

## Hepatitis C Caring Ambassadors Program Newsletter

January 2007



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### IN THE NEWS

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#### **Two U.K. Scientists Develop Cheaper Drug To Treat Hepatitis C**

<http://www.allheadlinenews.com/articles/7006024612>

Following trials by two U.K. scientists, the treatment for hepatitis C is likely to get cheaper as early as this year in India and other developing countries. The trials for a new drug called PEGylated-interferon alpha molecule is undertaken by Dr. Sunil Shaunak, professor of infectious diseases at Imperial College based at Hammersmith hospital, with scientists from the London School of Pharmacy.

The doctors have teamed up with an Indian company to manufacture a drug to treat hepatitis C. The Indian government is reportedly sponsoring clinical trials in the country. The process creates a new medicine which is no longer under patent to a multinational drug company and can be made and sold cheaply.

According to Hindustan Times, the new technology has made it possible for the doctors to open up the interferon protein, drop in a sugar molecule called PEG and close the protein. The PEGylated-interferon retains its shape and cures hepatitis C infection in many patients.

The British government believes that the joint efforts of Shaunak and his colleague Steve Brocchini from the London School of Pharmacy will reportedly reduce the cost of NHS in U.K. The drug would reportedly be manufactured by Hyderabad-based Shantha Biotech will in India, says the newspaper. [truncated]

#### **Pakistani Doctor to be Honoured for Research on Hepatitis C Treatment and Its Outcomes**

[http://www.app.com.pk/en/index.php?option=com\\_content&task=view&id=1398&Itemid=2](http://www.app.com.pk/en/index.php?option=com_content&task=view&id=1398&Itemid=2)

Saima Firdoos, a young Pakistani doctor of Shifa International Hospital will be honoured for a clinical research about Hepatitis C treatment and its outcomes in the form of five scientific papers to be presented in Kyoto, Japan on March 27-30, 2007 in Asia Pacific Association Study of Liver Diseases. The research papers were conducted by Dr.Saima Firdoos, under the guidance of a renowned Gastroenterologist/ Hepatologist and Professor of Medicine Shifa International Hospital Dr.Muzaffar Lateef Gill.

The titles of the papers are: Outcome of PEG-interferon alfa2b/Ribavirin in HEPC G3 Younger VS Old patients, Treatment outcomes of Chronic hepatitis C with Genotype 3 Patients with Pegays Vs Pegintron plus Ribavirin, Treatment outcomes of Hepatitis C Genotype 3 patients with reduced dose of Pegintron and Ribavirin, Long term outcomes of treatment of Hepatitis C Genotype 3 patients with thrice weekly standard Interferon and Ribavirin and Efficiency of Peg -Interferon Alfa 2a/Ribavirin for HEPC Genotype 3 Relapsers with standard interferon/Ribavirin.

#### **Caregiving: Lawford Says Get Tested**

<http://www.upi.com/ConsumerHealthDaily/view.php?StoryID=20061228-124229-7388r>

Actor and author Christopher Kennedy Lawford wants people to know -- especially his fellow baby boomers -- that they may be at risk for hepatitis C virus, or HCV, even if they've only had a few snorts of cocaine. "If you fall in any of the major risk factors -- illegal drug use, blood transfusion(s) before 1992, 10 or more sexual partners, dialysis or have had a tattoo -- you should get tested for hepatitis C because you are not going to know by the way you feel," Lawford told UPI's Caregiving.

"There are a lot of people who didn't think they did anything particularly risky who are at risk for hepatitis C -- you share a dollar bill to snort a line of cocaine or get a tattoo -- but there are some 4 million people estimated with hepatitis C and 70 percent don't know it."

Lawford, perhaps best-known as having played the character Charlie Brent on the ABC-TV soap opera "All My Children" in the early 1990s and as the nephew of President John F. Kennedy, was diagnosed with hepatitis C in 2001. He details the long list of illegal drugs he took from age 13 to 30 in his book "Symptoms of Withdrawal: A Memoir of Snapshots and Redemption," now out in paperback. He was treated and is healthy today. He calls himself one of the lucky ones. It is estimated that most chronic HCV infections are contracted through transfusion of unscreened blood or via injected drug use, according to the CDC.

"You hear about hepatitis C and you think Pamela Anderson and it's one of those rock 'n' roll diseases and that it can't happen to you," Lawford said. But HCV is the most common chronic infectious disease in Europe and North America, affecting an estimated 170 million people worldwide. It is transmitted by blood-to-blood contact, according to the Centers for Disease Control and Prevention in Atlanta.

However, studies have shown that the use of needles and syringes is not the only drug-related risk factor for HCV. A study in New York City, published in 2001 in the journal *Substance Use & Misuse*, found a higher-than-expected prevalence of hepatitis C infection among non-injecting drug users. In one study, 17 percent of the subjects who denied a history of injection drug use were found to be infected with HCV compared to a 2-percent infection rate in the general population. Among women from one of the study sites in East Harlem who reported use of non-injection heroin, the rate of infection was as high as 26 percent.

"If hepatitis C can be transmitted through the sharing of non-injecting drug paraphernalia such as straws or pipes, we need to include this information in public health messages targeted to this population," said Dr. Alan I. Leshner, director of the National Institute on Drug Abuse.

In another study in 2001, published in the *American Journal of Public Health*, researchers at the University of California at San Francisco found low-income women between the ages of 18 and 29 in San Francisco were infected with HCV at a level almost 2.5 times higher than the HCV infection rate for the general population in the United States.

"San Francisco had the highest HCV infection level, 4.3 percent -- nationally the level is 1.8 percent. Injection drug use is the strongest risk factor, but we were surprised to find that co-infection with herpes simplex virus type-2, or HSV-2, was also significantly associated with hepatitis C infection," said lead author Kimberly A. Page-Shafer. "This suggests that infection with HSV-2 may be a co-factor for sexual transmission of hepatitis C."

One of the problems of treating hepatitis C is that the infection can be dormant for decades and people may not realize that something they did in their 20s can make them sick when they are in their 50s. "Hepatitis C can stay dormant in your blood and liver before you develop any symptoms. I was tested for hepatitis C in 2001, but that might have been 15 or 20 years after I had contracted the illness," Lawford said. "It's my intention to make people aware that a simple \$40 blood test is a lot better than a having to get a liver transplant. This is a life-threatening disease, but there is a cure. "But you must be tested -- people have to be proactive and ask for the test. I would be dead if I had not been tested."

### **Racial Differences Seen in Steatosis in Patients with Hepatitis C**

[http://www.eurekalert.org/pub\\_releases/2007-01/jws-rds010207.php](http://www.eurekalert.org/pub_releases/2007-01/jws-rds010207.php)

Caucasian patients with chronic hepatitis C virus (HCV) are more likely to have hepatic steatosis, or fat in the liver, compared to African-American patients. However, steatosis is not associated with HCV treatment response. These findings are published in the January 2007 issue of *Hepatology*, the official journal of the American Association for the Study of Liver Diseases (AASLD).

Hepatic steatosis is common among patients with HCV and often indicates more advanced disease. Researchers, led by Hari Conjeevaram, M.D., M.S. Division of Gastroenterology at the University of Michigan at Ann Arbor, sought to investigate racial differences in the prevalence and severity of hepatic steatosis in patients with HCV, genotype 1. Additionally, they investigated the relationship between steatosis and body characteristics and other

measures of insulin resistance. "We also wanted to assess whether the presence and severity of hepatic steatosis and/or insulin resistance were important factors to predict virological response in this population," the authors write.

The researchers studied 194 African-American and 205 Caucasian patients with HCV, genotype 1. All patients were participating in a multi-center prospective study of peginterferon and ribavirin therapy. The researchers compared the prevalence and severity of steatosis and steatohepatitis to demographic, lifestyle and clinical characteristics. They also investigated relationships between sustained virological response and both steatosis and insulin resistance.

The researchers found hepatic steatosis in 61 percent of the African-American patients and 65 percent of Caucasian patients. In a univariable analysis, the steatosis was associated with HOMA-IR (a measure of insulin resistance), body mass index, waist circumference, serum triglycerides, aminotransferase levels, and histological scores for inflammation and fibrosis. After adjusting for those features, they found that African-Americans had a dramatically lower risk of steatosis. For a given degree of overweight and obesity or insulin resistance, African-Americans were approximately half as likely to have hepatic steatosis. After examining patient characteristics and their responsiveness to treatment, the authors report, "insulin resistance and fibrosis are important and obesity and steatosis may be less or not as important." The results may have been confounded by patients taking oral anti-diabetic agents, and by the possibility that HOMA underestimated the degree of insulin resistance in overtly diabetic patients.

Still, "the importance of these findings is that insulin resistance is a potentially modifiable factor, so that responses to antiviral therapy in hepatitis C may be improved by modulation of insulin signaling and improvements in insulin resistance and glucose control. These possibilities deserve prospective evaluation," they conclude.

### **Hep C Advocate Continued Fight**

<http://www.northernlife.ca/News/LocalNews/2006/12-29-06-HepC.asp?NLStory=12-29-06-HepC>

The year 2006 is almost gone, and Ernie Zivny is still waiting for the federal government to give him the money that would make his life much easier. He was a happy man July 25 when the government announced it would provide compensation for people who contracted Hepatitis C through tainted blood before 1986 and after 1990.

But more than five months later, none of the 5,500 people who have been earmarked to receive compensation received any money. Prime Minister Stephen Harper promised the victims would have their cheques by the end of this year or the beginning of next year, said Zivny. Zivny has been the face of "the forgotten victims" of Hepatitis C in Greater Sudbury for the past few years. He's dealt with his fate by joining the Circle C Support Group and fighting to receive compensation. The group provides support for all Hepatitis C victims in the Greater Sudbury area, regardless of how they contracted the disease.

In June, Zivny visited Ottawa along with seven other Sudburians. He asked federal health minister Tony Clement to wear a ribbon in support of Hepatitis C victims, but the politician refused. "It made us feel un-Canadian," Zivny said. Receiving compensation from the government won't make up for suffering from cirrhosis of the liver, an enlarged liver and spleen, diabetes, arthritis, pain and fatigue brought on by Hepatitis C, he said. But he's looking forward to what the money can do for him and his wife, Lynda. Perhaps they won't have to clip coupons and shop at discount stores anymore, he said.

### **Awareness and Testing For Hepatitis C Are Increasing, UK**

<http://www.medicalnewstoday.com/medicalnews.php?newsid=59344>

A new report from the Health Protection Agency shows that the number of people newly diagnosed with hepatitis C has increased; from 2,116 in 1996, to 7,580 in 2005. New figures also show that testing for hepatitis C has increased overall, for example, in GP surgeries, testing has increased by almost 60 per cent between 2002 and 2005.

The latest estimates on the number of adults infected with hepatitis C showed there were around 231,000 in 2003. Many of these infected people do not realise they have the virus as it can take years or even decades for symptoms to appear. Early treatment, however, is effective at clearing the virus in the majority of people. It is therefore

important that individuals at risk are tested by their GP or other health services.

Dr Helen Harris, a Hepatitis C expert from the Agency said “This is the second annual report on Hepatitis C from the Health Protection Agency, summarising current knowledge of the infection and the action being taken to tackle it. Hepatitis C is very under-diagnosed simply because people are unaware that they are carrying it. By increasing awareness of the infection, more people will be tested, will receive earlier and more effective treatment, and they can avoid passing it on to others.”

“We estimate that almost 6 in 10 people with hepatitis C injected drugs at some point in their past. If someone has ever shared equipment for injecting drugs - even if it was a long time ago, and even if they only did it once or twice - they could be at risk from hepatitis C. A simple blood test can establish whether someone has ever been infected with the virus”

Professor Pete Borriello, Director of the Agency's Centre for Infections said, “Testing for hepatitis C has increased significantly, however there is still much work to be done as a significant number of individuals remain undiagnosed. If you don't know you've got it, you can't do anything about it. Health services should consider this as they formulate strategies to increase testing.”

The report highlights the Department of Health's hepatitis C awareness campaign, FaCe It, which has now reached over 16 million people. The exhibition campaign visits cities across England and features large photographic portraits of people living with Hepatitis C. Hepatitis C in England - An Update 2006 is published by the Health Protection Agency and contributors....

... Between 70-80% of adults with hepatitis C become chronically infected. The preliminary estimates for 2003 suggest that 0.53% of the 15-59 year age group in England and Wales were chronically infected. Although prevalence estimates in older individuals are less secure, as the major risk factor for hepatitis C is injecting drug use, we expect the prevalence in older individuals to be lower than in the 15-59 year old population. Similarly, the prevalence in children under 15 years is expected to be very low.

Sentinel surveillance suggests that testing in GP surgeries has increased by almost 60% because 8584 individuals were tested in nine sentinel laboratories in 2005 compared to 5382 individuals being tested in the same laboratories in 2002. Laboratory confirmed diagnoses for hepatitis C rose from 6341 in 2003 to 7580 in 2005. This indicates that the rate of diagnoses has risen and therefore that more diagnostic testing is taking place. [truncated]

### **Clinical Trials on for Low-Cost Hepatitis C Drug**

[http://www.hindustantimes.com/news/181\\_1887046,00050003.htm](http://www.hindustantimes.com/news/181_1887046,00050003.htm)

Treatment for hepatitis C is likely to get cheaper in the near future, with clinical trials for a new drug — called PEGylated-interferon alpha molecule — beginning in India in 2007. The new affordable drug has been developed by Dr Sunil Shaunak, professor of infectious diseases at Imperial College based at Hammersmith hospital, with scientists from Imperial College and the London School of Pharmacy.

Calling their efforts “ethical pharmaceuticals, a revolutionary new model,” Shaunak said he and his colleagues have developed a cost-effective technology that allows them open up the interferon protein, drop in a sugar molecule called PEG and close the protein. The PEGylated-interferon retains its shape and cures hepatitis C infection in many of the 170 million people affected with the disease worldwide. The new method of pegylation does not infringe existing patents because it tweaks the molecular structure of an existing drug no longer under a 20-year patent to turn it into a new medicine that can be sold much cheaper.

The efforts of Shaunak and his colleague Steve Brocchini from the London School of Pharmacy will reduce the cost of treating hepatitis C to a fraction of the current cost. It will help millions in poor countries get a cure for hepatitis C, which is a leading cause of chronic liver disease and cancer. Hyderabad-based Shantha Biotech will manufacture the drug in India. “I have been greatly inspired by Shantha Biotech founder Varaprasad Reddy, whom I met about four years ago. The company has a record of manufacturing affordable health products. If clinical trials co-sponsored by the Indian government are successful, the new drug can be supplied the world over at an affordable price,” says Shaunak.

The new molecule, a report in the journal Nature said, appeared to be as effective as the existing drug used to treat Hepatitis C. "The aim of this work is to make affordable cures for infectious diseases for the poor people by doing most of the work in universities and hospitals using funds from charitable institutions and hospitals,"

### **Doctors Have Communicated Hepatitis C Virus to 88 Patients**

<http://english.sabah.com.tr/E9DE2425AEBC4D5E91622FA963BCA70C.html>

[Turkey] It was revealed that 88 patients were communicated with Hepatitis C virus in a private dialysis center in Diyarbakir. Center's chief physician Uğur Yüce has put up the argument that one of the four newly established dialysis centers has sabotaged their hospital. It was revealed that 88 out of 213 patients suffering from kidney failure have caught Hepatitis C virus. Center's chief physician Uğur Yüce said they are suspecting from a sabotage.

City Health Directorate has begun an investigation about the issue. Dr. Uğur Yüce said: There are four new dialysis centers opened in Diyarbakır and they have transferred our patients. We suspect that there is a sabotage. According to our data, the disease was communicated to the patients during the last two months.

### **Hepatitis Tests 'Like Witch Hunt'**

[http://news.bbc.co.uk/2/hi/uk\\_news/wales/6215780.stm](http://news.bbc.co.uk/2/hi/uk_news/wales/6215780.stm)

A former member of the General Dental Council has likened the handling of the case of a dentist from Gwynedd infected with hepatitis C to a "witch hunt". The health authorities wrote to 5,000 patients offering them various tests after the man was diagnosed with the disease, which over 1,000 accepted.

Brian Lux, president of the Dental Practitioners Association, questioned whether all the tests were necessary. The National Public Health Service said decisions were carefully considered. The dentist, who is not being named, reported he was infected with hepatitis C in October 2005. Many past and present patients took tests, including ones for hepatitis B and HIV, although no evidence was found to link any infection to the man.

Mr Lux, who has been advising the dentist, said it was not necessary to screen for HIV and hepatitis B as well, and questioned whether the screening was necessary at all. "Are you telling me you are not so strapped for cash you can waste - and I do say waste - this money on a useless exercise which denigrated a dentist, which put him under terrific pressure where he nearly had a nervous breakdown, all for what? "For nothing. We said at the outset you wouldn't find anything and you didn't. "What were you trying to prove at the public expense? I think we need some answers." Mr Lux, who likened the case to a "witch hunt", said it would have been fine to do a "lookback exercise" to check for hepatitis C.

However, he added: "There was no rhyme or reason to include hepatitis B and certainly it was an insult to the integrity of the dentist concerned to suggest by innuendo that he had HIV by saying, well have a test for HIV as well." Special clinics were run around Gwynedd to cope with all the screening. The National Public Health Service said the exercise had not been completed yet and every decision had been carefully considered. It added contacting patients was the only way to clarify whether people were at risk. Hepatitis C leads to swelling or inflammation of the liver. [truncated]

### **No HIV, Hepatitis for Tested Students**

[http://www.insidebayarea.com/argus/localnews/ci\\_4824058](http://www.insidebayarea.com/argus/localnews/ci_4824058)

Students who shared needles during a science experiment last month at John F. Kennedy Middle School all tested negative for signs of HIV and hepatitis B and C, according to the San Mateo County Health Department. A substitute teacher was fired Nov. 17 after he pricked students in Life Science classes with lancets during a science experiment. The teacher, whose name was not released by the district, was doing an experiment with his classes to look at students' blood cells under a microscope.

When he drew blood from each student, he did not use a fresh lancet for of them. On Nov. 21, the health department tested 29 students for HIV and hepatitis B and C. Based on this initial screening, health officials concluded no health risks are associated with the incident in the science class.

As part of the testing guidelines for HIV and hepatitis B and C, the health department will arrange to test the students again in May. Health department officials have said it is rare for children this age to contract these diseases. In the last 151/2 years, the county has seen seven cases of hepatitis B in children ages 12 to 14. There is less than one case of hepatitis C reported to the county each year, and most are adults. And in the last 26 years, 12 cases of HIV in children under 14 have been reported to the county.

### **Enanta Enters Agreement with Abbott**

<http://boston.bizjournals.com/boston/stories/2006/12/11/daily20.html>

The terms of the deal call for Watertown, Mass.-based Enanta to receive an upfront \$57 million payment including cash and an equity investment. Illinois-based Abbott agrees to pay up to \$250 million in additional payments assuming clinical and regulatory payments are met. In turn, Enanta will receive royalty payments and agrees to fund a portion of development and commercialization costs in exchange for a profit share of U.S. sales of any product developed from the collaboration.

The companies will work together to develop treatments for hepatitis C based on a kind of protease inhibitors. Enanta sees Abbott as being a vital partner for this based on its work in developing protease inhibitors to treat HIV.

Full financial benefits of the collaboration may be years away. The company's compounds included in the deal are in the preclinical stage.

### **Intercell Gains on Completion of Hep C Trial, Pelias Acquisition**

<http://www.forbes.com/markets/feeds/afx/2006/12/12/afx3246760.html>

Shares in Austrian pharma group Intercell AG continued their upward march gaining 1.43 pct to 17.75 eur by the early afternoon, after the company today reported the completion of a Phase II trial for its therapeutic Hepatitis C vaccine. 'We are well on track with the development of our therapeutic vaccine. It was key to demonstrate that IC41 can be safely administered together with standard therapy, thus enabling the way to potential future combination therapies', said chief scientific officer Alexander von Gabain in a statement.

From 16.99 eur last Wednesday, shares in Intercell have consistently performed stronger on the day after the Vienna-based company announced it will acquire fellow pharma firm Pelias in the first quarter next year. It will buy the pharma company, which specialises in vaccinations against hospital infections, via a 350,000 share capital increase. By 1.45 pm a total of 140,584 Intercell shares had changed hands on the ATX, which stood at 4304.85, 0.20 pct firmer.

### **An All-Around Education - LCCC Monthly Lectures Focus on the Health and Wellness of Students**

<http://www.timesleader.com/mld/timesleader/living/16219415.htm>

As a counselor at Luzerne County Community College, Maryann Kovalewski hears firsthand the health and wellness challenges facing students. In some cases, the problems are easily remedied. In other instances, they are far more complicated. To help break down the more complex problems, Kovalewski created an ongoing wellness program designed to benefit students and the local community. The program, now in its second year, has tackled everything from managing holiday stress to hepatitis, its most recent topic.

"It's whatever's going to be best for (the students)," said Kovalewski, estimating several dozen people attend the monthly talks. "At 18 or 19 you think you're invincible. What we say is you have to start taking care of yourselves now." Although the programs are designed with students in mind, Kovalewski hopes more community members take advantage of the expert discussants. Lecturers range from on-campus specialists to community professionals who volunteer their time. A satellite feed allows the college's Berwick campus to participate in the programs. Other branch campuses are likely to be included next year, she said. Joe Shamonsky, a registered nurse and communicable disease nurse consultant for the northeast district office of the Pennsylvania Department of Health, led the college's most recent lecture, "Hepatitis C: Prevention and Treatment."

Hepatitis, an inflammation of the liver, is commonly broken into categories A, B and C. Although many colleges and universities require hepatitis B vaccines for students, according to the Centers for Disease Control and Prevention, hepatitis C is an issue for anyone who may come in contact with infected blood. This includes, but is not limited to intravenous drug users, individuals with multiple sexual partners, and anyone who may share objects – toothbrushes, needles, razors – that contain blood.

A recent article in The Chronicle of Higher Education reported that 75 percent of undergraduates at a Midwestern university had one or more factors that placed them at risk for contracting hepatitis C. These behaviors include sharing jewelry or drug paraphernalia. Kovalewski looks at issues like this and others and determines their usefulness to the local population. [truncated]

### **Medical Services International Completes Testing of VScan Hepatitis C Test Kit in the United States**

<http://biz.yahoo.com/prnews/061213/nyw055.html?.v=79>

Medical Services International Inc is pleased to announce that it has completed testing of its VScan Hepatitis C test kit in the United States. The test results shows that the VScan Hepatitis C test kit met or exceeded required regulatory standards in the United States. In early 2007, the Company will begin the process to apply for regulatory approval in the United States.

It is reported in published literature that there are over 200 million people that have Hepatitis C and do not know it. Market studies show that there will be a large demand for a rapid test kit for Hepatitis C that can be used in the privacy of your own home. It is expected that once regulatory approval is obtained in the United States the market will exceed 5.0 million kits per year.

### **Feds Complete \$1B Deal for Hep C Victims**

[http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/20061215/hepC\\_victim\\_061213/20061215?hub=Canada](http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/20061215/hepC_victim_061213/20061215?hub=Canada)

[Canada] The federal government has announced completion of a \$1-billion compensation deal for the so-called "forgotten" victims of hepatitis C tainted blood scandal. The deal, announced today by Health Minister Tony Clement, must still be approved by courts in several provinces. The deal will provide one-time payments for thousands of people infected with the hepatitis C virus through tainted blood before 1986 or after 1990.

The victims are called forgotten because they were excluded from a previous federal-provincial compensation package announced in the 1990s. Prime Minister Stephen Harper said in July his government would provide such compensation, and lawyers have been working out details on how the money will be allocated. Harper said then that each of the 5,500 victims who contracted the disease before 1986 or after 1990 is expected to receive between a few thousand dollars to \$300,000.

Up to now, only those victims infected with hepatitis C between 1986 and 1990 were eligible for compensation under a federal-provincial package announced in 1998. The previous government denied liability for pre-1986 victims, claiming there was no test to detect the virus before 1986. But that argument was eventually disproved when it was revealed that effective blood screening tests were available before 1986. The Tories have always taken the position that all victims of the tainted blood scandal should be compensated equally. Mike McCarthy, lead plaintiff in the Ontario class action, praised the government for what he called a fair agreement.

### **Vertex Pharmaceuticals Announced Results of Safety Analysis on Hepatitis C Inhibitor; Stock Was Slightly Down**

<http://www.tradingmarkets.com/.site/news/STOCK%20ALERT/494012/>

Vertex Pharmaceuticals Inc. on Wednesday announced results from a planned interim safety analysis from PROVE 1, which is an ongoing Phase 2b clinical trial of the investigational hepatitis C virus protease inhibitor telaprevir or VX-950. PROVE 1 was a four-arm, double-blind, placebo-controlled Phase 2b clinical trial of telaprevir in treatment-naïve patients with genotype 1 HCV infection. The company said it enrolled 250 patients for the PROVE 1 study, who received Peg-interferon alfa-2a + ribavirin and a dose of telaprevir or placebo. The primary objective of the study was to assess the proportion of patients in each study arm who achieve a sustained viral response, defined as undetectable HCV RNA 24 weeks after the completion of dosing.

According to the company, of the 74 patients in the telaprevir groups for whom data were available at the end of 12 weeks, 65 demonstrated undetectable HCV RNA, compared to 17 of 33 of patients in the control arm. The company reported that adverse events including gastrointestinal disorders and rash were reported in the telaprevir groups. In the telaprevir groups, as of the cut-off date, 9% of patients had discontinued treatment due to adverse events, compared to 3% of patients in the control arm. Serious adverse events were noted in 3% of patients in the telaprevir groups and 1% of patients in the control group.

## **Pevion Biotech Announces Its Hepatitis C Vaccine Enters Clinical Phase I**

<http://www.pharmalive.com/News/index.cfm?articleid=400450&categoryid=21>

BERN, Switzerland, Dec. 18, 2006 – Pevion Biotech announced the start of phase I clinical testing of its virosome-based hepatitis C virus (HCV) vaccine. The therapeutic HCV vaccine is based on Pevion Biotech's proprietary PeviPRO™ and PeviTERT™ technologies and will be tested for its safety and immunogenicity.

Pevion Biotech has designed a therapeutic vaccine to treat patients who suffer from chronic hepatitis C virus infection. The vaccine is based on a combination of the PeviPRO™ and PeviTERT™ platforms using synthetic peptide antigens from the hepatitis C virus. Generally, a cellular immune response by cytotoxic T-lymphocytes (CTL) seems to be crucial in overcoming a hepatitis C virus infection. In-depth research in recent years has shown that the cellular immune response is even more effective when supported by helper T-cells. Pevion Biotech's HCV vaccine candidate utilizes this effect inducing specific CTL responses (PeviTERT™) together with a supportive helper T cell response (PeviPRO™). This virosome-based technological combination in a single product represents a new generation of modular therapeutic vaccines.

The phase I single-blind randomized placebo-controlled dose escalating study will be conducted under the lead of Professor Dr. med. Giuseppe Pantaleo at the Vaccine and Immunotherapy Center at the University Hospital in Lausanne, Switzerland, and comprises 30 healthy volunteers. The primary goal of the study is to examine the safety and tolerability of the synthetic vaccine. Secondary objectives include assessments of the vaccine's immunogenicity.

In the course of the study, each subject will receive multiple injections. During the clinical trial the volunteers will be closely monitored. The study is scheduled for completion by end of 2007. Peter Klein, CEO of Pevion Biotech, comments: "More than half of all HCV-infected patients do not experience significant long-term benefits from the current standard therapy using Interferon in combination with antiviral drugs. However, the very promising therapeutic vaccine approach of Pevion Biotech, which is aiming at a cellular immune-response, aims a new dimension of an effective therapy for patients suffering from chronic hepatitis C."

## **Coinfection with Both HIV and Hepatitis C Virus a Growing Problem**

<http://www.sciencedaily.com/releases/2006/12/061212091756.htm>

Although many individuals infected with the hepatitis C virus (HCV) are naturally able to control levels of the virus with their immune systems, those who also become infected with HIV, the virus that causes AIDS, may lose that ability. In a report in the December issue of PLOS Medicine, a group of researchers from the Partners AIDS Research Center at Massachusetts General Hospital (PARC-MGH) report one of the first studies of how HIV infection impacts immune system functions involved with HCV control. Their findings suggest that beginning antiretroviral therapy earlier than is generally recommended may help preserve HCV control in patients infected with both viruses.

"The global burden on health of chronic viral infections is immense, and HCV and HIV are chief among culprit viruses," says Arthur Kim, MD, of PARC-MGH, co-first author of the PLOS Medicine report. "Due to shared routes of transmission, infection with both viruses is common. Unfortunately, HCV behaves as an opportunistic infection in the presence of HIV and is becoming a leading cause of illness and death in persons with HIV."

In order to examine immune system factors associated with spontaneous control of HCV and how that control is altered by HIV infection, the researchers enrolled four groups of participants: 60 were infected with both viruses, and half of those had low HCV levels upon entering the study. The other two groups of 17 participants were infected with HCV only, with one group successfully controlling viral levels. Spontaneous HCV control is known to rely on the activity of CD4 helper T cells specifically targeted against the virus, and destruction of CD4 cells by HIV underlies the immune deficiency that characterizes AIDS. Therefore the researchers measured participants' T cell response to HCV at the outset of the study and at two- to six-month intervals during the study period.

The results showed that those individuals able to maintain low HCV levels in spite of HIV coinfection had stronger virus-specific responses for both CD4 T cells and the CD8 "killer" T cells than did those with elevated HCV counts. Not surprisingly, participants infected only with HCV had even more powerful antiviral T cell responses. About a quarter of those infected with both viruses who originally controlled HCV levels lost control during the two-and-a half-year study period, and their increased virus levels corresponded with an overall drop in

CD4 T cells. None of the viral controllers who were infected with HCV alone had any increase in viral levels during the study period. Loss of protective responses and susceptibility to recurrent HCV infection may help to explain the higher rates of persistent HCV observed in subjects who are HIV/HCV coinfecting, compared to those with HCV alone.

In analyzing factors that might be associated with the loss of HCV control in those infected with both viruses, the researchers made a surprising discovery. The factor most powerfully associated with maintaining HCV control was not the CD4 T cell count upon entering the study but the lowest previously recorded or 'nadir' CD4 count. That finding suggests that, for individuals infected with both viruses, beginning antiretroviral treatment before CD4 levels drop too low to maintain HCV responses may be desirable.

The researchers also found that, among those whose HCV levels rose, individuals who maintained some T cell responses had lower viral levels than did those with little or no T cell response. This suggests that the immune system retains a level of secondary immunity against HCV -- the kind of 'memory' response against a previously encountered pathogen seen in many infections. "Currently a nationwide trial is recruiting people for a study examining whether earlier treatment of HIV will improve hepatitis C treatment outcomes," Kim says. "Part of this study will investigate how earlier treatment may affect immune responses. It also will be important to follow the impact of loss of HCV control on liver disease, since this will probably have important consequences for patients with HIV." Kim is an instructor in Medicine at Harvard Medical School.

Bruce Walker, MD, director of the Partners AIDS Research Center at MGH and a Howard Hughes Medical Institute (HHMI) investigator is senior author of the PLOS Medicine report, and Julian Schulze zur Wiesch, MD, of PARC-MGH and HHMI is co-first author. The study's co-authors are Thomas Kuntzen, MD, Joerg Timm, Daniel Kaufmann, MD, Jared Duncan, Andrea Jones, Benjamin Davis, MD, Rajesh Gandhi, MD, Gregory Robbins, MD, Todd Allen, PhD, and Georg Lauer, MD, of PARC-MGH, Raymond Chung, MD, MGH Gastroenterology; and Alysse Wurcel, Lemuel Shattuck Hospital, Boston. The study was supported by grants from the National Institutes of Health, the Campbell Foundation, the American Liver Foundation, the German Academic Exchange Service, Doris Duke Charitable Foundation and the Howard Hughes Medical Institute.

### **Hepatitis in China: Liver Let Die?**

<http://www.biotecheast.com/modules.php?op=modload&name=News&file=article&sid=1491&topic=5>

With one third of CHB patients and one quarter of CHC patients globally, hepatitis is a major health problem in China, and the market has received considerable attention from Western pharmaceutical companies aiming to capitalize on the country's recent economic boom. Many Western pharmaceuticals have Chinese approval, but they have a high price and there is some contention over their effectiveness, therefore Chinese patients should consider these drugs a long-term investment and balance the trade-off between cost, efficacy and long-term liver complications.

#### Executive Summary

China is undergoing an economic boom, generating 12% of global economic trade, and it is currently the leading recipient of foreign investment. Since 34% of the world's chronic hepatitis B patients and 24% of the world's chronic hepatitis C patients live in China, the Chinese hepatitis B (HBV) and C (HCV) markets have historically represented a significant growth opportunity, with a realistic current valuation of \$1.0 billion (HBV) and \$0.9 billion (HCV). However, the Chinese healthcare system has been ranked 144th out of 191 by the WHO, prompting it to be denounced as one of the most unfair systems in the world. These problems, together with the inability of many patients to afford these drugs and concerns over their efficacy in Asian patients, are retarding Western pharmaceutical penetration.

Chinese physicians indicated that HBV incidence is decreasing and is set to continue to fall. In contrast to the seven major markets, where most patients acquire HBV sexually, the dominant route of HBV transmission is perinatal transmission, which increases the likelihood of becoming immune tolerant and impacts on HBV disease progression and the effectiveness of drug therapy. In China, physicians do not consider any of the currently available therapies a gold standard, although lamivudine is the most prescribed first-line therapy, while adefovir is the most prescribed second-line therapy.

Chinese physicians indicated that HCV incidence may be increasing. Blood transfusion is thought to be the

dominant HCV transmission route in China, while in the seven major markets, HCV is mainly acquired through intravenous drug use. The Chinese HCV treatment market is highly fragmented, with treatment differing significantly between regions. For example, in Hong Kong, all HCV patients receive pegylated interferon/ribavirin combination therapy, currently considered the global standard of care. However, across mainland China, unmodified interferons are more commonly prescribed than pegylated interferons, and interferon monotherapy is more frequently used than interferon/ribavirin combination therapy.

Due to the high cost of pharmaceuticals and the cost-conscious nature of the Chinese healthcare system, the hepatitis market faces a number of threats, including TCMs, generic drugs and counterfeit drugs.

Similar to the seven major markets, efficacy is the most important factor driving HBV and HCV pharmaceutical prescription in China, with cost and reimbursement in second place. Interestingly, the side-effect profile ranked third in China, while this

### **HGS Initiates First Trial in Hepatitis C Program**

[http://www.pharmaceutical-business-review.com/article\\_news.asp?guid=3FD7C56D-1B47-40CB-B17A-0E3414FEFD8C](http://www.pharmaceutical-business-review.com/article_news.asp?guid=3FD7C56D-1B47-40CB-B17A-0E3414FEFD8C)

The Albuferon phase III development program includes two trials to evaluate the efficacy, safety and impact on health-related quality of life of Albuferon in combination with ribavirin, versus peginterferon alfa-2a in combination with ribavirin. "We believe that Albuferon could become the interferon of choice in treatment regimens for this potentially devastating disease," said Thomas Watkins, president and CEO, HGS.

According to HGS, the current standard of care for hepatitis C patients, pegylated interferon alpha plus ribavirin, has side effects that continue to be a significant treatment-limiting issue. Albuferon requires half as many injections, and clinical results to date suggest the potential for less impairment of health-related quality of life, with efficacy and safety at least comparable to pegylated interferon. "There continues to be a significant need for more effective and better tolerated treatments for chronic hepatitis C," said John McHutchison, professor of Medicine and Director, GI/Hepatology Research, Duke Clinical Research Institute.

Albuferon is being developed by HGS and Novartis under an exclusive worldwide development and commercialization agreement entered into in June 2006. The company plans to make global marketing applications for Albuferon in 2009

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## **CLINICAL TRIALS, COHORT STUDIES, AND PILOT STUDIES**

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### **Hepatitis C and Risk of Lymphoma: Results of the European Multicenter Case-Control Study EPILYMPH**

Nieters A, et al. Gastroenterology. 2006 Dec;131(6):1879-86. Epub 2006 Sep 20.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17087949&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17087949&query_hl=5&itool=pubmed_DocSum)

**BACKGROUND AND AIMS:** Increasing evidence points toward a role of hepatitis C virus (HCV) infection in the etiology of malignant lymphomas. However, previous epidemiologic studies were limited in size to establish an association between HCV infection and specific lymphoma subtypes. We performed a large, multicenter, case-control study to address this question. **METHODS:** The study comprised 5 European countries and included newly diagnosed cases of any lymphoid malignancy recruited between 1998 and 2004. Controls were matched to cases by 5-year age group, sex, and study center. In-person interviews were conducted to collect data on demographic, medical, and family history as well as environmental exposures. Serum samples of 1807 cases and 1788 controls (excluding human immunodeficiency virus-positive and organ-transplantation subjects) were screened for HCV infection using an enzyme immunoassay. Positive as well as randomly selected negative samples were subjected to HCV RNA detection and HCV genotyping. **RESULTS:** HCV infection was detected in 53 (2.9%) lymphoma cases and in 41 (2.3%) control subjects (odds ratio [OR], 1.42; 95% confidence interval [CI]: 0.93-2.15). Restricted to individuals who tested positive for HCV-RNA (indicating persistent infection and active viral replication), the OR was 1.82 (95% CI: 1.13-2.91). In subtype-specific analyses, HCV prevalence was associated with diffuse large B-cell lymphoma (OR, 2.19; 95% CI: 1.23-3.91) but not with chronic lymphocytic leukemia or follicular, Hodgkin's, or T-cell lymphoma. The sample size was not sufficient to derive any conclusions for rare lymphoma entities such as splenic marginal zone lymphoma. **CONCLUSIONS:** These

results support a model that chronic HCV replication contributes to lymphomagenesis and establish a specific role of HCV infection in the pathogenesis of diffuse large B-cell lymphoma.

**Impact of Ribavirin Dose Reductions in Hepatitis C Virus Genotype 1 Patients Completing Peginterferon Alfa-2a/Ribavirin Treatment.** Reddy KR, et al. Clin Gastroenterol Hepatol. 2006 Dec 27; [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17196435&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17196435&query_hl=3&itool=pubmed_DocSum)

**BACKGROUND & AIMS:** To maximize sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) infection, treatment with pegylated interferon and ribavirin has been genotype-specific (1 vs non-1). We evaluated the effects of ribavirin and peginterferon alfa-2a dose reductions on SVR in patients infected with HCV genotype 1. **METHODS:** Data were pooled from 569 patients enrolled in 2 phase III trials of 48 weeks of treatment with peginterferon alfa-2a and ribavirin. All patients were evaluated for the effect of cumulative drug exposure on 4- and 12-week responses, and the 427 patients who completed treatment were evaluated for effect of drug exposure on SVR. **RESULTS:** Of patients who completed treatment, more had reductions ( $\leq 97\%$  cumulative dose) of ribavirin than of peginterferon alfa-2a (43% vs 27%). Neither early virologic response nor SVR was affected adversely by ribavirin reductions when the cumulative ribavirin exposure was greater than 60%. The SVR was reduced significantly ( $P = .0006$ ) in patients with less than the 60% cumulative ribavirin dose and was associated with prolonged periods of dose reduction, temporary interruptions, or premature cessation of ribavirin. Ribavirin dose reductions had minimal impact on SVR in patients who achieved rapid virologic response, defined as undetectable HCV RNA levels after 4 weeks, even when they received less than the 60% cumulative ribavirin dose. In contrast, SVR was reduced markedly in patients who had ribavirin dose reductions and did not achieve rapid virologic response. **CONCLUSIONS:** Minor ribavirin dose reductions to manage adverse events do not appear to affect SVR adversely, unless cumulative exposure is less than 60%. Prospective studies, however, are required to establish the impact of ribavirin dose reduction on SVR.

**Impact of peginterferon alpha-2b and ribavirin treatment on liver tissue in patients with HCV or HCV-HIV co-infection.** Sarmiento-Castro R, et al. J Infect. 2006 Dec 26; [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17194480&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17194480&query_hl=3&itool=pubmed_DocSum)

**OBJECTIVE:** To evaluate the effect of treatment with peginterferon alpha-2b and ribavirin on liver histology in patients with chronic hepatitis C (CHC) with or without HIV infection. **METHODS:** Patients received peginterferon alpha-2b (1.5mu/kg/week during the first 4weeks; 1.0mu/kg/week thereafter) plus ribavirin (800-1200mg/day, adjusted for weight) for 24 (genotypes 2/3) or 48weeks (genotypes 1/4). Paired liver biopsy specimens were obtained at baseline and at the end of follow-up. **RESULTS:** 108 paired biopsy specimens were available: 67 from HCV-monoinfected and 41 from co-infected patients. At the end of follow-up, necroinflammatory activity (NIA) was significantly reduced ( $P < 0.001$ ), and fibrosis scores improved by  $\geq 1$  point (Ishak et al criteria) in 65.7% of HCV-monoinfected patients. In co-infected patients, NIA was significantly reduced ( $P < 0.001$ ), and fibrosis scores improved by  $\geq 1$  point in 42.5% of cases. In both groups, results were better for patients who attained sustained virological response (SVR). HCV RNA was undetectable in the second biopsy specimens of all patients who attained SVR. **CONCLUSION:** Liver fibrosis is reduced significantly after a course of therapy in patients with chronic hepatitis C. Reduction of fibrosis is more significant in patients who are monoinfected with HCV and in those who attained SVR.

**Relationship between the severity of hepatitis C virus-related liver disease and the presence of Helicobacter species in the liver: A prospective study.** Castera L, et al. World J Gastroenterol. 2006 Dec 7;12(45):7278-84. [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17143941&query\\_hl=4&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17143941&query_hl=4&itool=pubmed_DocSum)

**AIM:** To determine the presence of Helicobacter species DNA in the liver of chronic hepatitis C (CHC) patients with and without cirrhosis as compared to controls, and to identify the bacterial species involved. **METHODS:** Seventy-nine consecutive patients (HBV and HIV negative) with a liver sample obtained after liver biopsy or hepatic resection were studied: 41 with CHC without cirrhosis, 12 with CHC and cirrhosis, and 26 controls (HCV negative). Polymerase chain reactions (PCRs) targeting Helicobacter 16S rDNA and species-specific were performed on DNA extracted from the liver. A gastric infection with H pylori was determined by serology and confirmed by (13)C-urea breath test. **RESULTS:** Overall, Helicobacter 16S rDNA was found in 16 patients (20.2%). Although positive cases tended to be higher in CHC patients with cirrhosis (41.6%) than in those without cirrhosis (17.0%) or in controls (15.4%), the difference was not statistically significant ( $P = 0.08$ ). H

pylori-like DNA was identified in 12 cases and H. pullorum DNA in 2, while 2 cases remained unidentified. Gastric infection with H pylori was found in only 2 of these patients. **CONCLUSION:** Our results do not confirm the association of Helicobacter species DNA in the liver of CHC patients with advanced liver disease. The lack of correlation between positive H pylori serology and the presence of H pylori-like DNA in the liver may indicate the presence of a variant of this species.

**Reliability and validity of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory (Full and FastScreen scales) in detecting depression in persons with hepatitis C.**

Golden J, Conroy RM, O'dwyer AM. J Affect Disord. 2006 Dec 5; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17156850&query\\_hl=4&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17156850&query_hl=4&itool=pubmed_DocSum)

**BACKGROUND:** We examined the performance the Beck Depression Inventory (BDI) and its short form (BDI-FS) and the Hospital Anxiety and Depression Scale depression (HADS-D) and anxiety (HADS-A) subscales in detecting depression in a group of patients with hepatitis C. **METHODS:** SCID-CV was used to establish DSM-IV diagnosis. Sensitivity, specificity, positive and negative predictive values were used to assess test performance and Cohen's Kappa to measure agreement with DSM diagnosis. **RESULTS:** Twenty-five of 88 participants had a DSM-IV depressive diagnosis. There was considerable non-overlap between 'caseness' on the BDI and HADS (Kappa=0.44). The HADS depression subscale had poor sensitivity (52%) and poor agreement with clinical diagnosis (Kappa=0.35). The full BDI had a sensitivity of 88% and a Kappa of 0.54 against a sensitivity of 84% and Kappa of 0.42 for the short form. The HADS anxiety subscale predicted depression as well as the depression subscale (sensitivity 88%, Kappa 0.47). **CONCLUSIONS:** Neither the BDI nor the HADS agrees well with the clinical diagnosis of depressive disorder, nor do they agree well with one another. The anxiety subscale of the HADS appears to measure depression at least as well as the depressive subscale.

**Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin.**

Snoeck E, et al. Br J Clin Pharmacol. 2006 Dec;62(6):699-709.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17118125&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17118125&query_hl=5&itool=pubmed_DocSum)

**AIM:** To assess the likelihood of a sustained virological response (SVR) vs. the likelihood of anaemia in patients with chronic hepatitis C. **METHODS:** Data from 1732 patients treated with peginterferon alfa-2a (40KD) plus ribavirin in two randomized, multinational studies were pooled. Probabilities of SVR and anaemia were modelled using the generalized additive logistic model, with numerous clinical variables considered for entry into the model. Baseline haemoglobin was only considered in the analysis for anaemia. **RESULTS:** The probability of anaemia increased from 6 to 16% as a function of the ribavirin dose kg(-1) (12-16 mg kg(-1)), whereas the relationship between SVR and ribavirin dose kg(-1) was influenced by hepatitis C virus (HCV) genotype. The probability of an SVR was not influenced by the ribavirin dose kg(-1) in patients with HCV genotype 2 or 3 infection, but increased as a function of ribavirin dose kg(-1) in patients with HCV genotype 1 infection (40-50% increase in probability of SVR for 12-16 mg kg(-1) dose ribavirin increase). The probability of an SVR in patients included with HCV genotype 1 decreased with increasing HCV RNA level to about 3 million copies ml(-1), but was relatively independent of increasing HCV RNA level thereafter. In addition, older age, a higher ribavirin apparent oral clearance and cirrhosis had a negative impact on achieving an SVR, but improved with increasing alanine aminotransferase (ALT) quotient. Sex and ribavirin dose kg(-1) were the most important prognostic factors for anaemia, followed by baseline haemoglobin, age, baseline ALT quotient and cirrhosis.

**CONCLUSION:** This study supports individualizing ribavirin dosages by HCV genotype and body weight, and highlights several clinical variables that influence the likelihood of an SVR compared with anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin.

**Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b.**

Abergel A, et al. J

Viral Hepat. 2006 Dec;13(12):811-20.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17109680&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17109680&query_hl=5&itool=pubmed_DocSum)

We compared sustained virological response (SVR) in chronic hepatitis C patients with severe fibrosis treated with pegylated interferon (Peg-IFN) alpha-2b 1.5 microg/kg/week or 0.75 microg/kg/week in combination with ribavirin 800 mg/day for 48 weeks. This was a multicentre randomized controlled study. SVR was observed in 44.5% (45/101) of patients treated with the standard dose of Peg-IFN and 37.2% (38/102) of patients treated with

the low dose (NS). In patients with genotypes 1, 4 and 5, SVR was observed in 25.0% of patients who received the standard dose and 16.9% of patients who received the low dose of Peg-IFN (P = NS). In patients with genotypes 1, 4 and 5 and low viraemia, SVR was obtained in 27.3% of patients treated with the standard dose and 25.8% of patients treated with the low dose (P = NS). In the high-viraemia subgroup, SVR was obtained in 24.0% and 9.1% of patients, respectively. In patients with genotypes 2 and 3, SVR was similar in both groups (73.2% vs 73.0%). Thus, (1) patients with genotypes 2 and 3 and severe fibrosis can be treated with low dose of Peg-IFN and ribavirin, (2) this study suggests that patients with genotypes 1, 4 and 5 and high viraemia could receive a standard dose of Peg-IFN associated with ribavirin for 48 weeks, (3) side effects limit the efficacy of the treatment with standard dose of Peg-IFN in patients with genotypes 1, 4 and 5 and low viraemia, (4) more studies are needed for patients with genotype 2 or 3 to define the optimal duration (24 or 48 weeks) in patients with severe fibrosis.

**A 24-week course of high-dose interferon-alpha plus ribavirin for Taiwanese chronic hepatitis C patients with persistently normal or near-normal alanine aminotransferase levels.** Yu ML, et al. *Liver Int.* 2006 Dec;26(10):1187-95

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17105583&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17105583&query_hl=5&itool=pubmed_DocSum)

**BACKGROUND/AIMS:** We aimed to evaluate the efficacy, advantage, and safety of a 24-week regimen with high-dose interferon-alpha (INF-alpha; 6 million units thrice weekly) plus ribavirin (1000-1200 mg/day) combination therapy for 46 Taiwanese chronic hepatitis C (CHC) patients with persistently normal or near-normal alanine aminotransferase (PNALT) levels. **METHODS:** Ninety-two age- and sex-matched CHC patients with elevated ALT levels (> 2 times the upper limit of normal range) with a ratio of 1:2, treated with the same regimen, served as a control. **RESULTS:** The sustained virologic response (SVR) rate was comparable between PNALT (67.4%) and elevated ALT (65.2%) groups (intention-to-treat analysis). The two groups had similar rates of discontinuation and incidence of adverse effects. Viral genotype 1b, baseline viral loads, body mass index, and age were significant factors negatively associated with SVR. Further decline of ALT levels throughout the follow-up period was observed in sustained responders of the PNALT group. None of the eight patients with ALT flares developed icteric hepatitis. The virologic efficacy was sustained in a 3-year extended follow-up period. **CONCLUSION:** high-dose INF-alpha with ribavirin combination therapy is effective, safe, and well tolerated in CHC patients with PNALT levels. The ALT assay might not be used as a single biochemical marker for determination of treatment consideration.

**Fibrosis in genotype 3 chronic hepatitis C and nonalcoholic fatty liver disease: Role of insulin resistance and hepatic steatosis.** Bugianesi E, et al. *Hepatology.* 2006 Dec;44(6):1648-55.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17133473&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17133473&query_hl=5&itool=pubmed_DocSum)

Hepatic steatosis has been associated with fibrosis, but it is unknown whether the latter is independent of the etiology of fat infiltration. We analyzed the relationship between clinical characteristics, insulin resistance (HOMA-R) and histological parameters in 132 patients with "viral" steatosis caused by genotype 3 chronic hepatitis C (CHC-3) and 132 patients with "metabolic" steatosis caused by nonalcoholic fatty liver disease (NAFLD), matched by age, BMI, and degree of liver fat accumulation. Tests of liver function were comparable in the two study populations. The prevalence of features of insulin resistance was higher in NAFLD, as was HOMA-R (P = .008). Logistic regression analysis confirmed that steatosis was associated with a high viral load and low serum cholesterol in CHC-3, and with high aminotransferase, glucose, ferritin and hypertriglyceridemia in NAFLD. At univariate analysis, advanced fibrosis was associated with steatosis in NAFLD, but not in CHC-3. Other parameters related to fibrosis severity were HOMA-R and a low platelet count in CHC-3, and high aminotransferases, HOMA-R, ferritin and low HDL-cholesterol in NAFLD. On multivariate analysis, only low platelet count (OR = 0.78; 95% CI, 0.67-0.92) and HOMA-R (OR = 2.98; 1.13-7.89) were independent predictors of advanced fibrosis in CHC-3. In NAFLD, severe fibrosis was predicted by fat grading (OR = 3.03; 1.41-6.53), ferritin (OR = 1.13; 1.03-1.25) and HOMA-R (OR = 1.16; 1.02-1.31). In conclusion, insulin resistance is an independent predictor of advanced fibrosis in both NAFLD and CHC-3, but the extent of steatosis contributes to advanced disease only in NAFLD. Virus-induced hepatic steatosis as seen in CHC-3 does not contribute significantly to liver fibrosis.

**Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial.** Everson GT, et al. *Hepatology.* 2006 Dec;44(6):1675-84.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17133499&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17133499&query_hl=5&itool=pubmed_DocSum)

In patients with chronic hepatitis C, advanced fibrosis and cirrhosis are associated with lower rates of sustained virologic response (SVR) to interferon (IFN)-based therapy. In this study, we assessed virologic response to retreatment with peginterferon alfa-2a and ribavirin (RBV), as a function of the baseline fibrosis score (Ishak staging) and platelet count, in 1,046 patients enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial. All patients had failed prior treatment with IFN or peginterferon +/- RBV and had Ishak fibrosis scores  $\geq 3$ . Four groups of patients with increasingly severe liver disease were compared: (A) bridging fibrosis (Ishak 3 and 4) with platelet counts  $>125,000/\text{mm}^3$  ( $n = 559$ ); (B) bridging fibrosis with platelet counts  $\leq 125,000/\text{mm}^3$  ( $n = 96$ ); (C) cirrhosis (Ishak 5 and 6) with platelet counts  $>125,000/\text{mm}^3$  ( $n = 198$ ); and (D) cirrhosis with platelet counts  $\leq 125,000/\text{mm}^3$  ( $n = 193$ ). SVR rates were 23%, 17%, 10%, and 9% in groups A, B, C, and D, respectively ( $P < .0001$  for trend). Reduction in SVR as a function of increasingly severe disease was independent of age, percent African American, HCV genotype, HCV level, and type of prior therapy. Dose reduction lowered SVR frequencies, but to a lesser extent than disease severity. By logistic regression, cirrhosis ( $P < .0001$ ) was the major determinant that impaired virologic response, independent of dose reduction or platelet count. In conclusion, disease severity is a major independent determinant of rate of SVR in patients with advanced chronic hepatitis C. New strategies are needed to optimize antiviral therapy in these "difficult-to-cure" patients.

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#### BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**Hepatitis C virus infects T cells and affects interferon-gamma signaling in T cell lines.** Kondo Y, et al. *Virology*. 2006 Dec 15; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17175001&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17175001&query_hl=3&itool=pubmed_DocSum)

It has been reported that hepatitis C virus (HCV) may infect and replicate in human T cells, particularly in perihepatic lymph nodes, but the extent and consequence of T-cell infection in patients is unclear. This study is conducted to characterize the parameters and functional consequences of HCV infection in T lymphocytes. By using a lymphotropic HCV strain, we showed that HCV could infect T cell lines (Molt-4 and Jurkat cells) in vitro. Both positive- and negative-strand HCV RNA were detected for several weeks after infection. Viral proteins could also be detected by immunofluorescence studies. Moreover, infectious HCV particles were produced from Molt-4 cell cultures, and could be used to infect naive T cell lines. HCV could also infect human primary CD4(+) T cells, particularly naive (CD45RA(+)CD45RO(-)) CD4(+) cells, in culture. The amounts of STAT-1 and phosphorylated STAT-1 proteins in the infected Molt-4 cells were significantly less than those in uninfected cultures, suggesting the possibility of defect in interferon-gamma signaling. Indeed, T-bet and STAT-1 mRNA levels after interferon-gamma stimulation in infected Molt-4 were suppressed. **In conclusion**, HCV could infect and transiently replicate in T cells and that HCV replication suppressed the IFN-gamma/STAT-1/T-bet signaling due to the reduction of STAT-1 and inhibition of its activation (phosphorylation).

**Hsp90 inhibitors suppress HCV replication in replicon cells and humanized liver mice.** Nakagawa SI, et al. *Biochem Biophys Res Commun*. 2006 Dec 22; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17196931&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17196931&query_hl=3&itool=pubmed_DocSum)

Persistent infection with hepatitis C virus (HCV) is a major cause of liver diseases such as chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Here we report that inhibition of heat shock protein 90 (Hsp90) is highly effective in suppressing HCV genome replication. In HCV replicon cells, HCV replication was reduced by Hsp90 inhibitors and by knockdown of endogenous Hsp90 expression mediated by small-interfering RNA (siRNA). The suppression of HCV replication by an Hsp90 inhibitor was prevented by transfection with Hsp90 expression vector. We also tested the anti-HCV effect of Hsp90 inhibition in HCV-infected chimeric mice with humanized liver. Combined administration of an Hsp90 inhibitor and polyethylene glycol-conjugated interferon (PEG-IFN) was more effective in reducing HCV genome RNA levels in serum than was PEG-IFN monotherapy. These results suggest that inhibition of Hsp90 could provide a new therapeutic approach to HCV infection.

**Serum procalcitonin levels in chronic hepatitis C patients under pegylated interferon-alpha plus ribavirin treatment.** Elefsiniotis IS, et al. *J Clin Virol*. 2006 Dec;37(4):329-31. Epub 2006 Sep 25.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=16996792&query\\_hl=6&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16996792&query_hl=6&itool=pubmed_DocSum)

**OBJECTIVES:** To evaluate the alterations of serum procalcitonin (PCT) levels in patients with chronic hepatitis C during pegylated interferon-alpha (PEG-IFNa) plus ribavirin (RIB) treatment and to correlate them with clinical and virological outcomes. **STUDY DESIGN:** Fifty-two consecutive patients (29 males, age=41.2+/-14.7 years) with chronic HCV-related liver disease (six cirrhotics) were evaluated for PCT levels at baseline and during the treatment course (at week 12, 24, 48 and 72) with PEG-IFNa plus RIB. Sustained virological response (SVR) was confirmed by undetectable serum HCV-RNA at the end of treatment and again 6 months after completion of treatment. **RESULTS:** Two patients exhibited culture-proved bacterial infections during the treatment course. Thirty-six patients (69.2%) exhibit SVR and 16 (30.8%) were non-responders. Serum PCT levels remained within normal limits (0.1-0.5 ng/mL) in all treated patients throughout the follow-up period except those two who exhibited bacterial infections during the treatment course. Virological responders exhibited significant decline of serum PCT levels over time compared to non-responders ( $p < 0.001$ ), even when adjusted for multiple baseline parameters ( $p = 0.037$ ). **CONCLUSION:** Serum PCT levels decline in chronic hepatitis C patients during PEG-IFNa plus RIB treatment, especially in the sustained virological responder group, while they elevate only when bacterial infections complicate the treatment course.

**Intrahepatic virus-specific IL-10-producing CD8 T cells prevent liver damage during chronic hepatitis C virus infection.** Abel M, et al. *Hepatology*. 2006 Dec;44(6):1607-16.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17133491&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17133491&query_hl=5&itool=pubmed_DocSum)

CD8 T cell killing of hepatitis C virus (HCV)-infected hepatocytes is thought to contribute to liver damage during chronic HCV infection, whereas the participation of HCV-nonspecific immune cells is unclear. To visualize the spatial relationship of HCV-specific CD8 T cells with parenchymal target cells, and to examine their local functional activity in relation to hepatocellular necrosis and fibrosis, we used HLA tetramers and confocal microscopy in biopsies from 23 HLA-A2 or HLA-B7 patients with chronic HCV infection. Intrahepatic tetramer+ (HCV-specific) CD8 T cells protected from hepatic necroinflammatory disease activity, independently of age, gender, viral load, and viral genotype. Indeed, tetramer+ cells were scattered in the liver within regions of weak fibrosis (low laminin expression) and low hepatocellular apoptosis (TUNEL method), and expressed IL-10 but not IFN $\gamma$ . By contrast, tetramer-negative CD8 T cells were associated with active necroinflammatory liver disease, colocalized with strong laminin expression and hepatocellular apoptosis, and expressed more frequently IFN $\gamma$  than IL-10. Overall, liver regions harboring HCV-specific CD8 T cells tended to be healthier than areas containing only inflammatory cells of undefined specificity. In conclusion, HCV-specific IL-10-producing CD8 T cells, although not cytotoxic and unable to control viral replication, can attenuate hepatocellular necrosis, liver fibrosis, and inflammation mediated by bystander T cells, and may thus represent antigen-induced regulatory CD8 T cells. Therapeutic modulation of the intrahepatic balance between specific and bystander CD8 T cells might be beneficial in patients with chronic hepatitis C.

**Evidence of a Genetic Basis for the Different Geographic Occurrences of Liver/Kidney Microsomal Antibody Type 1 in Hepatitis C.** Muratori P, et al. *Dig Dis Sci*. 2006 Dec 8; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17160474&query\\_hl=4&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17160474&query_hl=4&itool=pubmed_DocSum)

Antibodies to liver/kidney microsome type 1 occur in Italian patients with hepatitis C, but rarely develop in North American patients. Our goals were to compare the frequencies of the HLA markers associated with autoimmune expression in Italian and North American patients with chronic hepatitis C and to determine genetic bases for regional differences in antibody production. HLA B8, DR3, DR4, DR7, DR11, DR13, DQ2, and the B8-DR3-DQ2 haplotype were determined by microlymphocytotoxicity and polymerase chain reaction in 105 Italian patients (50 with microsomal antibodies), 100 North American patients (none with microsomal antibodies), and Italian and North American healthy control subjects. Italian patients with microsomal antibodies differed from North American patients without these antibodies by having a higher frequency of HLA DR7 (54% vs. 27%,  $P = 0.002$ ). HLA DR7 occurred more frequently in seropositive Italian patients than in seronegative counterparts (54% vs. 11%  $P < 0.0001$ ), Italian healthy control subjects (54% vs. 29%,  $P = 0.0009$ ), and North American healthy control subjects (54% vs. 19%,  $P < 0.0001$ ). The frequency of HLA DR7 was similar in North American patients and controls (27% vs. 19%,  $P = 0.2$ ), but it was lower than in Italian controls (19% vs. 29%,  $P = 0.059$ ). Seropositive Italian patients had a lower frequency of HLA DR11 than seronegative Italian patients and Italian controls (18% vs. 34%,  $P = 0.07$ , and 18% vs. 35%,  $P = 0.02$ , respectively). In contrast to seropositive Italian

patients, North American patients had HLA DR4 (30% vs. 12%,  $P=0.02$ ), HLA DR13 (29% vs. 10%,  $P=0.01$ ), and the B8-DR3-DQ2 haplotype (23% vs. 6%,  $P=0.01$ ) more often. Similarly, HLA DR4 and the B8-DR3-DQ2 phenotype were more frequent in North American patients than in Italian controls (30% vs. 16%,  $P=0.005$ , and 23% vs. 7%,  $P=0.00002$ , respectively). HLA DR7 is associated with the development of microsomal antibodies in Italian patients with chronic hepatitis C. The lower frequency of HLA DR7 in North America could contribute to the rarity of these antibodies in this region. HLA DR11 may be protective against the development of microsomal antibodies in Italian patients, whereas HLA DR4, HLA DR13, and the B8-DR3-DQ2 haplotype may be protective in North American patients.

#### **Identification of novel hepatitis C virus-specific cytotoxic T lymphocyte epitope in NS3 region.**

Ito K, et al. *Hepatology*. 2006 Dec;36(4):294-300. Epub 2006 Sep 22.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=16996788&query\\_hl=6&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16996788&query_hl=6&itool=pubmed_DocSum)

Hepatitis C virus (HCV)-specific cytotoxic T lymphocytes (CTL) are thought to be effective in limiting viral spread and in clearing virus during infection. Therefore, we attempted to establish HCV-specific CTL and identify novel HCV-specific CTL epitopes in a patient with acute hepatitis C by a novel screening method using recombinant vaccinia viruses (rVV) and synthetic peptides. CD8(+)CD45RA(-) T cells (memory T cells) were isolated from peripheral blood mononuclear cells (PBMC) of a patient with acute hepatitis C. HCV-specific CTL were cloned at limited dilutions and tested for HCV-specific CTL activity using a standard ( $^{51}$ Cr) release assay. CTL assay was performed using rVV expressing regions of HCV-J, and overlapping and truncated synthetic peptides from HCV-J. CTL recognizing the NS3 region were isolated by ( $^{51}$ Cr) release assay with rVV-HCV. Isolated CTL were restricted by HLA class I molecules B(\*)5603. We confirmed that isolated CTL recognized 8-mer amino acids in the NS3 region of HCV-J by ( $^{51}$ Cr) release assay with overlapping and truncated synthetic peptides. In conclusion, we isolated HCV-specific CTL restricted by HLA-B(\*)5603 and identified a novel HCV-specific CTL epitope (IPFYGKAI, amino acids 1373-1380) in the NS3 region. The identified HCV-specific CTL epitope might be useful for HCV therapy.

#### **Changes of soluble CD26 and CD30 levels correlate with response to interferon plus ribavirin therapy in patients with chronic hepatitis C.**

Yang SS, et al. *J Gastroenterol Hepatol*. 2006 Dec;21(12):1789-93

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17074015&query\\_hl=6&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17074015&query_hl=6&itool=pubmed_DocSum)

**BACKGROUND:** Clearance of hepatitis C virus (HCV) is attributed to host cellular immune responses, in which T helper cells play a critical role. The purpose of the present paper was therefore to study the serial changes of serum soluble markers released from T helper 1 (Th1) and 2 (Th2) and their correlations with treatment responses in chronic hepatitis C patients receiving interferon-alpha plus ribavirin for 24 weeks. **METHODS:** Serum markers (soluble CD26 and CD30 levels) of T helper cells were quantified before and 6 months after combination therapy in 33 chronic hepatitis C patients and in 20 healthy controls. **RESULTS:** Compared to healthy controls, chronic hepatitis C patients had significantly lower serum soluble CD26 levels before (140.4 +/- 63.9 ng/mL vs 200.6 +/- 60.3 ng/mL,  $P < 0.0001$ ) and after (115.9 +/- 32.9 ng/mL vs 200.6 +/- 60.3 ng/mL,  $P < 0.0001$ ) combination therapy. The level was even lower in those with non-sustained virologic response (non-SVR; 139.0 +/- 50.9 ng/mL vs 117.7 +/- 40.3 ng/mL,  $P = 0.039$ ). In contrast, soluble CD30 levels at 6 months after combination therapy were significantly lower in patients with SVR than those with non-SVR (6.4 +/- 3.5 U/mL vs 10.4 +/- 5.4 U/mL,  $P = 0.021$ ). **CONCLUSION:** Chronic hepatitis C patients have a weak Th1 response as reflected by lower soluble CD26 levels and the levels are even lower in non-sustained responders. In sharp contrast, downregulation of Th2 response with serial changes of soluble CD30 level is associated with successful treatment of HCV infection.

#### **Expression profiling of peripheral-blood mononuclear cells from patients with chronic hepatitis C undergoing interferon therapy.**

Tateno M, et al. *J Infect Dis*. 2007 Jan 15;195(2):255-67. Epub 2006 Dec 13.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17191171&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17191171&query_hl=3&itool=pubmed_DocSum)

**BACKGROUND:** Interferon (IFN) is now the standard treatment for chronic hepatitis C (CH-C); however, treatment efficacy is unpredictable before IFN therapy is started. **METHODS:** We investigated the gene-expression profiles of peripheral-blood mononuclear cells (PBMCs) from patients with CH-C showing different responses to IFN. Gene-expression profiles of PBMCs were analyzed in 21 patients with CH-C treated with IFN alone or in combination with ribavirin as well as in 6 healthy volunteers. Serial changes in the gene-expression

profiles of PBMCs from individual patients were evaluated before treatment, 2 weeks after the start of IFN therapy, and 6 months after the completion of IFN therapy. **RESULTS:** Interestingly, the gene-expression profiles of PBMCs from patients with CH-C and healthy volunteers differed substantially; early T cell-activation antigen CD69 was significantly up-regulated in patients with CH-C, but immune-related molecules such as chemokine (C-C motif) receptor 2 and interleukin 7 receptor were significantly down-regulated. Selected combinations of expressed genes obtained before treatment and during IFN therapy by use of a fuzzy neural network combined with the SWEEP operator method predicted the outcome of IFN therapy with peak accuracies of 91.0% and 90.2%, respectively. **CONCLUSIONS:** These findings suggest that the gene-expression profiles of PBMCs from patients with CH-C may be useful biomarkers for IFN therapy.

**Equal amounts of intracellular and virion-enclosed hepatitis C virus RNA are associated with peripheral-blood mononuclear cells in vivo.** Kaiser P, et al. J Infect Dis. 2006 Dec 15;194(12):1713-23. Epub 2006 Nov 13 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17109344&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17109344&query_hl=5&itool=pubmed_DocSum)

**BACKGROUND:** Hepatitis C virus (HCV) replicating in peripheral-blood mononuclear cells (PBMCs) may represent an extrahepatic viral reservoir. Quantitation of HCV RNA with regard to its subcellular distribution and longitudinal course is needed for better understanding of the largely unexplored in vivo dynamics and potential pathogenetic significance of HCV in PBMCs. **METHODS:** Plasma and PBMCs from 30 patients coinfecting with HCV and human immunodeficiency virus were evaluated in cross-sectional and longitudinal analyses, for up to 40 months. Differential extraction of virion-enclosed HCV RNA associated with cells was performed in parallel with extraction of total cellular HCV RNA. HCV RNA of either orientation was quantified by real-time polymerase chain reaction. **RESULTS:** HCV RNA was detected only in PBMCs from patients with viremia and at relatively stable quantities over time. Intracellular HCV RNA corresponding to ~60% of total cellular HCV RNA was strongly correlated with virion-enclosed HCV RNA but was only weakly associated with viral loads in plasma. In contrast, the ratio of HCV RNA load in PBMCs versus that in plasma was patient specific and stable over time. **CONCLUSIONS:** The substantial and patient-specific amounts of intracellular HCV RNA found by the present study support a concept of low-level replication in PBMCs. There was no evidence for persistent HCV infection in PBMCs after clearance of viremia in plasma.

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## HIV/HCV CO-INFECTION

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**[Early detection of hepatitis C virus infection using a new combined antigen-antibody detection assay: potential use in HIV co-infected individuals]** [Article in French] Schnuriger A, et al. Pathol Biol (Paris). 2006 Dec;54(10):578-86. Epub 2006 Oct 6. [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17030457&query\\_hl=6&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17030457&query_hl=6&itool=pubmed_DocSum)

**BACKGROUND:** The aim of this study was to determine the clinical benefit of a new combined antigen-antibody immunoenzymatic assay (Monolisa HCV Ag-Ab Ultra, Biorad) in the setting of acute HCV infection in HIV infected patients. **PATIENTS AND METHODS:** The performance of this assay was first evaluated in 160 HIV positive samples from uninfected and chronically HCV infected patients. To assess the performance of the Ag-Ab assay in the context of acute hepatitis C, 94 stored frozen serums from 20 recently diagnosed cases were retrospectively tested for HCV-RNA and presence of anti-HCV antibodies, in parallel with the new assay. **RESULTS:** In HIV infected patients, the sensitivity and specificity of the Ultra assay was 100% with a strong discrimination between positive and negative samples. In HCV acutely infected patients, the Ag-Ab assay significantly reduced the seronegative period, allowing an earlier diagnosis compared to a 3rd generation ELISA in 65% of the cases. The combined assay became positive on the same bleed as the first HCV-RNA detection for 13 patients out of 20. Nevertheless, in one case, characterized by an absence of seroconversion over one year but a continuous viral replication above 1 million IU/ml, the combined assay did not improve HCV infection diagnosis. **CONCLUSION:** Use of this new assay as a first line screening would significantly reduce the long seronegative window period seen in HCV infection allowing earlier HCV diagnosis and rapid clinical management. However, in case of clinical acute hepatitis C, sensitive HCV-RNA detection should remain the gold standard.

**Substance abuse treatment and receipt of liver specialty care among persons coinfecting with HIV/HCV who have alcohol problems.** Palepu A, et al. J Subst Abuse Treat. 2006 Dec;31(4):411-7. Epub 2006 Aug 14.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17084795&query\\_hl=5&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17084795&query_hl=5&itool=pubmed_DocSum)

We examined the association of substance abuse treatment with access to liver specialty care among 231 persons coinfecting with HIV and hepatitis C virus (HCV) with a history of alcohol problems who were recruited and followed up in the HIV-Longitudinal Interrelationships of Viruses and Ethanol cohort study from 2001 to 2004. Variables regarding demographics, substance use, health service use, clinical variables, and substance abuse treatment were from a standardized research questionnaire administered biannually. We defined substance abuse treatment services as any of the following in the previous 6 months: 12 weeks in a halfway house or residential facility, 12 visits to a substance abuse counselor or mental health professional, day treatment for at least 30 days, or any participation in a methadone maintenance program. Liver specialty care was defined as a visit to a liver doctor, a hepatologist, or a specialist in treating hepatitis C in the past 6 months. At study entry, most of the 231 subjects (89%, n = 205) had seen a primary care physician, 50% had been exposed to substance abuse treatment, and 50 subjects (22%) had received liver specialty care. An additional 33 subjects (14%) reported receiving liver specialty care during the follow-up period. In the multivariable model, we observed a clinically important although not statistically significant association between having been in substance abuse treatment and receiving liver specialty care (adjusted odds ratio = 1.38; 95% confidence interval = 0.9-2.11). Substance abuse treatment systems should give attention to the need of patients to receive care for prevalent treatable diseases such as HIV/HCV coinfection and facilitate its medical care to improve the quality of care for individuals with substance use disorders. The data illustrate the need for clinical care models that give explicit attention to the coordination of primary health care with addiction and hepatitis C specialty care while providing ongoing support to engage and retain these patients with complex health needs.

**Mortality in Siblings of Patients Coinfected with HIV and Hepatitis C Virus.** Hansen AB, et al. J Infect Dis. 2007 Jan 15;195(2):230-5. Epub 2006 Dec 11

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17191168&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17191168&query_hl=3&itool=pubmed_DocSum)

**BACKGROUND:** Coinfection with hepatitis C virus (HCV) is a poor prognostic factor for human immunodeficiency virus (HIV)-infected patients. We examined whether the increased mortality in these patients is partly explained by a familial excess risk of death. **METHODS:** Danish HIV-infected patients who had had at least 1 HCV test were included (n=3531). In addition, 336,652 population control subjects matched for sex, age, and residency were identified from the Danish Civil Registration System. For both HIV-infected patients and population control subjects, we identified all siblings born after 1951, with dates of death or emigration. Siblings of HIV-infected patients were classified according to the patients' HCV serostatus. Survival after age 20 years was compared among the groups of siblings. **RESULTS:** We identified 437 siblings of HIV/HCV-coinfected patients, 1856 siblings of HIV-monoinfected patients, and 285,509 siblings of population control subjects. Mortality was substantially higher in siblings of HIV/HCV-coinfected patients than in either siblings of HIV-monoinfected patients (mortality rate ratio [MRR], 2.97 [95% confidence interval {CI}, 1.98-4.45]) or siblings of control subjects (MRR, 4.23 [95% CI, 3.09-5.79]). Siblings of HIV-monoinfected patients had slightly higher mortality (MRR, 1.43 [95% CI, 1.10-1.85]) than siblings of control subjects. **CONCLUSIONS:** HCV infection is a marker of familial factors that affect the survival of HIV-infected patients independently of the pathogenicity of HCV.

**A novel anticancer agent ARC antagonizes HIV-1 and HCV.** Nekhai S, et al. Oncogene. 2006 Dec 18; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17173067&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17173067&query_hl=3&itool=pubmed_DocSum)

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) pose major public health concerns worldwide. HCV is clearly associated with the occurrence of hepatocellular carcinoma, and recently HIV infection has also been linked to the development of a multitude of cancers. Previously, we identified a novel nucleoside analog transcriptional inhibitor ARC (4-amino-6-hydrazino-7-beta-D-ribofuranosyl-7H-pyrrolo[2,3-d]-pyrimidine-5-carboxamide) that exhibited proapoptotic and antiangiogenic properties in vitro. Here, we evaluated the effect of ARC on HIV-1 transcription and HCV replication. Using reporter assays, we found that ARC inhibited HIV-1 Tat-based transactivation in different cell systems. Also, using hepatoma cells that harbor subgenomic and full-length replicons of HCV, we found that ARC inhibited HCV replication. Together, our data indicate that ARC could be a promising candidate for the development of antiviral therapeutics against HIV and HCV.

**Development of a tomato-based food for special medical purposes as therapy adjuvant for patients with HCV infection.** Vitaglione P, et al. Eur J Clin Nutr. 2006 Dec 20; [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17180159&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17180159&query_hl=3&itool=pubmed_DocSum)

**OBJECTIVE:** The present study aimed to develop a food for special medical purposes (FSMP) and to assess its efficacy as adjuvant therapy in patients with chronic hepatitis C virus (HCV). **DESIGN:** Open randomized clinical trials with a tomato-based FSMP used as adjuvant treatment to the pharmacological therapy with pegylated interferon and ribavirin. **SUBJECTS:** Eight healthy volunteers and 39 HCV patients. **Interventions:** For the bioavailability study, healthy subjects consumed 100 g/die FSMP for a week and their serum carotenoid profile at baseline, after the week of administration and 7 days later was determined. The same quantity of FSMP for 6 months by 20 of the 39 HCV patients was consumed in the clinical trial. Serum transaminase, haemoglobin (Hb) and hydroperoxide concentrations during the therapy were monitored in all patients. **RESULTS:** FSMP consumption caused a fourfold increase of lycopene serum concentration in healthy subjects. A significant increase of carotenoids after 1 month of consumption also in patients with HCV was recorded. Transaminase and Hb serum levels, as well as therapeutic response, were not influenced by FSMP. The decrease in serum hydroperoxides was independent from FSMP consumption in long-term responder patients, whereas nonresponder (NR) patients of FSMP group showed higher reductions than NR patients of Control group. **CONCLUSIONS:** The FSMP was effective in improving carotenoid status in healthy subjects. In HCV patients, it did not influence the therapeutic response, but it prevented carotenoid serum depletion and it was effective in improving the oxidative status during antiviral therapy in NR patients.

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#### MISCELLANEOUS

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**Non-injection drug use and Hepatitis C Virus: A systematic review.** Scheinmann R, et al. Drug Alcohol Depend. 2006 Dec 14; [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17174481&query\\_hl=4&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17174481&query_hl=4&itool=pubmed_DocSum)

This systematic review examined the evidence on the prevalence of the Hepatitis C Virus (HCV) in non-injecting drug users (NIDUs) who sniff, smoke or snort drugs such as heroin, cocaine, crack or methamphetamine. The search included studies published from January 1989 to January 2006. Twenty-eight eligible studies were identified and the prevalence of HCV in these NIDU populations ranged from 2.3 to 35.3%. There was substantial variation in study focus and in the quality of the NIDU data presented in the studies. The results of our systematic review suggested that there are important gaps in the research of HCV in NIDUs. We identified a problem of study focus; much of the research did not aim to study HCV in users of non-injection drugs. Instead, NIDUs were typically included as a secondary research concern, with a principal focus on the problem of transmission of HCV in IDU populations. Despite methodological issues, HCV prevalence in this population is much higher than in a non-drug using population, even though some IDUs might have inadvertently been included in the NIDU samples. **These studies point to a real problem of HCV in NIDU populations**, but the causal pathway to infection remains unclear.

**euHCVdb: the European hepatitis C virus database.** Combet C, et al. Nucleic Acids Res. 2006 Dec 5; [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17142229&query\\_hl=4&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17142229&query_hl=4&itool=pubmed_DocSum)

The hepatitis C virus (HCV) genome shows remarkable sequence variability, leading to the classification of at least six major genotypes, numerous subtypes and a myriad of quasispecies within a given host. A database allowing researchers to investigate the genetic and structural variability of all available HCV sequences is an essential tool for studies on the molecular virology and pathogenesis of hepatitis C as well as drug design and vaccine development. We describe here the European Hepatitis C Virus Database (euHCVdb, <http://euhcvdb.ibcp.fr>), a collection of computer-annotated sequences based on reference genomes. The annotations include genome mapping of sequences, use of recommended nomenclature, subtyping as well as three-dimensional (3D) molecular models of proteins. A WWW interface has been developed to facilitate

database searches and the export of data for sequence and structure analyses. As part of an international collaborative effort with the US and Japanese databases, the European HCV Database (euHCVdb) is mainly dedicated to HCV protein sequences, 3D structures and functional analyses.

**New therapeutic options for hepatitis C.** Waters L, Nelson M. *Curr Opin Infect Dis.* 2006 Dec;19(6):615-22  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17075339&query\\_hl=6&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17075339&query_hl=6&itool=pubmed_DocSum)

**PURPOSE OF REVIEW:** There is an urgent need for new anti-hepatitis C virus therapies and recently a number of agents have reached clinical trials with yet more in preclinical stages of development. New technologies for the in-vitro study of drugs have accelerated progress markedly, previously hampered by the lack of cell-culture systems or animal models for hepatitis C. **RECENT FINDINGS:** A number of agents have demonstrated potent antiviral activity and synergism with existing therapies. A better understanding of managing adverse events and tailoring treatment dose and duration have yielded improved treatment response rates. We review the mechanisms of both new and existing anti-hepatitis C virus drugs and the data for some promising new agents and strategies. **SUMMARY:** Although many of the agents reviewed are in the early stages of development they show great promise and the ever-increasing understanding of hepatitis C virus will undoubtedly lead to exploration of new targets. Much progress has been made in terms of maximizing success with currently licensed agents and lessons learned from the field of HIV can guide the careful use of new agents to minimize resistance in the future.

**Illness-related stigma, mood and adjustment to illness in persons with hepatitis C.** Golden J, et al. *Soc Sci Med.* 2006 Dec;63(12):3188-98. Epub 2006 Sep 28.  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17010490&query\\_hl=6&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17010490&query_hl=6&itool=pubmed_DocSum)

We examined stigma in persons with hepatitis C and its relationship with mood and adjustment to illness. We studied 87 persons awaiting interferon treatment for hepatitis C at St James's Hospital, Dublin. Stigma was assessed using Fife's Experience of Illness scale. A structured clinical interview was used to establish DSM-IV diagnosis. The Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory (BDI) were also used as measures of mood. Factor analysis and clustering around latent variables analysis were used to assess scale structure and reliability. The stigma scale had an overall reliability of 0.94. A strong dimension of fear of disclosure emerged, from item analysis, together with dimensions of social isolation and social rejection. Stigma was higher in those in manual occupations and the unemployed than in those in non-manual occupation. There were high levels in those with disease associated with injecting drug use and iatrogenic disease caused by transfusion or anti-D blood products, and low levels in those who had been treated for haemophilia with contaminated products or whose hepatitis was of unknown origin. Adjusted for confounders, a 1-decile increase in stigma score had an odds ratio of 1.4 for DSM-IV depression and similar associations with depression on the HADS and BDI. Stigma was also associated with poorer work and social adjustment, lower acceptance of illness, higher subjective levels of symptoms and greater subjective impairment of memory and concentration. These associations were replicated in the non-depressed subsample. The results underline the strong link between stigma and well-being in hepatitis C. However, they also suggest that stigma is a complex construct that will require further research to elucidate.

**Evaluation of the Abbott RealTime HCV assay for quantitative detection of hepatitis C virus RNA.** Michelin BD, et al. *J Clin Virol.* 2006 Dec 19; [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17185031&query\\_hl=3&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17185031&query_hl=3&itool=pubmed_DocSum)

**BACKGROUND:** The Abbott RealTime HCV assay for quantitative detection of HCV RNA has recently been introduced. **OBJECTIVES:** In this study, the performance of the Abbott RealTime HCV assay was evaluated and compared to the COBAS AmpliPrep/COBAS TaqMan HCV test. **STUDY DESIGN:** Accuracy, linearity, interassay and intra-assay variations were determined, and a total of 243 routine clinical samples were investigated. **RESULTS:** When accuracy of the new assay was tested, the majority of results were found to be within +/-0.5log(10) unit of the results obtained by reference laboratories. Determination of linearity resulted in a quasilinear curve up to 1.0x10<sup>6</sup>IU/ml. The interassay variation ranged from 15% to 32%, and the intra-assay variation ranged from 5% to 8%. When clinical samples were tested by the Abbott RealTime HCV assay and the results were compared with those obtained by the COBAS AmpliPrep/COBAS TaqMan HCV test, the results for 93% of all samples with positive results by both tests were found to be within +/-1.0log(10) unit. The viral loads for all patients measured by the Abbott and Roche assays showed a high correlation (R(2)=0.93); quantitative

results obtained by the Abbott assay were found to be lower than those obtained by the Roche assay.

**CONCLUSIONS:** The Abbott RealTime HCV assay proved to be suitable for use in the routine diagnostic laboratory. The time to results was similar for both of the assays.

**Monitoring HCV RNA viral load by locked nucleic acid molecular beacons real time PCR.**

Morandi L, et al. J Virol Methods. 2006 Dec 14; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=17175034&query\\_hl=4&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17175034&query_hl=4&itool=pubmed_DocSum)

Locked nucleic acids (LNA) based real time PCR was used in particular situations where there are difficulties in primer design due to sequence complexity. In this study a new real time RT-PCR assay was developed using LNA modified primers and LNA molecular beacon probes to monitor hepatitis C virus (HCV) viral load in plasma and serum samples. The technique did not suffer from an heterogeneity of the HCV genome and, in addition, an internal RNA control was amplified in the same reaction tube with different short primers and beacon probe. Due to the short consensus LNA primers length, the PCR efficiency was close to 100% with no formation of hairpin loop structures. In summary a new LNA molecular beacon based real time RT-PCR assay was used successfully to measure quantitatively the total level of HCV RNA in both experimental and clinical specimens. The high sensitivity (50IU/ml), the wide range of genotype detection, increased specificity and robustness obtained with this test are particularly useful for screening large number of specimens and measuring viral loads to monitor the progress of the disease.