug Claritin nearly evaporate after the expiration of its patent last year. The expiration prompted Schering-Plough to move the drug to over-the-counter status.

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Schering-Plough’s second-quarter earnings dropped 71 percent from a year earlier to just \$182 million.

The company hired Fred Hassan, a turnaround specialist from Pharmacia Corp., as its new chief executive in April. Hassan promptly withdrew the company’s previous earnings outlook and has since said that second-half earnings may fall well short of analysts’ expectations.

In a Securities and Exchange Commission filing addressing investor questions and concerns, the company said its ongoing business might not be enough to fund many of its expenses.

“For the remainder of 2003 and possibly beyond, cash provided by operating activities will not be sufficient to fund working capital, capital expenditures and dividends if these items remain at levels comparable to that in the first and second quarters,” it said.

Schering-Plough said on Tuesday it believes cash on hand, short-term investments, committed lines of credit and access to capital markets would be sufficient to meet its financial requirements.

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“They are most at risk within the pharmaceuticals group of cutting their dividend,” said analyst Jason Fox of H&R Block Advisors. “If you need to conserve cash, one of the surest ways of alleviating a cash crisis is to do something about this dividend you have to pay out every quarter.”

An additional drain on Schering-Plough’s reserves has been a \$500 million fine, or consent decree, levied by the U.S. government last year in connection with shoddy manufacturing practices at four plants in New Jersey and Puerto Rico.

Schering-Plough shares fell 15 cents, or 0.92 percent, to close at \$16.10 on the New York Stock Exchange. The stock reached a six-year low of \$15.22 in March.

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## **Liver Function Tests**

[KidsHealth.org](http://KidsHealth.org)

Liver function tests(LFTs) measure liver injury, rather than liver function. They are a group of blood tests that measure substances in the blood that reflect whether the liver has been injured and the extent of the injuries. Sometimes these tests are also called a liver panel. The tests usually include the following: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, total protein, and total and direct bilirubin.

The liver is a complex organ, located in the upper right corner of the abdomen, which has many vital roles. The liver stores fuel for the body that has been produced from sugars, and it is involved in the processing of fats and proteins. Bile produced by the liver is involved in the digestion and absorption of fat in the intestines. The liver also makes proteins that are essential for blood clotting, and it helps remove poisons and toxins from the body.

When a blood sample is collected from a child to measure LFTs, the skin is cleaned with alcohol first, then a needle is inserted into a vein and blood is drawn into specific tubes. These blood samples are then sent to a laboratory and processed by machines. The tests are done simultaneously, which takes about 20 minutes. Emergency test results are reported within an hour. For routine tests processed at the site of collection,

results are usually available within 3 to 6 hours. If samples are shipped to a central processing facility, they are usually available the next day.

#### The Liver Function Tests

##### Alanine Transaminase (ALT)

Alanine transaminase is an enzyme that is important in the processing of proteins. This enzyme is found in large amounts in the liver, and small amounts of this enzyme are also found in the heart, muscle, and kidney. When the liver is injured or inflamed, the levels of ALT in blood usually rise; therefore, this test is done to check for signs of liver disease. The ALT is elevated, for example, in some viral infections of childhood that may affect the liver, such as mononucleosis.

##### Aspartate Transaminase (AST)

Aspartate transaminase is an enzyme that plays a role in many aspects of body metabolism. This enzyme is found in many body tissues including the heart, muscle, kidney, brain, and lung. It is also present in the liver. If there is cell injury or death in any of these tissues, AST is released into the bloodstream; therefore, elevated AST levels can be seen in a variety of conditions, including liver disease. For example, the AST may be elevated in viral hepatitis, mononucleosis, or following a heart attack.

##### Alkaline Phosphatase (ALP)

Alkaline phosphatase is an enzyme found in the liver and bone. Blood levels of the enzyme are elevated in some types of liver disease. Children - especially teens - normally have higher blood levels of ALP than adults. This is related to rapid growth of their bones. Compared to the transaminases, alkaline phosphatase tends to be higher in diseases associated with injury to the bile-secreting part of the liver's activity.

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## **Schering-Plough Warns, Dividend Cut Ahead?**

by Jed Seltzer and Toni Clarke

NEW YORK (Reuters) - Schering-Plough Corp. said on Tuesday cash from operations would not cover major expenses for the rest of the year, and analysts said the drugmaker might cut or eliminate its dividend.

The company, which faces federal investigations into its manufacturing and marketing practices, made a similar statement in May. Its shares were down 4 percent.

It reiterated that while cash from operations would not cover the costs of working capital, capital expenditures and its dividend, these costs could be taken care of through investments, debt and \$3.63 billion in cash.

However, some analysts said Schering-Plough was likely to cut the dividend, which costs it \$250 million per quarter, to help preserve cash for strategic moves, such as acquiring or developing new drugs.

“It is my belief that the company does not have the cash flow to a sufficient level to pay a dividend and make important investments in new products,” said Richard Lawrence, an analyst at Parker Hunter Inc.

The company has seen sales of its allergy drug Claritin nearly evaporate after the expiration of its patent last year. The expiration prompted Schering-Plough to move the drug to over-the-counter status.

Also, sales of its other lucrative franchise, its line of hepatitis C drugs, is suffering in the face of competition from Roche Holding AG (ROCHg.VX).

Schering-Plough’s second-quarter earnings dropped 71 percent from a year earlier to just \$182 million.

The company hired Fred Hassan, a turnaround specialist from Pharmacia Corp., as its new chief executive in April.

In a Securities and Exchange Commission filing addressing investor questions and concerns, the company said its ongoing business might not be enough to fund many of its expenses.

“For the remainder of 2003 and possibly beyond, cash provided by operating activities will not be sufficient to fund working capital, capital expenditures and dividends if these items remain at levels comparable to that in the first and second quarters,” it said.

In May, the company made the same statement, referring to the level of first-quarter spending.

Schering-Plough said on Tuesday it believes cash on hand, short-term investments, committed lines of credit and access to capital markets would be sufficient to meet its financial requirements.

Schering-Plough, based in Kenilworth, New Jersey, has said it is evaluating all of its financial expenditures, including its quarterly dividend of 17 cents per share.

“They are most at risk within the pharmaceuticals group of cutting their dividend,” said analyst Jason Fox of H&R Block Advisors. “If you need to conserve cash, one of the surest ways of alleviating a cash crisis is to do something about this dividend you have to pay out every quarter.”

An additional drain on Schering-Plough’s reserves has been a \$500 million fine, or consent decree, levied by the U.S. government last year in connection with shoddy manufacturing practices at four plants in New Jersey and Puerto Rico.

The company said on July 7 that earnings for the second half of 2003 could be lower than earnings for the first half, which were 24 cents per share.

Schering-Plough shares were down 65 cents at \$15.60 in late-morning trade on the New York Stock Exchange. The stock reached a six-year low of \$15.22 in March.

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## **Schering-Plough May Borrow to Meet 2nd-Half Cash Needs**

Schering-Plough Corp. warned that it expects to borrow money to meet domestic cash-flow needs for working capital, capital expenditures and dividends for the second half of the year if those items remain at levels seen in the first half.

In a filing with the Securities and Exchange Commission on Tuesday, Schering said foreign operations are expected to provide enough cash to fund foreign capital needs and foreign capital expenditures.

Schering management doesn't expect to use funds held by foreign subsidiaries to fund U.S. cash flow needs; however, it said it retains the option of drawing on those funds if circumstances change.

Schering said cash flow was sufficient in the first quarter because collection of accounts receivable offset the decline in sales of prescription Claritin, its former blockbuster allergy drug that now faces generic and nonprescription competition. Claritin sales have plummeted since it became an over-the-counter medication last year.

But in the second quarter, cash flow from operations was offset by a second payment of \$250 million to settle allegations of widespread manufacturing deficiencies at four plants with the Food and Drug Administration.

"As a result, the company funded all its cash needs for capital expenditures and dividends through short-term borrowings," the SEC filing said.

Schering-Plough spokesman William O'Donnell told Dow Jones Newswires that the information in Tuesday's filing was a reiteration of a matter that had been discussed in previous company reports.

He said after the first quarter, the company put together a similar FAQ, or frequently asked questions list. "We're just updating that FAQ for the second quarter," he said.

With Schering-Plough quickly running out of cash, the company's dividend of 68 cents a share may be the first thing to go.

Independent analyst Hemant Shah said "it's mind boggling that the dividend hasn't been cut yet." Wall Street is expecting the company to earn only 46 cents a share this year, so it would be paying all that and more back to shareholders with that dividend.

Next year, Schering-Plough is expected to earn only 59 cents a share. A healthy company should only be paying out a dividend worth 50% of its annualized earnings per share, Mr. Shah says.

He expects the company to slash the dividend by more than half. “No pharmaceutical company has ever cut its dividend that sharply,” Mr. Shah said. “ But no pharmaceutical company has gone through what Schering-Plough is going through.”

Sales of the company’s allergy franchise are spiraling after losing patent protection on Claritin. Roche Holding AG’s Pegasys is eating up market share of its now top-selling PEG-Intron franchise of hepatitis C drugs.

And then there’s the U.S. government. The Food and Drug Administration still has the company’s manufacturing processes under a microscope, and the company recently had to shell out millions as part of a consent decree. Schering-Plough also faces criminal indictment in a probe by federal prosecutors who suspect the drug company of giving kickbacks to doctors in return for prescribing its drugs.

In addition, the federal government is investigating whether the company’s former chief executive broke Securities and Exchange Commission fair-disclosure rules.

This article was compiled from reports by the Associated Press and Hollister H. Hovey and Tony Cooke of Dow Jones Newswires.

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## **Doctor Held Over ‘Infecting Patients with Hepatitis C’**

Israeli police are holding a doctor suspected of infecting dozens of patients with hepatitis by injecting them with the same needle he used to take drugs.

The doctor was fired from the Soroka Hospital in the southern city of Beersheba four months ago for using drugs and is infected with the hepatitis C virus.

He is suspected of using the same syringes to inject himself and to anaesthetise patients, exposing them to the disease.

“Police have launched an investigation and the suspect has been taken into custody for questioning,” police spokesman Itai Dotan said.

According to a statement from the hospital, the case was discovered last week after six patients were found to be carrying the virus. The hospital then examined their medical records, which revealed that all had undergone surgery with the same anaesthetist.

The doctor, who was not identified, participated in 989 operations during the 22 months he worked at the hospital.

Hospital director Eitan Hai-Am told Army Radio that letters had been sent to all 989 patients inviting them to come for blood tests for the virus. He estimated that dozens could be infected.

“One of the possibilities is that before an operation he would draw some of the anaesthetic, inject himself with some and then inject the patient with the rest,” Hai-Am told the radio.

Hepatitis C is a viral infection of the liver. The virus causes no symptoms in most cases and the majority of carriers do not know they are infected.

However, the virus can eventually lead to cirrhosis or liver cancer. It can take as long as 20 years for hepatitis C to cause liver failure, and those infected rarely show symptoms.

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August 13th, 2003

## **Retreatment with Interferon and Ribavirin Versus Interferon Alone in Interferon Responder-Relapser HCV Patients**

by hivandhepatitis.com

Low pretreatment viral load has consistently been shown to be an independent predictor of sustained response (SR) in patients with chronic hepatitis C infection.

In this prospective, multicentre, randomized, controlled study researchers assessed the efficacy of interferon (IFN) plus ribavirin vs IFN alone in low viremic patients (<2 millions copies/mL) who had relapsed to a previous course of IFN and the efficacy of 24 vs 48 week combination therapy in high viremic patients.

Two hundred and ninety-seven patients were randomly assigned to one of the four regimens after stratification on pretreatment viral load. All patients received IFN-alfa-2b [Intron A] (6 million units thrice weekly for 24 weeks and 3 million units thrice weekly for 24 weeks).

Patients with low viremia received either IFN alfa-2b alone for 48 weeks (R1: 42 patients) or IFN alfa-2b plus ribavirin (600 mg/day) for 24 weeks and IFN alfa-2b alone for the next 24 weeks (R2: 48 patients).

Patients with high viral load received either IFN alfa-2b plus ribavirin for 24 weeks and then IFN alfa-2b alone for the next 24 weeks (R3: 104 patients) or IFN alfa-2b plus ribavirin for 48 weeks (R4: 103 patients).

In low viremic patients the rate of SR was 37.7% in group R1 and 59.6% in group R2 ( $P < 0.05$ ). In high viremic patients, the rate of SR was 44.7% in group R3 and 51.4% in group R4 ( $P$ : NS).

Thirty-one patients discontinued treatment (10.4%) without difference regarding treatment regimen. In the regimen using ribavirin we found no difference in terms of SR between patients receiving a dose of ribavirin below 10.6 mg/kg/day (55%) or over 10.6 mg/kg/day (58%).

Histological improvement occurred in 70.2% of patients regardless of the regimen. Logistic regression showed that genotype 2 and 3, Knodell score <6 and alanine aminotransferase pretreatment level >3 upper limit of normal were significantly and independently correlated with SR.

The authors conclude, “In low viremic patients who relapsed to a previous IFN treatment, combination therapy using high-dose IFN and low-dose ribavirin is better than high-dose IFN alone.”

“In high viremic patients there was no benefit in increasing the duration of combination therapy from 24 to 48 weeks. In this study, it was found that low dose of ribavirin can be used safely and there is no effect of ribavirin dose on SR.”

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## **Japanese Red Cross to Revise Donor System After Tainted Blood Scare**

The Japanese Red Cross Society told the health ministry it would store blood plasma for longer after a ministry probe revealed thousands of units of tainted blood had likely been used, a report said.

The plan was submitted Wednesday following a ministry probe into suspected hepatitis B infections which found 6,419 units of possibly contaminated blood products had been shipped from since June 2002 through July 2003.

The ministry found the Red Cross was not recalling the blood of people who donated multiple times before testing positive for communicable viruses, even though earlier contributions could have fallen in the early “window period” where the virus can escape detection.

The Red Cross said it would store frozen blood plasma for two months before use starting next year, increasing the period to six months two years later, Jiji Press news agency said.

If a donor tested positive for HIV, hepatitis or other viruses, the longer storage period would increase the chance that previously donated blood products could be recalled before being used.

The society would also study overseas blood donor systems and consider reducing from 50 the number of blood samples it tests at one time, a technique blamed for causing false negative results, the report said.