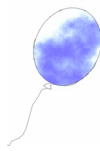


HEPATITIS C CARING AMBASSADORS PROGRAM NEWSLETTER

June, 2005

| | |
|--|----|
| IN THE NEWS..... | 1 |
| CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES..... | 12 |
| BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES..... | 19 |
| HIV/HCV COINFECTION..... | 22 |
| COMPLEMENTARY & ALTERNATIVE THERAPIES..... | 24 |
| MISCELLANEOUS WORKS..... | 25 |



IN THE NEWS

Huge posters focus on hepatitis C

<http://news.bbc.co.uk/1/hi/england/nottinghamshire/4636719.stm>

A lecturer who had hepatitis C for 20 years without knowing it will be featured in a new awareness campaign. Nick Green of Nottingham was diagnosed with the disease a year ago, two decades after blood tests showed problems with his liver. An exhibit, to run across the UK, will include a 3m-high poster of Mr Green. Mr Green has the disease despite falling outside the high risk categories.

"My main symptom was a lot of extreme pain in my liver - and stomach area, also extreme fatigue, loss of concentration and appetite, mood swings and depression. "I felt ill every day and still do - with insomnia alongside that - not able to relax and sleep well."

The photo exhibit of people living with hepatitis C - prepared by photographer Michele Martinoli, was first unveiled in London's Leicester Square in March. The Nottingham exhibit at the city's Market Square will be held on 7 and 8 July.

Former Beach Boys band member David Marks, who also has hepatitis C, said 80% of the estimated 200,000 people infected in the UK are unaware of their condition, which can go undetected for up to 30 years. Mr Marks said: "People need to take a few minutes out of their day to step back and face their pasts, have I ever injected drugs using shared equipment, even just once? "Have I had an unsafe tattoo or piercing? If the answer is yes, call the Hepatitis C Information Line for advice about hepatitis C and whether you should consider being tested." Ms Martinoli, who also had hepatitis C, said: "There is a social stigma around the disease caused by lack of awareness.

"It's important that we bring hepatitis C out of the shadows to get people to face up to the illness in the same way we did with HIV in the eighties and nineties."

AVI BioPharma Submits IND for NEUGENE Antisense Drug Targeting Hepatitis C Virus

http://home.businesswire.com/portal/site/google/index.jsp?ndmViewId=news_view&newsId=20050630005165&newsLang=en

AVI BioPharma, Inc. today announced that it has submitted an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA) for its NEUGENE(R) antisense drug AVI-4065 targeting hepatitis C virus (HCV). The application provides the FDA with preclinical safety, toxicology and manufacturing data in support of clinical evaluation of AVI-4065 in humans who are chronically infected with HCV.

"With a response rate of less than 50 percent for patients receiving existing treatments for the most common type of HCV infection, there remains a large unmet medical need for new and effective treatments," said Denis R. Burger, Ph.D., chief executive officer at AVI. "Our previous work in other viral research, including West Nile virus, has given us valuable insights on dosing, administration and pharmacokinetic data with which to begin this clinical program. That data, combined with the strong safety results we have seen in over 250 patients treated with NEUGENE drugs to date, greatly increases our confidence in the potential success of AVI-4065 for treating HCV."

As proposed in the IND application, the initial multicenter Phase IB clinical trial will include up to 50 patients in three treatment groups: normal subjects and two groups of patients with chronic, active HCV, including patients who are newly diagnosed, and those who have failed the current standard of care, which is interferon and ribavirin. The study will assess the safety, tolerability, pharmacokinetics and viral response to daily subcutaneous administration of AVI-4065 at two dosage levels for a specific period of time.

Mark Holodny, M.D., F.A.C.P., C.I.C., associate professor of medicine at Stanford University School of Medicine and director of the HIV Clinical Program and AIDS Research Center at Veterans Affairs Medical Center in Palo Alto, Calif., will serve as the principal investigator for this intended multicenter study.

HCV is a single-stranded RNA virus known to undergo a high rate of mutation, which may help the virus develop resistance to many current and development-stage antiviral medications. Because HCV and other single-stranded RNA viruses have relatively simple genetic structures, they are attractive targets for AVI's NEUGENE antisense, which is designed to target conserved portions of the viral genetic code that are not likely to mutate over time, after drug exposure.

Another NEUGENE drug, AVI-4020, is currently being studied in a clinical trial of patients exhibiting presumptive neuroinvasive disease caused by West Nile virus. In addition, NEUGENE drugs are being tested against a variety of hemorrhagic, infectious and toxin-producing agents in collaboration with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the Walter Reed Army Institute of Research (WRAIR), and the Centers for Disease Control and Prevention (CDC).

Canada Red Cross tries to put blood scandal to rest

<http://www.alertnet.org/thenews/newsdesk/N30536851.htm>

TORONTO - Victims of Canada's tainted blood scandal had a chance to air their stories in an Ontario court on Thursday as the Canadian Red Cross was formally sentenced for distributing blood products contaminated by donors who suffered from HIV and hepatitis C.

A court in Hamilton, Ontario, handed the agency the maximum fine of C\$5,000 (\$4,065) for violating the Food and Drugs Act. It has already provided C\$70 million in compensation to more than 10,000 victims and Canadian governments agreed in 1998 on a C\$1.1 billion compensation plan.

The Red Cross was sentenced after nine people read victim-impact statements in a hearing that spanned 3-1/2 hours. "They talked about how devastating the disease is to them," said John Plater, a lawyer and member of the Canadian Hemophilia Society, who was also made ill by the tainted blood. "But they also talked about how devastating and how frustrating (it was) trying to get answers and bring these people to account and how many years it has taken. "That really struck a chord with me ... the wasted time."

About 1,000 Canadians were infected with HIV, the virus that causes AIDS in the 1980s before the Red Cross began testing blood donations. An estimated 20,000 people have been infected with hepatitis C, a debilitating and often deadly liver disease. The Red Cross pleaded guilty in May to violating the country's Food and Drugs Act -- the first time the charity admitted it broke the law.

Thursday's sentence included C\$1.5 million for a scholarship fund for students affected by the tragedy and for a project to improve health care practice. According to the Red Cross the sentence "closed a sad chapter in its history." "This afternoon was particularly painful and I have maybe only one word to describe that -- tragedy," said Pierre Duplessis, the Canadian Red Cross's chief executive. The Red Cross was forced to seek bankruptcy protection in the late 1990s and has transferred its blood supply operations to a government-funded agency.

"Blood is over, it's done, it's finished, so hopefully for us, we will be able to turn that page in our history," Duplessis said.

Sexual transmission of HCV found in Swiss HIV-positive gay men

<http://www.aidsmap.com/en/news/F741093C-4F71-4684-8119-C5753CDB611C.asp>

Unprotected sex is associated with new hepatitis C virus infections in Swiss HIV-positive gay men, according to a study published in the August 1st edition of *Clinical Infectious Diseases*. This finding supports other studies which have found evidence of the sexual transmission of hepatitis C virus between HIV-positive gay men.

Swiss investigators believe that their study has added weight to the earlier research, "being the first report of an association on unprotected sex with an increased incidence of hepatitis C virus infection in HIV-infected [gay] men that was determined on the basis of a prospective longitudinal cohort that included regular hepatitis C virus testing and reports about condom use and injecting drug use."

Although it is well established that there is a high prevalence of hepatitis C virus infection amongst HIV-positive individuals, there is little information concerning the incidence of new hepatitis C infections in this population. The few studies that have investigated this have found a low incidence of new infections related to heterosexual intercourse, although genital ulceration is thought to facilitate heterosexual transmission.

Although there is little evidence of sexual transmission in HIV-negative gay men, data from studies conducted amongst HIV-positive gay men in London and some other western cities suggest increasing hepatitis C infection rates among HIV-positive men engaging in unprotected anal sex and harder sexual practices such as fisting.

In the Swiss HIV cohort, hepatitis C prevalence is measured and information regarding injecting drug use and condom use is collected every six months. Investigators were therefore able to study the incidence of hepatitis C virus infection related to sexual behaviour and drug use.

Since 1998 patients in the Swiss Cohort have been regularly tested for hepatitis C virus and frozen plasma samples from before this time have been retrospectively tested. Syphilis test results are also available for approximately two-thirds of patients.

Individuals complete questionnaires regarding their drug use and sexual behaviours on entry to the study and every six months thereafter. Overall prevalence of hepatitis C virus infection was 33% amongst 7899 members of the cohort enrolled since 1988. Over 90% of these infections were in injecting drug users.

Hepatitis C virus incidence was calculated on data from 3327 individuals. A total of 104 new hepatitis C virus infections were detected in these patients in a total of just over 16,000 patient years of follow-up. This provided an incidence of 0.64 cases per 100 person years. Incidence was highest amongst injecting drug users at 7.4 cases per 100 person years, compared to 0.23 cases per 100 person years amongst individuals with no history of injecting drugs.

Amongst gay men who had not injected drugs, but who had had unprotected anal sex had an incidence rate of 0.7 per 100 person years compared to 0.2 per 100 person years for gay men reporting neither injecting drug use nor unprotected sex. This difference was statistically significant ($p = 0.02$) and the incidence rate ratio was 3.5. The investigators also found a trend for incident hepatitis C virus infections amongst younger gay men and a significant association between infection with syphilis and hepatitis C virus infection ($p = 0.03$). No significant relationship was found between unprotected sex and infection with hepatitis C virus amongst heterosexuals in the cohort.

"Data of the large, prospective Swiss HIV Cohort Study indicate that unsafe sexual behaviour amongst [gay] men is associated with new acquisitions of hepatitis C virus infection", conclude the investigators.

[Rauch A et al. Unsafe sex and increased incidence of hepatitis C virus infection amongst HIV-infected men who have sex with men: the Swiss Cohort Study. *Clin Infect Dis* 41 (On-line edition), 2005.]

State cuts inmate hepatitis funds

<http://www.lsj.com/apps/pbcs.dll/article?AID=/20050623/NEWS01/506230334/1001/news>

Funding to test and treat Michigan prisoners for hepatitis C has been eliminated in House and Senate spending plans for 2005-06, effectively killing a plan to attack the potentially fatal and communicable disease festering inside the state's 42 prisons.

Lawmakers in recent weeks have cut \$1.2 million from next year's corrections budget specifically set aside for a new hepatitis C program. Gov. Jennifer Granholm wants to use the money to survey inmates when they arrive at prisons and begin testing those most at risk for harboring the blood-borne virus, as is recommended by the U.S. Centers for Disease Control and Prevention. That would have meant more prisoners would have been treated, lowering the risk that they would leave prison unaware they carry the virus and infect others.

"We can't do that now," corrections spokesman Russ Marlan said. "If we are going to aggressively treat hepatitis C, we're going to need the funding." Department officials don't know exactly how many prisoners are infected. A 2003 Lansing State Journal investigative report found that up to 18,000 of Michigan's 48,000 prisoners are believed to harbor the virus. About 55 were being treated. Department officials couldn't say Wednesday how many inmates are being treated now. Prison officials have said it would cost \$130 million a year to treat every infected inmate.

Sen. Martha Scott, D-Highland Park, failed in two efforts to restore the funding during last week's debate on the Department of Corrections budget. Scott said the program is vital to help ensure the safety of the general public, particularly women who are unknowingly infected with the disease by men recently released from prison. "These guys are coming out and infecting the public," Scott said. "If we don't take some precautions here, it'll cost us later."

State Sen. Alan Cropsey, R-DeWitt, defended the cut by saying the department's \$1.8 billion budget already includes \$172 million for health care. As such, Cropsey said, there's no need to create a separate fund to treat hepatitis C. "I just don't think it's wise to be segmenting diseases," Cropsey said. "It's not good public policy to say

that as legislators we will play doctor to the prisoners." The cut also leaves correctional officers at risk, said Mel Grieshaber, executive director of the Michigan Corrections Organization, which represents prison guards. "Hepatitis C is such a tremendous problem in our prisons," Grieshaber said. "We can't ignore it and keep people safe."

The House and Senate spending plans will go to a conference committee to hammer out differences. Just how much attention this issue gets is uncertain. Much of the debate in the corrections budget has centered on whether to close the Newberry Correctional Facility and Camp Manistique in the Upper Peninsula or the private Michigan Youth Facility in Baldwin. But Greg Bird, Granholm's budget spokesman, said the governor will fight to have the hepatitis C money restored. Granholm proposed the program last year. She initially wanted to give the corrections department \$5.9 million. After much haggling, legislators agreed to give the program \$1.2 million.

Department officials had planned to implement a program in March to survey all new inmates in hopes of finding those most at-risk for the virus. Those prisoners then would have been tested, and anyone positive would have been monitored or treated, depending on the severity of their disease. But Marlan said officials canceled that plan when they were told in early spring that funding would not be restored this year. The \$1.2 million remaining in the current budget now will be used to cover hepatitis C treatments in the past year, Marlan said.

Shorter Hepatitis C Treatment Works for Some

<http://my.webmd.com/content/article/107/108651.htm>

Some people with hepatitis Chepatitis C may get by with only three months of treatment, an Italian study shows. The findings apply only to people infected with type 2 or type 3 hepatitis C virus. They do not apply to people infected with the more common type 1 virus. In the U.S., about 70% of hepatitis C infections are type 1, about 5% are type 2, and about 20% are type 3.

Treatment for hepatitis C isn't easy. The drugs of choice are a once-a-week form of interferon alpha (peg-interferon) plus ribavirin, an antiviral drug. The side effects -- including flu-like symptoms, fatigue, and depression -- can be very hard to handle. Current guidelines call for six months of treatment for hepatitis C type 2 and type 3 infections. A year of treatment is needed for type 1 infections.

But Alessandra Mangia, MD, of Casa Sollielo della Sofferenza Hospital, in San Giovanni Rotondo, Italy, and colleagues report that some patients with hepatitis C type 2 or type 3 infections may be able to cut their treatment time in half.

Side effects force some patients to quit treatment early. Usually, that means treatment failure; usually -- but not always. "We saw that a few patients, who withdrew from therapy before the standard six-month period, had sustained virologic responses anyway despite their short course of treatment," Mangia tells WebMD. "And we saw that some patients show a very fast reduction of hepatitis C virus levels after their first interferon treatment."

Did early response to treatment predict who would do well with short-term therapy? The researchers designed an experiment. They enrolled 283 people with hepatitis type 2 or type 3 infection. Seventy of the patients got the full six months of peg-interferon plus ribavirin. The other 213 patients started with the same treatment. If, after four weeks, their blood levels of hepatitis C virus became undetectable, these "fast responders" got only three months of treatment -- called variable-length treatment.

Mangia and colleagues report their findings in the June 23 issue of *The New England Journal of Medicine*. The researchers had good news for patients with hepatitis C type 2 or 3 that had no evidence of the virus after four weeks of treatment. "Patients treated for 12 weeks were spared the expense and inconvenience of extended treatment and still had a high response rate."

The response rates were similar between those treated for three months and those treated for six months. Overall, 76% of patients getting standard treatment and 77% of patients getting the variable-length treatment had a sustained virologic response. But there were some differences.

At first, early responders -- those who had undetectable levels of hepatitis C virus after four weeks of treatment -- looked the same in both the standard and variable treatment groups. Ninety-three percent of early responders treated for six months and 95% of those treated for three months still had no detectable virus at the end of treatment. Six months later, that percentage dropped from 93% to 91% in those treated for six months. But it dropped from 95% to 85% in those treated for three months.

Although it sounds like the variable-length group have more viral "rebound," Mangia notes that the results were very similar between the two groups. And of the 13 patients who rebounded after three months of treatment, 10

agreed to 24 more weeks of treatment. This second course of treatment was successful for nine of these 10 rebounders. "Only this small number of persons rebounded, without any major side effects, and without any reduction in the response rate for [further] treatment," Mangia says.

But these numbers worry hepatitis C expert Robert Fontana, MD, associate professor of medicine and medical director for liver transplant at the University of Michigan in Ann Arbor. "Is this really an efficient way to manage patients? If you are going to go through this therapy, you would rather get rid of the virus," Fontana tells WebMD. "Yes, you have less of the side effects with 12 vs. 24 weeks of treatment. But if someone is tolerating it well, why risk the relapse? Plus there is the whole psychological letdown from learning you've had a rebound. ... If you can get by with less treatment, great. But when you start to have a trend toward rebound, I don't think it's worth the risk."

Mangia says her hospital already is using the variable-treatment strategy for all patients with type 2 or type 3 hepatitis C infection. Based on the study findings, Fontana doesn't think this is a good idea. He praises the Mangia study. Though he notes that it was carefully done and that it addresses crucial issues in hepatitis C treatment, he says doctors and patients would do better to focus on managing side effects than by trying to shorten treatment.

"During the first 12 weeks, the most severe side effects are flu-like symptoms," Fontana says. "Beyond 12 weeks, the depression, the weakness, and the sort of mental aspect becomes more prominent. That is where a lot of patients going out to 48 weeks just can't hack it. By reducing the dose, by seeing patients more often, by introducing antidepressants, and by helping with sleep, you can get a lot of those patients through."

Nabi Biopharmaceuticals Gains Orphan Medicinal Product Designation For Civacir(TM) in Europe

<http://biz.yahoo.com/prnews/050622/flw018.html?.v=14>

Nabi Biopharmaceuticals today announced that, following the favorable opinion of the European Medicines Agency or EMEA (adopted by the Committee of Orphan Medicinal Products), the European Commission has granted Orphan Medicinal Product (OMP) designation to Civacir(TM) [Hepatitis C Immune Globulin (Human)], Nabi Biopharmaceuticals' product candidate for the prevention of recurrent hepatitis C virus-induced liver disease in liver transplant recipients.

The OMP designation will result in reduced Marketing Authorization Application (MAA) fees, free access to scientific advice from the EMEA and other potential research and development incentives. Furthermore, if a product with OMP designation is the first to receive marketing authorization in Europe for its designated indication, the product will be entitled to 10- year market exclusivity, which means that a similar drug is prevented from receiving authorization for the same indication during this period. Civacir has already been granted Orphan Drug designation from the U.S. Food and Drug Administration (FDA).

"The Orphan Drug designation and today's OMP status promises to accelerate Civacir's development and reduce our development costs. We are particularly pleased by getting this designation in Europe because of the pioneering role European investigators have played in demonstrating the utility of hepatitis B immune globulins in liver transplant patients," said Henrik S. Rasmussen, M.D., Ph.D., senior vice president, clinical, medical and regulatory affairs, Nabi Biopharmaceuticals.

Dr. Rasmussen continued, "Nabi Biopharmaceuticals is building a growing commercial hepatitis franchise in Europe. HEBIG(TM), our hepatitis B immune globulin that was recently submitted for registration in Europe, along with Civacir, represents a comprehensive approach to addressing post-liver transplant consequences of viral hepatitis. We look forward to advancing both of these products to the marketplace, in line with our strategy to provide the best solutions for patients, while reducing the financial burden on healthcare systems."

Civacir is an investigational human polyclonal antibody product that contains antibodies to the hepatitis C virus (HCV). Civacir is being developed for the prevention of recurrent hepatitis C virus-induced liver disease in liver transplant recipients. Civacir is also being evaluated for the treatment of chronic hepatitis C virus infections.

The National Institutes of Health (NIH) has funded and conducted a Phase I/II clinical trial of Civacir in HCV-positive liver transplant patients at four study sites in the U.S. This randomized, controlled study evaluated the safety of dosing patients with Civacir during and after transplant surgery, the level of HCV-specific antibodies in trial subjects following dosing, liver enzyme levels (a measure of liver damage) and HCV levels in the transplanted livers. Data from the trial were reported in February 2004 and revealed that Civacir was well tolerated in liver transplant patients and produced a trend towards a reduction in ALT (serum alanine aminotransferase, an important liver enzyme that measures liver function) levels. Based on the results from this trial, the company expects to now

be able to define the continued development strategy for this agent following discussions with the FDA and the EMEA.

Peregrine Pharmaceuticals Presents Data Supporting Broad Spectrum Anti-Viral Potential of Tarvacin(TM) at BIO 2005

<http://biz.yahoo.com/prnews/050622/law007.html?v=12>

Peregrine Pharmaceuticals, Inc. today presented new data at the Biotechnology Industry Organization 2005 (BIO 2005) annual meeting in Philadelphia, PA. supporting the broad anti-viral potential of Tarvacin(TM). The data presented at BIO 2005 showed that Tarvacin(TM) binds to enveloped virus particles representing 6 different virus families, binds to virally infected cells and inhibits viral replication in multiple virus systems. The data also indicated that Tarvacin(TM) provided significant protection against Cytomegalovirus (CMV) and Pichinde virus (an in vivo Lassa fever model) infections.

- * Tarvacin(TM) binds to viruses from six different enveloped virus families, including specific binding to HIV 1 and 2, Influenza A and B, Measles, Respiratory Syncytial Virus (RSV), Bovine Viral Diarrhea (a surrogate in vitro Hepatitis C virus model), and Pichinde virus.

- * Tarvacin(TM) binds to cells infected with Influenza, Vaccinia (a model for Smallpox) and Pichinde viruses.

- * Anti-Phosphatidylserine antibodies inhibited replication of RSV, Vesicular Stomatitis Virus and Pichinde viruses.

- * Anti-Phosphatidylserine antibodies provided significant protection in animals infected with cytomegalovirus (CMV) with 100% of the Anti-Phosphatidylserine antibodies treated animals surviving and only 20% of animals receiving control treatment surviving.

- * Tarvacin(TM) provided significant protection in animals administered lethal viral loads of Pichinde virus (a model of Lassa fever) with 50% of the Tarvacin(TM) treated animals surviving and none of the animals receiving control treatment surviving.

- * Animals lethally infected with Pichinde virus that survived following Tarvacin(TM) therapy had long term immunity to reinfection.

"These data further illustrate why we are excited about the Tarvacin(TM) anti-viral program," stated Steven King, president and CEO of Peregrine. "We are looking forward to initiating the Tarvacin(TM) Hepatitis C clinical trial, continuing our collaboration with National Institute of Allergy and Infectious Diseases (NIAID) and expanding into other collaborations to further explore the potential of the program for the treatment of viral infections."

Peregrine received FDA approval to begin a Tarvacin(TM) phase I clinical trial in Hepatitis C infected patients in late May 2005. In April of 2005, Peregrine and the National Institute of Allergy and Infectious Diseases (NIAID) entered into a collaborative effort to screen Tarvacin(TM) for activity both in vitro and in vivo against a wide variety of enveloped viruses of health and bioterrorism concern including Hepatitis C, influenza and SARS. Peregrine is continuing to evaluate Tarvacin(TM) for the treatment of a variety of viral infections that could lead to additional therapeutic indications in this area. In addition, Peregrine is currently recruiting patients in a Tarvacin(TM) phase I clinical trial that is open to patients with advanced solid tumor cancer.

Anti-Phospholipid Therapy is Peregrine's novel approach to treating cancer, viral infections and certain other diseases. It is based on the finding that aminophospholipids, which are basic components of the inner surface of the cellular membrane, become exposed in certain disease states. Tarvacin(TM) is a chimeric monoclonal antibody that binds to the phospholipid, phosphatidylserine, and is part of Peregrine's Anti-Phospholipid Therapy platform. Tarvacin(TM) binds directly to tumor blood vessels to inhibit growth and development of solid tumors. Tarvacin(TM) has also shown promise in the treatment of viral infections and is expected to recognize a broad spectrum of enveloped viral types. Tarvacin(TM) is currently being evaluated for the treatment of both cancer and viral diseases. Peregrine has received FDA approval to initiate two separate Phase I clinical trials in advanced solid cancer and chronic Hepatitis C virus indications.

Aethlon Medical To Initiate Hepatitis-C Studies

<http://www.investors.com/corporatenews/nw24.asp?v=6/15>

San Diego, California – Aethlon Medical, Inc., a Company pioneering the development of medical devices that mimic the immune response of clearing viruses and toxins from circulation, announced today that it plans to initiate clinical trials to treat patients in India who are infected with the Hepatitis-C Virus (HIV). The Company reported that site selection for the trials is under way, and that patient enrollment should begin in the coming months.

Aethlon CEO, James A. Joyce stated, "This is a tremendous opportunity for us to demonstrate the safety and effectiveness of our HIV-Hemopurifier." Joyce continued, "We are passionate in our efforts to provide a new treatment option to the large population of HCV infected individuals that are unresponsive to the current standard of care."

Hepatitis C protease inhibitor, VX-950, reduces viral levels

http://www.xagen.com/news/medicinews_net_news/64254db8396e404d9223914a0bd355d2.html

A Phase Ib clinical trial showed that the oral hepatitis C virus (HCV) protease inhibitor, VX-950, for 5 and 14 days was well-tolerated in both healthy volunteers and in patients with chronic HCV infection. In addition, patients treated with 750 mg of VX-950 every eight hours achieved a median reduction of HCV-RNA of 4.4 log₁₀, equivalent to a 25,000-fold reduction in viral levels, at the end of 14 days of treatment.

At the end of 14 days of treatment, 4 of 8 patients in the 750 mg dose group tested HCV-RNA negative in the quantitative Roche COBAS TaqMan assay (<30 IU/mL); 2 of these 4 patients tested undetectable in the qualitative Roche TaqMan assay (limit of detection 10 IU/mL). A patient in another VX-950 dose group also achieved plasma HCV-RNA below the limit of quantitation by the end of treatment. All patients in the clinical trial had genotype 1 HCV infection, the most difficult strain to treat, and were either non-responsive to prior treatment or treatment-naïve.

" Preliminary results from this early Phase Ib clinical study suggest that the investigational drug VX-950 produces a rapid and profound reduction in HCV-RNA as a single agent," said Henk W. Reesink, at Academic Medical Center in Amsterdam. " In the best dose group in the Phase Ib clinical study, VX-950 reduced HCV viral load in some patients to below the limit of detection of the most sensitive assays in two weeks. VX-950 was also well-tolerated in this study. These data further support the view that HCV protease is the most potent single mechanism for suppressing hepatitis C viral replication."

VX-950 is an oral inhibitor of hepatitis C virus protease, an enzyme essential for viral replication. Vertex completed a Phase Ia clinical study of VX-950 in healthy volunteers in 2004, which indicated that VX-950 was well-tolerated in ascending single doses up to 1250 mg. Pharmacokinetic results from the Phase Ia study suggested that VX-950 can achieve liver concentrations substantially greater than IC₅₀ and IC₉₀ observed in non-clinical studies.

Preclinical studies, presented at various medical conferences in 2003 and 2004, demonstrated that VX-950 significantly reduces levels of HCV RNA in both an in vitro replication system and infectious virus assays.

Human Genome Sciences Initiates Phase 2b Clinical Trial of Albuferon(TM) in Combination With Ribavirin in Treatment-Naïve Patients With Chronic Hepatitis C

<http://biz.yahoo.com/prnews/050601/dcw002.html?v=13>

Human Genome Sciences, Inc. announced today that it has begun dosing patients in a Phase 2b clinical trial of Albuferon(TM) (albumin-interferon alpha) in combination with ribavirin to evaluate the efficacy and safety of Albuferon in patients with chronic hepatitis C virus (HCV) genotype 1 who are naive to interferon alpha-based treatment regimens. Genotype 1 accounts for nearly 70% of all HCV infections in North America and is generally regarded as the most difficult HCV genotype to treat.(1)

The trial is a randomized, open-label, multi-center, active-controlled, dose-ranging study conducted in Australia, Canada, Czech Republic, France, Germany, Israel, Poland and Romania. A minimum of 440 patients will be enrolled in the Phase 2b study and randomized into four treatment groups, three of which will receive subcutaneously administered Albuferon (900 mcg at 14-day intervals, 1200 mcg at 14-day intervals, and 1200 mcg at 28-day intervals(1)). The fourth treatment group will serve as the active control group and will receive weekly 180-mcg doses of subcutaneously administered Pegasys (peginterferon alfa-2a). All patients will receive weight-based oral daily ribavirin at 1000 or 1200 mg in two divided doses. The primary objectives of the Phase 2b study are to evaluate the efficacy and safety of Albuferon in combination with ribavirin in interferon alpha-naïve patients with chronic hepatitis C genotype 1. The primary efficacy endpoint will be sustained virologic response, defined as undetectable virus at 24 weeks after completion of 48 weeks of treatment.

John McHutchison, M.D., Coordinating Center Principal Investigator for the Phase 2b study, and Professor of Medicine and Director, GI/Hepatology Research, Duke Clinical Research Institute and Duke University Medical Center, Durham, NC, said, "The current standard of care for the treatment of chronic hepatitis C is a combination of pegylated interferon alpha and ribavirin. This combination produces cures in approximately 42-46 percent of all

genotype 1 HCV patients completing therapy, leaving more than 50 percent who relapse or do not respond. Clearly, chronic hepatitis C represents a significant unmet medical need. The preclinical and clinical evidence to date supports the continued evaluation of the potential of Albuferon to help meet this need. The next logical step is the current study of Albuferon in combination with ribavirin in a larger population of treatment-naïve genotype 1 patients with chronic hepatitis C."

David C. Stump, M.D., Executive Vice President, Drug Development, said, "Based on the preclinical and clinical results that have emerged thus far, we believe that Albuferon has the potential to become an important therapeutic option for the treatment of chronic hepatitis C. The Phase 2b study announced today is the largest Albuferon trial to date. We recently reported the positive results of a Phase 2 study of Albuferon monotherapy in interferon alpha-naïve patients with genotype 1 hepatitis C. The data that emerged demonstrate that Albuferon is well tolerated, has a prolonged half-life and shows robust antiviral activity, with durable dose-dependent reductions in HCV viral load. The data also enabled our identification of the range of active doses that will be evaluated in the larger Phase 2b trial announced today. In February 2005, we disclosed preliminary data from a separate ongoing Phase 2 clinical trial of Albuferon in combination with ribavirin, which show that Albuferon can be administered safely and repetitively at 2-week or 4-week intervals in combination with ribavirin in patients who have failed to respond to previous interferon alpha-based treatment regimens. The results of clinical and preclinical studies to date afford confidence in the ability to administer Albuferon safely in combination with ribavirin to treatment-naïve patients. We are hopeful that Albuferon will one day provide an important therapeutic option for the treatment of chronic hepatitis C."

The results of a Phase 2 clinical trial of Albuferon monotherapy in interferon alpha-naïve patients with genotype 1 chronic hepatitis C were presented at the 40th Annual Meeting of the European Association for the Study of the Liver (EASL). Data presented on 56 patients demonstrate that Albuferon exhibited robust antiviral activity in genotype 1 HCV. A mean reduction in HCV viral load of 3.2 log at Day 28 was observed in the combined 900 mcg and 1200 mcg dose cohorts, with 69% of patients (18/26) in these cohorts showing a >2-log reduction in HCV viral load at Day 28. Undetectable viral load was observed at Day 42 (28 days after the second injection) in 23% of patients (6/26) in the combined 900 mcg and 1200 mcg dose cohorts. Robust dose-dependent viral kinetics were observed, with the majority of patients in the 900 mcg and 1200 mcg cohorts exhibiting a second-phase decline in viral load of >0.3 log per week, which has previously been shown to be predictive of sustained virologic response (SVR) in treatment with the pegylated interferons. Reductions in viral load of equal to or greater than 2 log are reported in approximately 42% of genotype 1 HCV patients treated with pegylated interferon alpha products in combination with ribavirin. The results presented at EASL demonstrate that Albuferon remained in the blood substantially longer than is reported for recombinant interferon alpha and pegylated interferon alpha. Albuferon exhibited a median half-life of 148 hours, supporting dosing at intervals of 2-4 weeks. This compares with a reported mean (range) elimination half-life of 80 hours (50-140 hours) for Pegasys and 40 hours (22-60 hours) for PEG-Intron. Albuferon was well tolerated with adverse events that were transient and mostly mild to moderate in severity. There were no discontinuations due to reductions in hematologic cell counts. No subjects developed newly emergent antibodies to alpha interferon.

Albuferon is a novel, long-acting form of interferon alpha. Recombinant interferon alpha is approved for the treatment of hepatitis C, hepatitis B and a broad range of cancers. Human Genome Sciences modified interferon alpha to improve its pharmacological properties by using the company's proprietary albumin fusion technology.

Hepatitis C: hope on the distant horizon

http://www.pharmaceutical-business-review.com/article_feature.asp?guid=41D48563-D6E0-

While progress in the hepatitis C virus market is expected to be slow until 2011, the launch of polymerase and protease inhibitors thereafter is expected to fuel rapid growth. The market is expected to exceed \$4 billion by 2012 and this growth may even result in a new treatment paradigm. Driven by a favorable epidemiology and high unmet medical need, the hepatitis C pipeline is both rich and varied. The chronic hepatitis C (CHC) treatment market is currently dominated by market leaders Roche and Schering-Plough, which market both components of the CHC standard of care - a combination of pegylated interferon (Peg-IFN) alpha and ribavirin (RBV).

Historical growth in the hepatitis C market has been high, with a compound annual growth rate (CAGR) of 28.5% experienced between 1999 and 2003. This was mainly fuelled by the launch of RBV in 1998 and the second-generation interferons, Peg-IFN alpha-2b and -2a in 2000 and 2002, respectively - both of which significantly improved the efficacy of therapy.

However, treatment outcomes following Peg-IFN plus RBV combination therapy are highly heterogeneous and depend on the viral genotype with which a patient is infected. Indeed, sustained viral response (SVR) rates in the 'easy-to-treat' genotypes 2 and 3 can be up to 88% of cases. In contrast, less than half of those who harbor hepatitis C virus (HCV) genotype 1 successfully respond to therapy. Significantly, genotype 1 accounts for between 70 to 75% of the patient pool in the West and, therefore, current therapy meets less than 50% of the CHC medical need. This has led to the accumulation of patients that have failed first-line therapy with the current standard of care, known as non-responders, and patients who responded to therapy but subsequently relapsed. Moreover, as a result of the slow rate of HCV disease progression, the wave of patients seeking treatment is still gaining momentum and expected to peak from 2014 onwards. Incremental improvements in short term.

The combination of high patient potential and significant medical unmet need have attracted big pharma and small biotech alike, creating a pipeline consisting of 28 drugs in clinical development and a range of potential drug candidates at the preclinical stage. However only 14% of these molecules are currently in phase III, with none of these specifically targeting the HCV particle per se. Instead, they act by enhancing the host antiviral response and therefore, no major paradigm changes are expected to occur in HCV therapy for at least the next five years.

Research by Datamonitor found that among the three drugs that are closest to market, only Valeant's RBV follow-up drug viramidine is perceived as a key addition to HCV therapy. The drug has similar efficacy to its predecessor but differentiates itself based on its more favorable toxicity profile.

The highest hopes for effective future HCV therapy are being pegged on the small molecules able to specifically interfere with HCV replication, in particular the NS3 protease inhibitors. This new paradigm was first highlighted as a realistic goal by Boehringer Ingelheim (BI), whose protease inhibitor BILN 2061 demonstrated an unprecedented drop in viral load after only two days of therapy. However, the enthusiasm was largely dampened when BI was forced to suspend further development of the drug due to cardiac toxicity in animals.

With the most developed protease inhibitor - Vertex/Mitsubishi's VX-950 - still at least seven years from reaching the market, hopes are now centered on the polymerase inhibitors, most notably Idenix/Novartis's NS5B polymerase inhibitor valopicitabine (NM283). However clinical development has also led to general disappointment when early-stage trials showed only moderate reductions in viral load with NM283 monotherapy. This led to subsequent clinical trials being designed for combination therapy with Peg-IFN, with the end goal of potentially replacing RBV with NM283.

Is future therapy without an interferon backbone realistic? Early results from the NM283 clinical trials raise the question about the future role of Peg-IFN in HCV therapy: will it remain the backbone for several years to come or eventually fade from use? Some people believe that future HCV therapy is more likely to consist of combination therapy, based on Peg-IFN plus one or more specific antivirals. Others take a more optimistic view nurtured by faith in that antivirals could be capable of curing HCV infection on their own.

Given the consequences of untreated HCV infection, which include liver cirrhosis, hepatocellular carcinoma, liver transplant and death, many physicians will require convincing data before replacing a proven therapeutic option with antiviral monotherapy. As such, Peg-IFN is expected to retain a relatively strong market presence, despite the plethora of drugs in the pipeline, resulting in a CAGR of 9.9% for the interferon class between 2004 and 2013.

Innogenetics sees three-year delay in hepatitis C vaccine launch - press report

<http://www.forbes.com/markets/feeds/afx/2005/06/15/afx2093249.html>

Chairman of biotechnology company Innogenetics NV Rudy Marien said that the launch of a vaccine for hepatitis C will be delayed by at least three years due to an extension of clinical trials, according to a report in daily De Standaard. 'It will take at least an extra three years,' he said. Innogenetics said earlier that the trials were 'inconclusive' and have to be extended by 15 months.

How hepatitis-C virus evades immune system in acute and chronic infections

<http://www.medicalnewstoday.com/medicalnews.php?newsid=25898>

Researchers at Johns Hopkins have uncovered how a majority of the genetic changes in the hepatic-C virus, the most common cause of liver disease, allow it to evade the body's immune system during infection. Hepatitis C infection can lead to cirrhosis, cancer and even death. In a series of experiments that describe the virus' transition from an acute to chronic infection, the Hopkins team found that one-half of the virus' changes in its genome are in sites under attack by the body's immune system. As the virus evolves and these changes weaken the body's immune

response, a second set of changes at other sites in the genome are reverting back to an "ancestral" set of amino acids.

"We think this piecemeal exchange is helping the virus evade the body's immune system," says study investigator and infectious disease specialist Stuart Ray, M.D., an associate professor at The Johns Hopkins University School of Medicine. "In a newly infected person, the virus may need to adopt new mutations to escape recognition by the immune system's T cells, which fight infection, but it may need to lose the mutations that had protected it in someone else. Despite pressure to change, the virus is always restoring its shape."

The Hopkins findings, published in a pair of studies in the *Journal of Experimental Medicine* this week, are believed to be the first description of the precise genetic changes taking place in the virus during the acute phase of infection, when hepatitis C initially escapes the body's defenses and establishes itself in the body. As the infection moves into the chronic stage, the immune response becomes weak and less effective, but until now, no one could explain exactly why.

A second, related experiment produced similar findings when the Hopkins team partnered with researchers in Ireland to perform what is believed to be the first comparison of genetic changes across multiple genes in strains from chronically infected people to the original strain that infected them.

Ray, who served as senior investigator on the first study and led the second, believes the newly identified ancestral component of the viral genome, called a consensus sequence, could serve as the basis for development of a vaccine that is effective against both acute and chronic infections, thereby stemming the epidemic that currently afflicts more than 170 million people worldwide, including 3 million Americans.

Conventional wisdom, the researchers say, was that the large numbers of mutations were simply random in the virus' ever-changing genome, but the new study suggests that Darwinian genetic selection is at play. That is, the virus' genome changes in ways that make it more reproductively "fit" in the face of each immune system it encounters, changing what is must to evade the immune system in one host, then restoring itself when the pressure is off.

What Ray's team found when the immune response weakens was that the virus naturally mutates toward a set of 3,000 common amino acids, what the researchers considered the virus' most preferred state. During the acute phase, Ray says, the virus is under severe pressure from the immune response and forced to drift away from the consensus sequence, using mutations to evade the immune response. However, the drift was reversible and, once the virus successfully evaded a particular immune cell, its amino acids reverted back to the consensus set.

To assess the genetic changes in the early stages of infection, the researchers decoded, or sequenced, the virus' genome, made up of RNA, which is very similar to the more widely known DNA that makes up the genome of most organisms. The RNA was gathered from eight newly infected patients in Baltimore, Md., all of whom were offered treatment and were participants in a larger study of infectious diseases in intravenous drug users. The sample group was unusual, allowing analyses before and during the early stages of infection. One patient self-recovered, while the rest proceeded to chronic infection.

Using advanced blood-sorting techniques, the Hopkins team extracted millions of immune system cells, including the systems' principal fighters, called T cells, from blood samples taken between 30 days and six months after infection, when the body's initial immune response kicks in and subsequently peaks.

Immune responses were mapped using a series of more than 500 overlapping synthetic peptides, or strings of amino acids whose code was already known. This allowed the researchers to compare changes observed in the RNA sequence to corresponding shifts in the body's immune response to the infection.

When specifically recognized by T cells, the peptides trigger production of interferon gamma, a protein that acts as a signal to many other immune cells to respond to a new infection. Reductions in the production of interferon gamma would indicate, the scientists say, that the immune system was weakening in its response to the virus' mutations.

After analyzing the genetic changes in the sites, called epitopes, where the T cells specifically bind to the virus, the researchers found no changes had occurred during the one year of follow-up in the one patient who self-recovered. However, in the remaining seven patients, there were changes in 69 percent of T-cell epitopes, showing that the virus had mutated at key locations necessary for chronic infection to proceed.

Additional analysis showed that changes in T-cell epitopes were 13 times more frequent than changes in the remaining genome of the virus. The researchers examined the binding ability of T cells obtained early in infection to recognize 10 viral peptides known to have changed during the first six months of infection. Eight showed

severely reduced capacity to stimulate production of interferon gamma, offering confirmation that the virus was mutating to evade the immune system.

Analysis of the viral RNA in the blood of seven patients with chronic infections revealed that eight of 16 changes in genome matched to the consensus sequence, confirming the presence of selective evolutionary pressure toward restoration of an ancestral form of the virus.

In the second study, using blood samples collected in Cork, Ireland, the researchers compared the genetic makeup of the virus in 22 chronically infected women to the original strain that had infected them more than 20 years before. The women were among hundreds accidentally infected in 1977 by a blood product tainted with hepatitis C, providing the researchers with unique access to the source of the infection, which came from a single donor unaware of having the illness.

Using computer analysis techniques developed at Hopkins, the scientists mapped these changes against the genetic makeup of the women's immune response. The researchers found that when viral mutations were clustered in epitopes specific to each woman's immune system, the changes were directed away from the consensus sequence, suggesting immune escape. However, when mutations were clustered in epitopes that were not specific, the mutations were reversions back to the consensus sequence.

When the individual genome changes in each woman were mapped on a grid, each woman formed a unique cluster indicating individual, evolutionary selection. However, some of the changes were shared, suggesting convergence, which would not have occurred had the virus simply mutated at random.

"Our results raise the possibility that a hepatitis-C consensus sequence could be the best practical option for a vaccine," says infectious disease specialist David Thomas, M.D., a professor of medicine at Hopkins who served as senior author of the study of Irish women. "If we can focus vaccine development on the common genetic element in chronically infected patients, then we may be able to make a more effective vaccine."

Researchers Create Infectious Hepatitis C Virus in a Test Tube

<http://www.newswise.com/articles/view/512363/>

A team of researchers led by scientists at The Rockefeller University has produced for the first time an infectious form of the hepatitis C virus (HCV) in laboratory cultures of human cells. The finding, reported in the June 9 issue of *Science Express*, will allow scientists to study every stage of the HCV life cycle and develop drugs to treat this life-threatening disease that affects more than 170 million people around the world.

"The inability to reproduce aspects of the hepatitis C virus life cycle in cell culture has slowed research progress on this important human pathogen," says senior author Charles M. Rice, Ph.D., Maurice R. and Corinne P. Greenberg Professor and head of the Laboratory of Virology and Infectious Disease at Rockefeller.

"This system lays the foundation for future test tube studies of the virus life cycle and may help in the development of new drugs for combating HCV," adds Rice, who is the scientific director of the Center for the Study of Hepatitis C, a collaborative research and clinical effort of Rockefeller, Weill Medical College of Cornell University, and NewYork-Presbyterian Hospital

Like all viruses, HCV cannot replicate by itself; instead it takes over the machinery of a host cell to make copies of itself. Much about the life cycle of HCV remains poorly understood because scientists have been unable to reproduce an infectious form of HCV that they can observe in cell cultures. The method developed by Rice and his colleagues, including scientists at the Massachusetts Institute of Technology and the Scripps Research Institute, changes that.

"The hallmark of viruses is their ability to exist in a form outside the host cell capable of infecting new cells," says first author Brett Lindenbach, Ph.D., a postdoctoral fellow in Rice's lab. "Our method replicates and produces virus particles that can infect new cells, initiating replication in them and leading to the production of more virus particles."

Although little is known about the HCV life cycle, researchers think that in humans the virus enters a liver cell and delivers its RNA and proteins into the cell cytoplasm. HCV carries its genetic information in its RNA, which is separated from the protein, copied, and then joined with new protein components before being released from the liver cell to infect other cells.

Lindenbach, Rice and their colleagues named their infectious cell culture virus HCVcc. Already HCVcc is yielding new knowledge about HCV. In a separate set of experiments, the researchers used HCVcc to confirm that a

molecule called CD81, which sits on the surface of the human cell membrane, plays a crucial role in the entry of HCV.

Scientists have known that a protein produced by HCV, called E2, binds to CD81, and they believed that this interaction is necessary for the virus to bind to target cells. The Rockefeller researchers showed that CD81 molecules that are not attached to the surface of host cells compete with membrane-bound CD81 and inhibit entry of HCV into the cell. They also showed that HepG2 cells, which do not express CD81 but can support HCV RNA replication, could not be infected by HCVcc unless they express CD81.

New Approach To Hepatitis C

http://abclocal.go.com/kgo/health/edell/062005_he_hepatitis_help.html

A new drug is offering hope for millions of Hepatitis C patients. As Dr. Dean Edell reports, this drug may help patients stay healthier with fewer side-effects. Superstar Billy Graham took home the Worldwide Wrestling Federation title in 1977, but what happened in the ring brought him a challenge he never expected.

Superstar Billy Graham, retired professional wrestler: "We cut our foreheads to produce blood to make the match look more authentic." Graham thinks that may be how he contracted Hepatitis C. The disease is most commonly spread through blood.

Vijayan Balan, M.D., hepatologist: "Hepatitis C is a virus that can infect the liver and cause cirrhosis if it is untreated." Dr. Vijayan Balan is a liver specialist working on a new treatment. Right now, patients must take medication once a week that can induce days of flu-like symptoms. Now a new drug, Albuferon, is only taken once a month and causes fewer side-effects.

Albuferon is a combination of Interferon, which helps fight infection and Albumin, which allows the medication to stay in the body longer. Studies show the drug is safe. Soon it will be tested in up to 1,000 people across the country. Graham says a drug that's easier to handle would have had him back in the gym sooner and able to focus on the good times. The first phase of the study showed Albuferon is safe and well tolerated by patients. Right now, more than 1000 people are taking the drug.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Natural history of major complications in hepatitis C virus-related cirrhosis evaluated by per-rectal portal scintigraphy. Kawamura E, et al. World J Gastroenterol. 2005 Jul 7;11(25):3882-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15991287&query_hl=1

AIM: To examine the correlation between the porto-systemic hypertension evaluated by portal shunt index (PSI) and life-threatening complications, including hepatocellular carcinoma (HCC), liver failure (Child-Pugh stage progression), and esophagogastric varices. **METHODS:** Two hundred and twelve consecutive subjects with HCV-related cirrhosis (LC-C) underwent per-rectal portal scintigraphy. They were allocated into three groups according to their PSI: group I, $PSI \leq 10\%$; group II, $10\% < PSI < 30\%$; and group III, $30\% \leq PSI$. Of these, selected 122 Child-Pugh stage A (Child A) subjects were included in analysis (a mean follow-up period of 5.9 ± 5.4 years, range 6 mo-21 years). **RESULTS:** No significant correlation between PSI and cumulative probability of HCC incidence was observed. Cumulative probability of Child A to B progression was tended to be higher in group III than in group I, and significantly higher in group III than in group II (62% vs 34%, 62% vs 37%; $P = 0.060$, < 0.01 ; respectively). Cumulative probability of varices tended to be higher in group III than in group I (31% vs 12%, $P = 0.090$). On multivariate analyses, significant correlation between PSI and Child A to B progression was observed, and no significant correlation between PSI and HCC incidence or varices progression was observed. **CONCLUSION:** Patients with LC-C of Child A will progress to Child B rapidly after their PSI reaches 30% or higher. PSI can be used to predict occult progressive porto-systemic shunting and liver failure non-invasively. It indicates that PSI may play an important role in follow-up of the porto-systemic hypertension gradient for outpatients with LC unlike hepatic venous catheterization.

Non-interferon-based therapy: an option for amelioration of necro-inflammation in hepatitis C patients who cannot afford interferon therapy. El-Zayadi AR, et al. Liver Int. 2005 Aug;25(4):746-51.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15998425&query_hl=1

Objectives: Interferon (IFN) therapy is not affordable by the majority of Egyptian patients. Our aim was to tailor an effective and inexpensive regimen that ameliorates hepatic necro-inflammatory activity among chronic hepatitis C (CHC) patients. **Methods:** One hundred and seventy naive CHC patients with elevated alanine aminotransferase (ALT) (>1.5-fold) and detectable hepatitis C virus (HCV)-RNA by polymerase chain reaction, who cannot afford IFN-based therapy were randomly allocated either to non-interferon-based therapy (N-IFN-BT) (group I) or silymarin therapy (group II). Group I comprised 87 patients (biopsy proved chronic hepatitis in 62 patients) who were administered a daily combination of ribavirin (600-800 mg) plus amantadine (200 mg) and ursodeoxycholic acid (UDCA) (500 mg) for 24 weeks. Group II comprised 83 patients who were administered Silymarin 450 mg/day for 24 weeks. **Results:** Statistical evaluation was conducted on 82 patients from group I and 72 from group II because of the withdrawal of five and 11 patients from Groups I and II, respectively. Age, sex, social status and biochemical parameters were comparable in both groups. Normalization of ALT at the end of treatment was achieved in 58.5% and 15.3% ($P<0.001$), whereas end of treatment virologic response (ETVR) was achieved in 2.4% and 0% of Groups I and II, respectively. Twenty-four weeks after cessation of therapy, sustained biochemical response (SBR) was achieved in 28% and 2.8% ($P<0.001$), while sustained virologic response (SVR) was maintained in 2.4% and 0% of the patients in Groups I and II, respectively. In Group I, histopathological examination revealed a decreased activity index by an average score of 1.5 points among 38/62 of the rebiopsied patients. **Conclusion:** Twenty-four weeks N-IFN-BT achieved a fourfold-higher ETBR and a tenfold-higher SBR compared with silymarin therapy, which reflects an improvement of necroinflammatory activity as proven by repeat histopathology.

Effect of interferon on incidence of hepatocellular carcinoma in patients with chronic hepatitis C. Soga K, Shibusaki K, Aoyagi Y. Hepatogastroenterology. 2005 Jul-Aug;52(64):1154-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16001651&query_hl=1

BACKGROUND/AIMS: The aim of this study was to evaluate whether IFN prevents the development of HCC in patients with chronic hepatitis C. **METHODOLOGY:** 103 patients with chronic hepatitis C received IFN and 30 control patients were enrolled in this study. **RESULTS:** In 33 patients (32.0%) who received IFN, alanine aminotransferase (ALT) decreased to normal range and HCV RNA became negative (complete response: CR). In 7 patients (6.7%), ALT decreased to less than 50 IU/L or stayed within the normal range, but HCV RNA remained positive (biochemical response: BR). In 63 patients (61.1%) and 30 control patients, ALT did not change and HCV RNA remained positive (no response: NR). HCC developed in 5 (4.9%) of the 103 patients who received IFN and 7 (23.3%) of the control patients ($p<0.01$). In 5 patients who developed HCC, the response to IFN was NR and no HCC developed in patients with CR or BR. In addition, 5-year cumulative rate of development of HCC in 63 IFN NR patients and in control was 7.9% and 23.3% ($p<0.05$). **CONCLUSIONS:** IFN decreased the development of HCC in not only patients with CR or BR but also patients with NR.

Effect of interferon, ribavirin and ursodeoxycholic acid in patients with hepatitis C infection. Ljubuncic P, et al. Hepatogastroenterology. 2005 Jul-Aug;52(64):1191-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16001659&query_hl=7

BACKGROUND/AIMS: Combination therapy of interferon-alpha (IFNalpha) and the oral nucleoside analog, ribavirin is the standard treatment for individuals suffering from hepatitis C virus (HCV) infection. Several studies have shown combination therapy of IFN and antioxidants is therapeutically beneficial in these patients. Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid possessing antioxidant properties. This study evaluated the clinical outcome and extent of oxidative stress in a group of non-responding and disease-relapsed HCV patients treated with IFNalpha, ribavirin and UDCA (triple therapy) for 6 months. **METHODOLOGY:** Twenty patients with chronic HCV disease were treated with triple therapy for six months. During this period, they were monitored for the presence of HCV RNA, standard serum parameters of liver function and the plasma levels of lipid peroxides (LP) and glutathione (GSH) as indices of oxidative stress. The patients were reassessed six months after completion of treatment. **RESULTS:** During the 6-month treatment period, the health status of the patients improved reflected by falls in the serum activities of alanine and aspartate aminotransferases and gamma-glutamyl transpeptidase and an initial lowering of viral (HCV RNA) load. Six months after cessation of treatment, the patients showed biochemical and virological evidence of disease relapse. The elevated plasma LP levels normalized during the

treatment period and remained within normal levels 6 months after completion of treatment. Plasma GSH levels fluctuated within the normal range over the 12-month observation period. **CONCLUSIONS:** Treatment of individuals with chronic HCV hepatitis with triple therapy comprising IFN α , ribavirin and UDCA improves the health status, as well as lowering the extent of oxidative stress in these individuals. This treatment regimen also resulted in a sustained lowering of plasma lipid peroxide levels in the face of laboratory evidence of disease relapse. This preliminary study is unable to provide an apt explanation for the persistence of normal plasma LP levels in the face of evidence of disease relapse 6 months after completion of treatment. However, we believe these preliminary findings are sufficiently intriguing to warrant further study. Such investigations should include more patients with assessment of the extent of hepatic fibrosis during and after completion of treatment to determine whether this treatment can modify the natural progress of the disease.

Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD)/ribavirin. Ferenci P, et al. J Hepatol. 2005 Jun 27; [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15990196&query_hl=21

BACKGROUND/AIMS: Prediction of sustained virological response (SVR) during treatment would allow clinicians to identify patients most likely to benefit from therapy. **METHODS:** Retrospective analysis of data from 1121 adults with chronic hepatitis C treated for 48 weeks with peginterferon alfa-2a (40KD) 180 μ g/week plus placebo or ribavirin (1000/1200mg/day), or interferon alfa-2b 3 MIU three times/week plus ribavirin in a randomized, multinational, study. **RESULTS:** 67% of patients treated with peginterferon alfa-2a (40KD)/ribavirin with early virological responses (HCV RNA negative or ≥ 2 log₁₀ decrease) at week 12 had SVRs at week 72 (HCV RNA < 50 IU/mL). The negative predictive value (NPV) was 97%. The probability of an SVR increased with the rapidity of HCV RNA suppression. The highest SVR rates were achieved in patients with rapid virological responses at week 4, but the corresponding NPV (74%) is too low for a decision criterion. In patients with early virological responses by week 12, the SVR rate was approximately 20% lower in those who received $< 80\%$ compared with patients who received $\geq 80\%$ of the planned ribavirin dose. **CONCLUSIONS:** Early, sustained suppression of HCV replication portends an SVR. Cessation of treatment may be contemplated in patients without a ≥ 2 log₁₀ reduction in HCV RNA after 12 weeks.

Comprehensive analyses of CD8⁺ T cell responses during longitudinal study of acute human hepatitis C. Cox AL, et al. Hepatology. 2005 Jun 16;42(1):104-112 [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15962289&query_hl=12

We comprehensively studied the cellular immune response during acute human hepatitis C virus (HCV) infection by monthly prospective sampling of persons at high risk of infection. In 19 of 23 subjects, interferon-gamma-secreting T cells specific for 1 or more peptides spanning the entire HCV polyprotein were detected 1 to 3 months after infection. The median time to development of interferon gamma responses to HCV peptides was 33 days (range, 29-50 days), and these responses peaked between 180 and 360 days. Nineteen subjects had sufficient follow-up to determine outcome, with 15 (79%) developing persistent viremia and 4 (21%) clearing viremia spontaneously. Of those with progression to chronic infection and detectable T cell responses, all lost recognition of one or more antigens recognized during acute infection, and the median reduction in the magnitude of responses was 85%. Most significantly, despite ongoing viremia, those who had persistent infection did not develop new epitope specificities after the first 6 months of infection. **In conclusion,** in most individuals, the CD8⁺ T cell responses generated early in HCV infection decline in peripheral blood and are not replaced with new responses.

Optimal dosing frequency of pegylated interferon alfa-2b monotherapy for chronic hepatitis C virus infection. Lurie Y, et al. Clin Gastroenterol Hepatol. 2005 Jun;3(6):610-5.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15952104&query_hl=12

BACKGROUND & AIMS: Pegylated interferon alfa-2b (PEG-IFN- α 2b) has been shown to provide superior efficacy to IFN- α 2b in patients with chronic hepatitis C (predominantly genotype 1) infection as measured by viral clearance. This study was conducted to determine the optimal dosing regimen of PEG-IFN- α 2b required to obtain a maximum decrease of hepatitis C viral RNA. **METHODS:** This was a 24-week, open-label, multicenter, parallel-group, randomized, active-controlled trial in the United Kingdom, France, and Israel. Individuals (n = 61)

with chronic hepatitis C infection, genotype 1, received IFN-alfa 2b 3 mIU 3 times weekly for 24 weeks, or PEG-IFN-alfa 2b 1.5 or 3.0 mug/kg/wk, as total weekly full or split doses, for 12 weeks. At week 12, serum RNA titer was measured, and all PEG-IFN-alfa 2b patients continued with 1.5 mug/kg/wk for a further 12 weeks. Results: Mean serum hepatitis C RNA levels decreased in all groups at weeks 12 and 24. PEG-IFN-alfa 2b 1.5 mug/kg/wk was superior to IFN-alfa 2b in decreasing mean serum hepatitis C RNA ($P < .05$ at week 12). The efficacy of split-dose PEG-IFN-alfa 2b 1.5 or 3.0 mug/kg/wk regimens was not significantly different from full-dose PEG-IFN-alfa 2b 1.5 mug/kg/wk. However, there was a significant decrease in neutrophil count in groups receiving PEG-IFN-alfa 2b 3.0 mug/kg/wk or lower, multiple-dose per week regimens. **CONCLUSIONS:** PEG-IFN-alfa 2b 1.5 mug/kg once weekly is the optimal dosing frequency for patients with chronic hepatitis C with predominantly genotype 1 infection. More frequent dosing or increasing the dose to 3.0 mug/kg/wk did not result in improved antiviral effects, but did decrease neutrophil counts.

Effect of significant histologic steatosis or steatohepatitis on response to antiviral therapy in patients with chronic hepatitis C. Harrison SA, et al. Clin Gastroenterol Hepatol. 2005 Jun;3(6):604-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15952103&query_hl=12

BACKGROUND & AIMS: Treatment of chronic hepatitis C (CHC) results in an average sustained viral response (SVR) rate of 54%-63%. Most previous studies have not separately reported SVR rates for patients who have CHC and concomitant significant hepatic steatosis (>33%) or histologic evidence of steatohepatitis (SH). The aim of this study was to evaluate SVR in patients with CHC plus steatosis or SH on biopsy examination, compared with a group of controls with CHC and no significant steatosis or SH. **METHODS:** Our surgical pathology database and clinical files were queried for CHC between 1997 to 2002. Biopsy specimens with both CHC and significant steatosis (>33%) or SH were categorized as group 1. Of the patients treated with antiviral therapy, information on either SVR (hepatitis C virus [HCV] RNA negative at 6 months posttreatment) or lack of SVR (nonresponse as early as 12 weeks into therapy and relapsers) with either interferon (IFN)/ribavirin or pegylated IFN/ribavirin was found in 84 patients. A control group (group 2) of 231 CHC patients was identified by using a 2-year database (January 2000-June 2001) of patients without evidence of greater than 33% steatosis or SH. Results: The overall SVR was 28% in group 1, compared with 44% for group 2 ($P = .001$). For HCV genotype 1, the SVR was 23% vs 34% for group 2 ($P = .19$). For HCV genotypes 2 and 3, the SVR was 42% vs 78% for groups 1 and 2 ($P = .008$), respectively. **CONCLUSIONS:** Overall SVR for patients with HCV and significant steatosis or SH is considerably lower than for HCV and steatosis less than 33% and no SH.

Gender and liver fibrosis in chronic hepatitis: the role of iron status. Rigamonti C, et al. Aliment Pharmacol Ther. 2005 Jun;21(12):1445-1451.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15948811&query_hl=12

SUMMARY BACKGROUND : The role of gender in the progression of fibrosis in chronic hepatitis C is still under investigation. **AIM:** To investigate whether gender affects the progression of liver disease and/or hides other risk factors. **METHODS:** A prospective series of 121 consecutive patients with chronic hepatitis C underwent liver biopsy. Grading and staging for chronic hepatitis were each evaluated according to Ishak's classification. **RESULTS:** In univariate and multivariate analysis on the whole group of patients, male gender was not associated either with significant liver fibrosis (Ishak's score >2) or with cirrhosis (Ishak's score >4). On the contrary, in univariate analysis on patients aged ≤ 50 years, male gender was nearly significantly ($P = 0.06$) predictive of liver fibrosis, whereas it was not in patients >50 years. Hepatic iron grading, along with age, was an independent factor associated with fibrosis. Moreover, the values of all the variables which describe iron status were significantly higher in males aged ≤ 50 years in comparison with females of the same age. **CONCLUSIONS:** In chronic hepatitis C, male gender may be predictive of liver fibrosis only in patients aged ≤ 50 years. Among fibrogenetic factors hidden by gender, iron status could play a major role.

Comprehensive clinical assessment improves the accuracy of predicting cirrhosis in chronic hepatitis C.

Gordon A, Bailey MJ, et al. J Gastroenterol Hepatol. 2005 Jun;20(6):825-32.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15946128&query_hl=12

ABSTRACT BACKGROUND: The diagnosis of cirrhosis in chronic hepatitis C (CHC) is important but difficult in those who are unable to undergo liver biopsy. Thus, the aims of the present study were to compare separately and in combination, clinical markers of liver disease, the discriminant score (DS) and serum hyaluronic acid (HA) for their ability to predict cirrhosis in CHC. **METHODS:** Two groups of consecutive patients (groups 1 and 2) with CHC were analyzed. Clinical data and routine laboratory results at the time of liver biopsy were collected, and serum HA levels were assayed. A clinical examination score (CES) was constructed using the sum of clinical markers of liver disease in group 1 and was validated in group 2, the DS was calculated, and a serum HA score (HAS) was produced. Combination scores were constructed using the sum of the CES, DS and HAS. Histological analysis of liver biopsies was performed by hepatopathologists blinded to clinical results. **Results:** One hundred and fifty-one patients with CHC (group 1, n = 47; group 2, n = 104) including 27 with cirrhosis were assessed. Serum HA was more accurate than either CES or DS in the prediction of cirrhosis. The combination of CES, DS and HAS enabled the most accurate prediction of cirrhosis with a sensitivity and specificity of 78% and 93%, and a positive predictive value and negative predictive value of 75% and 94%, respectively. **CONCLUSIONS:** A comprehensive clinical assessment utilizing clinical and laboratory data more accurately predicts the presence and absence of cirrhosis in CHC than individual markers.

Risk factors for hepatitis C virus infection in patients on long-term hemodialysis. Khokhar N, Alam AY, Naz F, Mahmud SN. J Coll Physicians Surg Pak. 2005 Jun;15(6):326-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15924834&query_hl=12

OBJECTIVE: To estimate the frequency of hepatitis C virus (HCV) infection in patients on hemodialysis at Shifa International Hospital and determine the association of various risk factors in the acquisition of hepatitis C infection. **Design:** A cross-sectional analytical study. **Place and Duration of Study:** Shifa International Hospital from January 2002 to June 2003. **PATIENTS AND METHODS:** All patients on long-term hemodialysis in Nephrology Unit of Shifa International Hospital were studied. Their medical records were reviewed for the presence of anti-HCV in all patients. Any risk factors were noted from the patient's records and from the history of those patients who were regularly attending the dialysis unit. **Results:** A total of 97 patients on hemodialysis were included. Out of these, 23 (23.7%) were found to be anti-HCV positive. The mean age of HCV positive patients was 55.2+/-15.5 years while for the anti-HCV negative patients it was 54.9+/-15.1 years. There were 18 (78.3%) males in the HCV positive group while 46 (62.2%) males in the HCV negative group. The mean duration of dialysis among HCV positive patients was 2.9+/-2.7 years while the mean duration of dialysis in HCV negative patients was 1.51+/-0.86 years (p-value 0.000). Anti-HCV positive group had significantly greater proportion of patients with a history of dialysis more than 2 years (43.5% vs 9.5%), adjusted odds ratio being 0.45 (95% CI 0.27-0.75). No significant difference in other risk factors between the two groups was found. When years of dialysis were treated as categorical variable, significant difference between the anti-HCV positive and negative groups was found. The risk of getting HCV was found to be significantly associated with increasing years of dialysis, (adjusted p-value 0.002). **CONCLUSION:** Patients on hemodialysis in our unit had 23.7% positivity of anti-HCV and history of dialysis over more than 2 years was noted to be a significant risk factor for acquisition of infection in these patients.

Pilot study of interferon gamma for chronic hepatitis C. Rushbrook SM, et al. J Hepatol. 2005 Jul;43(1):67-71. Epub 2005 Apr 26.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15913831&query_hl=12

BACKGROUND/AIMS: Currently, there are no effective therapies available for patients with chronic hepatitis C who have failed to respond to optimal interferon alfa-based regimens. The aims of this pilot study were to assess the antiviral activity and safety of interferon gamma in chronic hepatitis C. **METHODS:** Patients with chronic hepatitis C, genotype 1, who had not responded to or who had relapsed after therapy with interferon alfa and ribavirin were enrolled in a trial of interferon gamma 1b given in doses of 100, 200 or 400 mug subcutaneously three times weekly for 4 weeks. Frequent blood samples were obtained for HCV RNA levels. **RESULTS:** Fourteen patients were enrolled. Geometric mean HCV RNA levels remained unchanged. Serum aminotransferase levels also did not change, while there were significant decreases in neutrophil counts (-41% from baseline) and hematocrit (-5%). Low grade fever and malaise were common with the first injection of interferon gamma, but no serious side effects were encountered. **CONCLUSIONS:** Although relatively well tolerated, interferon gamma in doses of 100-

400µg thrice weekly had no effect on HCV RNA levels in patients with chronic hepatitis C who had failed to achieve a sustained response to interferon alfa-based therapies.

Systemic autoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC Registry): patterns of clinical and immunological expression in 180 cases. Ramos-Casals M, et al. *J Intern Med.* 2005 Jun;257(6):549-57.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15910559&query_hl=12

OBJECTIVES: To describe the clinical and immunologic characteristics of a large series of patients with systemic autoimmune diseases (SAD) associated with chronic hepatitis C virus (HCV) infection. **METHODS:** We analysed 180 patients diagnosed with SAD and chronic HCV infection seen consecutively at our centres during the last 10 years. The clinical and immunological patterns of disease expression were compared with 180 SAD-matched patients without chronic HCV infection. **RESULTS:** A total of 180 HCV patients fulfilled the classification criteria for the following SAD: Sjogren's syndrome (n = 77), systemic lupus erythematosus (n = 43), rheumatoid arthritis (n = 14), antiphospholipid syndrome (n = 14), polyarteritis nodosa (n = 8) and other SAD (n = 24). One hundred and thirty (72%) patients were female and 50 (28%) male, with a mean age at SAD diagnosis of 50 years. The main immunologic features were antinuclear antibodies in 69% of patients, cryoglobulinaemia in 62%, hypocomplementaemia in 56% and rheumatoid factor (RF) in 56%. Compared with the SAD-matched HCV-negative group, SAD-HCV patients presented a lower prevalence of females (P = 0.016), an older age at SAD diagnosis (P = 0.039) and a higher prevalence of vasculitis (P < 0.001) and neoplasia (P < 0.001). Immunologically, SAD-HCV patients presented a lower prevalence of antinuclear (P = 0.036), anti-extractable nuclear antigen (P = 0.038) and anti-DNA (P = 0.005) antibodies, and a higher frequency of RF (P = 0.003), hypocomplementaemia (P < 0.001) and cryoglobulins (P < 0.001). **CONCLUSIONS:** In comparison with an SAD-matched HCV-negative population, SAD-HCV patients were older and more likely to be male, with a higher frequency of vasculitis, cryoglobulinaemia and neoplasia. This complex pattern of disease expression is generated by a chronic viral infection that induces both liver and autoimmune disease.

Antioxidant levels in peripheral blood, disease activity and fibrotic stage in chronic hepatitis C. Bandara P, George J, McCaughan G, et al. *Liver Int.* 2005 Jun;25(3):518-26.

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed>

BACKGROUND: This study addressed the suggested association between levels of the antioxidants glutathione (GSH), vitamin C and vitamin E in peripheral blood and the histological activity and fibrosis stage in chronic hepatitis C (CHC). We then determined whether regular antioxidant supplementation influenced these antioxidant levels or disease severity. **METHODS:** Clinical, biochemical, histological and demographic data were collected from 247 CHC patients at the time of liver biopsy. Whole blood total GSH, plasma vitamin C and E were assessed by high-performance liquid chromatography. Statistical analyses were performed to test for associations between the variables and to identify independent predictors for hepatic necroinflammatory and fibrosis scores. **RESULTS:** GSH and vitamin C, but not vitamin E correlated with both portal/periportal activity (r=-0.19, P=0.004; r=-0.19, P=0.009 respectively) and fibrosis stage (r=-0.18, P=0.007; r=-0.18, P=0.009 respectively). GSH was an independent negative predictor of portal/periportal inflammation (P=0.02) and fibrosis (P=0.01). Vitamin C was an independent negative predictor of fibrosis stage (P=0.02). Antioxidant intake was associated with higher vitamin C (P<0.0001) and vitamin E (P=0.005) levels, but not GSH. **CONCLUSIONS:** Whole blood GSH and plasma vitamin C are negatively associated with hepatic portal/periportal inflammation and fibrosis stage in CHC. Controlled intervention studies with vitamin C and agents that boost endogenous GSH levels are warranted.

Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. Mangia A, et al. *N Engl J Med.* 2005 Jun 23;352(25):2609-17.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15972867&query_hl=13

BACKGROUND: We hypothesized that in patients with hepatitis C virus (HCV) genotype 2 or 3 in whom HCV RNA is not detectable after 4 weeks of therapy, 12 weeks of treatment is as effective as 24 weeks. **METHODS:** A total of 283 patients were randomly assigned to a standard 24-week regimen of peginterferon alfa-2b at a dose of 1.0 µg per kilogram weekly plus ribavirin at a dose of 1000 mg or 1200 mg daily, on the basis of body weight. Of

these, 70 patients were assigned to the 24-week regimen (standard-duration group) and 213 patients to a variable regimen (variable-duration group) of 12 or 24 weeks, depending on whether tests for HCV RNA were negative or positive at week 4. The primary end point was HCV that was not detectable by polymerase-chain-reaction (PCR) assay 24 weeks after the completion of therapy. **RESULTS:** In the standard-duration group, 45 (64 percent) patients had HCV that was not detectable by PCR assay at week 4, as compared with 133 (62 percent) in the variable-duration group (difference [the rate in the standard-duration group minus that in the variable-duration group], 2 percent; 95 percent confidence interval, -11 to 15 percent). Fifty-three patients (76 percent) in the standard-duration group and 164 patients (77 percent) in the variable-duration group had a sustained virologic response (difference, -1 percent; 95 percent confidence interval, -13 to 10 percent). Fewer patients in the variable-duration group receiving the 12-week regimen had adverse events and withdrew than in the group receiving the 24-week regimen ($P=0.045$). The rate of relapse (defined as HCV not detectable at the end of treatment but detectable at the end of follow-up) was 3.6 percent in the standard-duration group and 8.9 percent in the variable-duration group ($P=0.16$). Overall, the rate of sustained virologic response was 80 percent among patients with HCV genotype 2 and 66 percent among those with genotype 3 ($P<0.001$). **CONCLUSIONS:** A shorter course of therapy over 12 weeks with peginterferon alfa-2b and ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a response to treatment at 4 weeks.

Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD)/ribavirin. Ferenci P, et al. *J Hepatol.* 2005 Jun 27; [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15990196&query_hl=9

BACKGROUND/AIMS: Prediction of sustained virological response (SVR) during treatment would allow clinicians to identify patients most likely to benefit from therapy. **METHODS:** Retrospective analysis of data from 1121 adults with chronic hepatitis C treated for 48 weeks with peginterferon alfa-2a (40KD) 180µg/week plus placebo or ribavirin (1000/1200mg/day), or interferon alfa-2b 3 MIU three times/week plus ribavirin in a randomized, multinational, study. **RESULTS:** 67% of patients treated with peginterferon alfa-2a (40KD)/ribavirin with early virological responses (HCV RNA negative or ≥ 2 log₁₀ decrease) at week 12 had SVRs at week 72 (HCV RNA <50 IU/mL). The negative predictive value (NPV) was 97%. The probability of an SVR increased with the rapidity of HCV RNA suppression. The highest SVR rates were achieved in patients with rapid virological responses at week 4, but the corresponding NPV (74%) is too low for a decision criterion. In patients with early virological responses by week 12, the SVR rate was approximately 20% lower in those who received $<80\%$ compared with patients who received $\geq 80\%$ of the planned ribavirin dose. **CONCLUSIONS:** Early, sustained suppression of HCV replication portends an SVR. Cessation of treatment may be contemplated in patients without ≥ 2 log₁₀ reduction in HCV RNA after 12 weeks.

Influence of metabolic syndrome, viral genotype and antiviral therapy on superimposed fatty liver disease in chronic hepatitis C. Liu CJ, et al. *Antivir Ther.* 2005;10(3):405-15.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15918331&query_hl=12

BACKGROUND/AIMS: The prevalence and clinical implications of non-alcoholic fatty liver disease in patients with chronic hepatitis C remain unknown in Taiwan. **METHODS:** We addressed the relevant issues by analysing 95 naive Taiwanese patients infected with either hepatitis C virus (HCV) genotype 1 ($n = 57$) or 2 ($n = 38$), receiving interferon alone ($n = 41$) or in combination with ribavirin ($n=54$) therapy. A single pathologist scored steatosis and steatohepatitis at baseline and 24 weeks after antiviral treatment. **RESULTS:** At baseline, steatosis and steatohepatitis were present in 44 (46%) and four (4%) patients, respectively. Variables associated with steatosis in logistical regression were hyperglycaemia ($P = 0.01$), hypertriglyceridaemia ($P = 0.004$) and body mass index ≥ 27 ($P = 0.009$), but not HCV genotype or viral load. The grade of steatosis correlated well with the number of metabolic syndrome parameters ($P = 0.018$). Interferon monotherapy, advanced age and HCV genotype 1, but not steatosis, correlated with lower sustained response rate. After treatment, steatosis improved in 19 and worsened in nine, which also did not correlate with HCV genotype ($P = 0.850$) or sustained response to antiviral therapy ($P = 0.246$). **CONCLUSIONS:** Hepatic steatosis in Taiwanese patients with chronic hepatitis C was associated with features of the metabolic syndrome, but did not correlate with HCV genotype, advanced fibrosis or the response to antiviral therapy.

Serum copper and zinc concentrations in patients with chronic hepatitis C. Cesur S, et al. J Infect. 2005 Jul;51(1):35-37.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15979488&query_hl=1

The aim of this study was to measure the alterations in serum trace elements, including zinc and copper in patients with chronic hepatitis C and to compare them with the results of healthy individuals. Seventeen patients with chronic hepatitis C and 17 healthy individuals were included in this study. Serum zinc and copper concentrations were measured by using atomic absorption spectrophotometer of patients with chronic hepatitis C and the results were statistically compared with those of healthy individuals. Serum zinc concentrations were 105.6+/-22.8µg/dl in patients with chronic hepatitis C and 94.41+/-19µg/dl in healthy controls, respectively. Serum copper concentrations were 103.17+/-20.8µg/dl in patients with chronic hepatitis C and 90.8+/-14.3µg/dl in healthy subjects, respectively. Serum zinc and copper concentrations were not found statistically different in patients with chronic hepatitis C compared with those of healthy individuals ($p>0.05$). **In conclusion**, serum trace element concentrations did not show statistical alterations in patients with chronic hepatitis C compared to healthy subjects.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Hepatitis C virus-core and non structural proteins lead to different effects on cellular antioxidant defenses.

Abdalla MY, et al. J Med Virol. 2005 Aug;76(4):489-97.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15977232&query_hl=1

Chronic hepatitis C virus (HCV) infection leads to increased oxidative stress in the liver. Hepatic antioxidant enzymes provide an important line of defense against oxidative injury. To understand the antioxidant responses of hepatocytes to different HCV proteins, we compared changes in antioxidative enzymes in HCV-core and HCV-nonstructural protein expressing hepatocyte cell lines. We found that expression of HCV-core protein in hepatocyte cell lines leads to increased oxidative stress as determined by increased in the oxidant-sensitive probe 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate (CM-DCFH(2)) fluorescence, decreased reduced glutathione (GSH), and increased oxidation of thioredoxin (Trx). Although the expression of HCV-nonstructural (HCV-NS) proteins led to increased oxidative stress as well, the antioxidant enzymatic responses were different. Over-expression of HCV-NS proteins increased antioxidant enzymes (MnSOD and catalase), heme oxygenase-1 (HO-1), and GSH, indicating different mechanism(s) of prooxidative activity than HCV-core protein. **Our findings show** that different HCV proteins induce different antioxidant defense responses in hepatocytes. These findings may facilitate understanding the interaction of different HCV proteins with infected liver cells and help identify possible factors contributing to hepatocyte damage during HCV infection.

A combination of genetic polymorphisms increases the risk of progressive disease in chronic hepatitis C.

Richardson MM, et al. J Med Genet. 2005 Jul;42(7):e45.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15994870&query_hl=1

BACKGROUND: There is increasing interest in the influence of host genetic factors on hepatic fibrosis, and whether genetic markers can reliably identify subjects at risk of developing severe disease. We hypothesised that hepatitis C virus (HCV) infected subjects with progressive fibrosis, classified using strict criteria based on histology at biopsy in addition to disease duration would be more likely to inherit several genetic polymorphisms associated with disease progression compared with subjects with a low rate of disease progression. **METHODS:** We examined polymorphisms in eight genes that have been reported to have an association with hepatic fibrosis. **RESULTS:** Associations between polymorphisms in six genes and more rapidly progressing fibrosis were observed, with individual adjusted odds ratios ranging from 2.1 to 4.5. The relationship between rapidly progressing fibrosis and possession of > or =3, > or =4, or > or =5 progression associated alleles was determined and the adjusted odds ratios increased with increasing number of progression associated alleles (9.1, 15.5, and 24.1, respectively). Using logistic regression analysis, a predictive equation was developed and tested using a second cohort of patients with rapidly progressing fibrosis. The predictive equation correctly classified 80% of patients in this second cohort. **CONCLUSIONS:** This approach may allow determination of a genetic profile predictive of rapid disease progression in HCV and identify patients warranting more aggressive therapeutic management.

T-cell response relative to genotype and ethnicity during antiviral therapy for chronic hepatitis C. Kaplan DE, et al. *Hepatology*. 2005 Jun;41(6):1365-75. PMID: 15915458 [PubMed - in process]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15915458&query_hl=12

Viral genotype and host ethnicity are important predictors of viral clearance during antiviral therapy for chronic hepatitis C virus (HCV) infection. Based on the role of T cells in natural HCV clearance, we hypothesized that T cells may contribute to the genotypic and ethnic difference in treatment outcome. To test this hypothesis, T-cell response to HCV antigens (core, nonstructural NS3/4 and NS5) and control phytohemagglutinin (PHA) was monitored prospectively and was correlated with virological outcome in 41 patients chronically infected with HCV (27 genotype 1, 14 genotype 2 or 3; 19 black persons, 22 white persons) undergoing combined interferon alfa and ribavirin therapy. Interestingly, in patients with genotype 2 or 3 infection, enhanced virological response coincided with a greater T-cell response to HCV NS3/4 antigen at baseline (50% vs. 15%; $P = .026$) that augmented further during therapy (29% vs. 4%; $P = .035$) compared with genotype 1-infected patients. However, HCV-specific T-cell response remained weak in genotype 1-infected patients regardless of virological outcome or ethnicity.

Furthermore, virological outcome was associated with a suppressed baseline proliferative response to phytohemagglutinin ($P < .03$) that increased during therapy ($P < .003$) independent of ethnicity or genotype. **In conclusion**, HCV-specific T-cell response was associated with HCV genotype but not with therapeutic clearance of HCV infection. The association between treatment outcome and phytohemagglutinin response suggests more global and antigen-nonspecific mechanisms for therapeutic HCV clearance.

Regulatory T cells suppress in vitro proliferation of virus-specific CD8+ T cells during persistent hepatitis C virus infection. Rushbrook SM, et al. *J Virol*. 2005 Jun;79(12):7852-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15919939&query_hl=12

The basis of chronic infection following exposure to hepatitis C virus (HCV) infection is unexplained. One factor may be the low frequency and immature phenotype of virus-specific CD8(+) T cells. The role of CD4(+)CD25(+) T regulatory (T(reg)) cells in priming and expanding virus-specific CD8(+) T cells was investigated. Twenty HLA-A2-positive patients with persistent HCV infection and 46 healthy controls were studied. Virus-specific CD8(+) T-cell proliferation and gamma interferon (IFN-gamma) frequency were analyzed with/without depletion of T(reg) cells, using peptides derived from HCV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). CD4(+)CD25(+) T(reg) cells inhibited anti-CD3/CD28 CD8(+) T-cell proliferation and perforin expression. Depletion of CD4(+)CD25(+) T(reg) cells from chronic HCV patients in vitro increased HCV and EBV peptide-driven expansion ($P = 0.0005$ and $P = 0.002$, respectively) and also the number of HCV- and EBV-specific IFN-gamma-expressing CD8(+) T cells. Although stimulated CD8(+) T cells expressed receptors for transforming growth factor beta and interleukin-10, the presence of antibody to transforming growth factor beta and interleukin-10 had no effect on the suppressive effect of CD4(+)CD25(+) regulatory T cells on CD8(+) T-cell proliferation. **In conclusion**, marked CD4(+)CD25(+) regulatory T-cell activity is present in patients with chronic HCV infection, which may contribute to weak HCV-specific CD8(+) T-cell responses and viral persistence.

T cells with a CD4+CD25+ regulatory phenotype suppress in vitro proliferation of virus-specific CD8+ T cells during chronic hepatitis C virus infection. Boettler T, et al. *J Virol*. 2005 Jun;79(12):7860-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15919940&query_hl=12

Chronic hepatitis C virus (HCV) infection is associated with impaired proliferative, cytokine, and cytotoxic effector functions of HCV-specific CD8(+) T cells that probably contribute significantly to viral persistence. Here, we investigated the potential role of T cells with a CD4(+)CD25(+) regulatory phenotype in suppressing virus-specific CD8(+) T-cell proliferation during chronic HCV infection. In vitro depletion studies and coculture experiments revealed that peptide specific proliferation as well as gamma interferon production of HCV-specific CD8(+) T cells were inhibited by CD4(+)CD25(+) T cells. This inhibition was dose dependent, required direct cell-cell contact, and was independent of interleukin-10 and transforming growth factor beta. Interestingly, the T-cell-mediated suppression in chronically HCV-infected patients was not restricted to HCV-specific CD8(+) T cells but also to influenza virus-specific CD8(+) T cells. Importantly, CD4(+)CD25(+) T cells from persons recovered from HCV infection and from healthy blood donors exhibited significantly less suppressor activity. Thus, the inhibition of virus-specific CD8(+) T-cell proliferation was enhanced in chronically HCV-infected patients. This was associated

with a higher frequency of circulating CD4(+)CD25(+) cells observed in this patient group. Taken together, our results suggest that chronic HCV infection leads to the expansion of CD4(+)CD25(+) T cells that are able to suppress CD8(+) T-cell responses to different viral antigens. Our results further suggest that CD4(+)CD25(+) T cells may contribute to viral persistence in chronically HCV-infected patients and may be a target for immunotherapy of chronic hepatitis C.

Serum adiponectin correlates with viral characteristics but not histologic features in patients with chronic hepatitis C. Liu CJ, et al. J Hepatol. 2005 Jun 16; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15964656&query_hl=8

BACKGROUND/AIMS: Adiponectin induces insulin sensitivity and modulates inflammatory responses. We thus studied the implications of adiponectin in patients with chronic hepatitis C virus (HCV) infection inherently linked to insulin resistance. **METHODS:** We analyzed the association of serum adiponectin levels with clinical, virologic, and histologic findings in 95 naive Taiwanese patients with chronic hepatitis C before and after antiviral therapy. **RESULTS:** At baseline, 14 (15%) of the 95 patients were obese and 26 (27%) had type 2 diabetes mellitus. Fifty-seven patients were infected with HCV genotype 1 and 38 with genotype 2. Steatosis and periportal fibrosis was present in 44 (46%) and 69 (73%), respectively. In multivariate analysis, male gender, insulin resistance, high HCV load and genotype 2 were significantly associated with a lower serum adiponectin level. In contrast, intrahepatic gene expression of adiponectin receptors was higher in genotype 2 compared with genotype 1. Serum adiponectin level did not correlate with other clinical or histologic parameters. After treatment, change of steatosis also did not correlate with the change of adiponectin level ($P=0.61$). **CONCLUSIONS:** Adiponectin correlated with hepatitis C viral factors at both serum and liver tissue levels. The interactions among adiponectin, insulin resistance and chronic HCV infection merit further studies.

Inhibition of hepatitis C virus translation and subgenomic replication by siRNAs directed against highly conserved HCV sequence and cellular HCV cofactors. Korf M, et al. J Hepatol. 2005 Jun 16; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15964661&query_hl=8

BACKGROUND/AIMS: Small interfering RNAs (siRNAs) are an efficient tool to specifically inhibit gene expression by RNA interference. Since hepatitis C virus (HCV) replicates in the cytoplasm of liver cells without integration into the host genome, RNA-directed antiviral strategies are likely to successfully block the HCV replication cycle. Additional benefit might arise from inhibition of cellular cofactors of HCV replication, such as proteasome alpha-subunit 7 (PSMA7) or Hu antigen R (HuR). **METHODS:** In this study, we investigated direct and cofactor-mediated inhibition of HCV by a panel of DNA-based retroviral vectors expressing siRNAs against highly conserved HCV sequences or the putative HCV cofactors PSMA7 and HuR. Effects were determined in HCV IRES-mediated translation assays and subgenomic HCV replicon cells. **RESULTS:** PSMA7- and HuR-directed siRNAs successfully inhibited expression of the endogenous genes, and PSMA7 and HuR silencing significantly diminished HCV replicon RNA and NS5B protein levels. HCV-directed siRNAs substantially inhibited HCV IRES-mediated translation and subgenomic HCV replication. Combinations of PSMA7- and HuR-directed siRNAs with HCV-directed siRNAs revealed additive HCV RNA inhibitory effects in monocistronic replicon cells. **CONCLUSIONS:** A dual approach of direct- and cofactor-mediated inhibition of HCV replication might avoid selection of mutants and thereby become a powerful strategy against HCV.

Small Hairpin RNAs Efficiently Inhibit Hepatitis C IRES-Mediated Gene Expression in Human Tissue Culture Cells and a Mouse Model. Wang Q, et al. Mol Ther. 2005 Jun 10; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15953767&query_hl=13

Treatment and prevention of hepatitis C virus (HCV) infections remain a major challenge for controlling this worldwide health problem; existing therapies are only partially effective and no vaccine is currently available. RNA interference offers the potential of a novel therapeutic approach for treating HCV infections. Toward this end, we evaluated small hairpin interfering RNAs (shRNAs) targeting the conserved internal ribosome entry site (IRES) element of the HCV genome for their ability to control gene expression in human cells and animals. We used a reporter gene plasmid in which firefly luciferase (fLuc) expression is dependent on the HCV IRES. Direct delivery of HCV IRES shRNAs efficiently blocked HCV IRES-mediated fLuc expression in transfected human 293FT cells as well as in a mouse model in which nucleic acids were delivered to liver cells by hydrodynamic transfection via

the tail vein. These results indicate that shRNAs, delivered as RNA or expressed from viral or nonviral vectors, may be effective agents for the control of HCV and related viruses.

Prediction of viremia for cases of hepatitis C virus (HCV) infection using a third-generation anti-HCV enzyme immunoassay test. Huang WS, et al. *Hepatology*. 2005 May-Jun;52(6):893-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15966227&query_hl=2

BACKGROUND/AIMS: Positive results for anti-hepatitis C virus (HCV) testing reveal subjects are infected by HCV, with presence of HCV RNA indicating persistent infection. In this study, we attempted to evaluate the validity of the HCV viremia using a commercially available, third-generation anti-HCV test. **METHODOLOGY:** Sample rate/cut-off rate (S/CO) ratios for 1,907 anti-HCV-positive tests (S/CO >1, AxSYM HCV 3.0; Abbott, IL, USA), which had been performed during the last three years, were retrospectively analyzed. Cases with S/CO values between 1 and 100 were divided into 20 groups according to S/CO range (in increments of 10) and ALT (normal or elevated). Ten random cases were obtained for each of the 20 groups. If cases in any group numbered < or =10, all were recruited. Totally, 193 cases were enrolled for HCV RNA detection (COBAS Amplicor; Roche Diagnostics, NJ, USA). **RESULTS:** The S/CO distribution was biphasic, with two S/CO peaks in the ranges 1-10 (10.7%) and 81-90 (24.2%). Regardless of the ALT level, all samples with S/COs < or =10 were negative for HCV RNA. Of the samples with S/CO values >10, the optimal cut-off was 40 with sensitivity and specificity for both of 81%. In conclusion, subjects with S/CO values < or =10 (10.7%) were more likely to be cases of past infection or of non-specific reaction. Most (90%, 108/120) of the subjects with S/COs >40 represent current or persistent infection. To predict viremia in subjects with S/COs between 10 and 40, 6.7% of all anti-HCV-positive subjects was invalid by a cross-sectional observation. **CONCLUSIONS:** Follow-up or further study is recommended. The third-generation EIA test plays a semiquantitative role for the prediction of viremia in HCV infection.

Stable human lymphoblastoid cell lines constitutively expressing hepatitis C virus proteins. Wolk B, et al. *J Gen Virol*. 2005 Jun;86(Pt 6):1737-46. PMID: 15914852 [PubMed - in process]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15914852&query_hl=12

The cellular immune response plays a central role in virus clearance and pathogenesis of liver disease in hepatitis C. The study of hepatitis C virus (HCV)-specific immune responses is limited by currently available cell-culture systems. Here, the establishment and characterization of stable human HLA-A2-positive B-lymphoblastoid x T hybrid cell lines constitutively expressing either the NS3-4A complex or the entire HCV polyprotein are reported. These cell lines, termed T1/NS3-4A and T1/HCVcon, respectively, were maintained in continuous culture for more than 1 year with stable characteristics. HCV structural and non-structural proteins were processed accurately, indicating that the cellular and viral proteolytic machineries are functional in these cell lines. Viral proteins were found in the cytoplasm in dot-like structures when expressed in the context of the HCV polyprotein or in a perinuclear fringe when the NS3-4A complex was expressed alone. T1/NS3-4A and T1/HCVcon cells were lysed efficiently by HCV-specific cytotoxic T lymphocytes from patients with hepatitis C and from human HLA-A2.1 transgenic mice immunized with a liposomal HCV vaccine, indicating that viral proteins are processed endogenously and presented efficiently via the major histocompatibility complex class I pathway. **In conclusion,** these cell lines represent a unique tool to study the cellular immune response, as well as to evaluate novel vaccine and immunotherapeutic strategies against HCV.

HIV/HCV COINFECTION

Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection.

Mocroft A, et al. *AIDS Res Hum Retroviruses*. 2005 Jun;21(6):527-36.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15989457&query_hl=1

Low adherence and toxicities among HIV-positive patients starting highly active antiretroviral therapy (HAART) can lead to discontinuation of therapy and treatment failure. Little is known about hepatitis C (HCV) status and discontinuation of HAART. Poisson regression was used to determine factors related to discontinuation of any part of an initial HAART regimen due to treatment failure (TF) or toxicities and patient/physician choice (TOX), and to investigate the relationship between HCV and discontinuation of a HAART regimen in 1198 patients starting HAART after 1999 from the EuroSIDA study. At 1 year after starting HAART, 70% of patients remained on their original regimen, 24% had changed, and 6% were off all treatment. The most frequent reason for discontinuation was toxicities (30.4%). The incidence of any discontinuation was significantly lower after 1999 compared to before

[incidence rate ratio (IRR) 0.43; 95% CI 0.35-0.53, $p < 0.0001$], this pattern was most marked for toxicities (IRR 0.28; 95% CI 0.20-0.39, $p < 0.0001$) and patient/physician choice (IRR 0.49; 95% CI 0.33-0.73, $p < 0.0001$). Patients with HCV had a higher incidence of discontinuation due to TOX (IRR 1.46, 95% CI 1.13-1.88, $p = 0.0042$) compared to patients without HCV. Patients with HCV were more likely to discontinue all or part of their HAART regimens due to toxicity or patient/physician choice. Managing adverse events must remain a key intervention in maintaining HAART. There is a need for further studies to describe the relationship between HCV, specific antiretrovirals, and different treatment strategies.

Epidemiology of chronic hepatitis C virus in patients infected by human immunodeficiency virus. Study of 767 patients. Rubio Caballero M, et al., *Med Clin (Barc)*. 2005 Jun 11;125(2):56-8. Spanish.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15970184&query_hl=8

BACKGROUND AND OBJECTIVE: To study the epidemiological aspects of hepatitis C virus (HCV) infection in patients co-infected by human immunodeficiency virus (HIV). **PATIENTS AND METHODS:** This study was carried out in 767 HIV infected patients who were followed-up at the HIV/AIDS Unit of the Internal Medicine Department of the Arnau de Vilanova University Hospital of Lleida (Spain). In addition to clinical records and information about the probable contagion route, gender and starting year of intravenous drug use, patients were analyzed for the presence of hepatitis C antibodies, viral load and HCV genotype, alanine aminotransferase concentration, CD4+ lymphocytes and viral load of HIV. The stage of HIV infection was also recorded.

RESULTS: 546 patients (71.18%) had antibodies to HCV, and 499 of them (91.39%) were intravenous drugs users. Of the HCV+ patients, 61 (11.17%) seemed to have cleared the virus spontaneously. Commonest HCV genotype was 1 (52.57%), followed by 3 (25.56%) and 4 (18.76%). In patients with genotype 1, subtype 1a was the more frequent (65.49%) The variation of the genotypes according to the year of contagion showed a progressive increase of genotype- 1 and a progressive decrease of genotype 3. The distribution of patients in the different clinics stages of HIV infection was homogeneous. **CONCLUSIONS:** In our health care area, most HIV+ patients, especially the intravenous drug users, are co- infected with HCV. Commonest genotype was 1 and commonest subtypes was 1a

Detection of Hepatitis C Virus (HCV) in Serum and Peripheral-Blood Mononuclear Cells from HCV-Monoinfected and HIV/HCV-Coinfected Persons. Blackard JT, et al. *J Infect Dis*. 2005 Jul 15;192(2):258-65. Epub 2005 Jun 7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15962220&query_hl=8

It has been speculated that hepatitis C virus (HCV) replicates in peripheral-blood mononuclear cells (PBMCs), which, therefore, may be a site for interaction with human immunodeficiency virus (HIV). We used strand-specific real-time polymerase chain reaction to detect HCV RNA in 28 HCV-monoinfected and 20 HIV/HCV-coinfected women. At the first visit, positive-strand HCV RNA was detected in serum samples from 89% of the women, whereas positive-strand HCV RNA was detected in PBMC samples from 32% and 55% of the HCV-monoinfected and HIV/HCV-coinfected women, respectively. After initiation of antiretroviral therapy, the HIV/HCV-coinfected women were significantly more likely to have detectable positive- and negative-strand HCV RNA in the PBMC compartment than were the HCV-monoinfected women. HIV and HCV RNA levels were not correlated. Serum HCV RNA levels were correlated over time; HCV RNA levels in the serum and PBMC compartments were not.

These data suggest differential regulation of HCV RNA in the serum and PBMC compartments and may partially explain the limited HCV antiviral response rates observed in coinfecting persons.

Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. Salmon-Ceron D, et al. *J Hepatol*. 2005 Jun;42(6):799-805.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15973779&query_hl=1

BACKGROUND/AIMS: We analyzed the characteristics of HIV infected patients who died from liver disease, focusing on hepatitis virus co-infection. **METHODS:** One-hundred and eighty-five French hospital departments involved in HIV/AIDS management prospectively notified all deaths occurring in 2000. Patients whose hepatitis C (HCV) and hepatitis B (HBV) serostatus was known were classified as being infected by HCV alone, HBV alone (HBsAg positive), both HCV and HBV, or neither HCV nor HBV. **RESULTS:** Among 822 HIV infected patients, 29% were infected by HCV alone, 8% by HBV alone, and 4% by both HCV and HBV. The most frequent causes of death were liver disease (31% of cases) and AIDS (29%) among HIV-HCV co-infected patients, and AIDS (38%) and liver disease (22%) among HIV-HBV co-infected patients. Liver disease was a more frequent cause of death among patients co-infected by both HCV and HBV (44% of cases). Hepatocellular carcinoma was present in 15%

of patients who died from liver disease, and was associated with HBV co-infection. Nearly half the patients who died from liver disease had more than 200 CD4/mm³. **CONCLUSIONS:** Liver disease is now a leading cause of death among HIV-HCV co-infected patients and is becoming an important cause of death among HIV-HBV co-infected patients. The risk of death from liver disease is highest in patients co-infected by both HCV and HBV.

Incidence and risk factors for mitochondrial toxicity in treated HIV/HCV-coinfected patients. Laguno M, et al. *Antivir Ther.* 2005;10(3):423-9. PMID: 15918333 [PubMed - indexed for MEDLINE]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15918333&query_hl=12

BACKGROUND: Coinfection with hepatitis C virus (HCV) and HIV is not uncommon and therapies for both infections are currently available. A major drawback, however, could be a potentially higher risk for mitochondrial toxicity (MT), defined as the elevation of pancreatic enzymes or lactate levels due to the nucleoside analogue reverse transcriptase inhibitors contained in both therapies. **METHODS:** Prospective analyses of clinical and laboratory data, including plasma lactate levels and pancreatic enzymes, of 113 consecutive HIV/HCV-coinfected patients were assigned to receive ribavirin (RBV) plus interferon (IFN)-alpha. **RESULTS:** Fourteen patients (12%) showed increased levels of amylase/lipase and/or hyperlactataemia. No patient developed clinical pancreatitis. Four patients with hyperlactataemia had clinical symptoms of lactic acidosis and recovered uneventfully by 2 weeks after treatment withdrawal. The variables significantly associated with MT in the univariate analysis were: therapy with didanosine (ddl), ddl plus stavudine (d4T), previous history of diabetes and the baseline lactate level. However, ddl use was the only independent risk factor for MT identified in the multivariate analysis. MT was not associated with gender, age, alcohol consumption, type of IFN, degree of steatosis and fibrosis in liver biopsy, presence of lipodystrophy, CD4+ cell count, HCV or HIV viral load, mitochondrial DNA and COXII-expression in liver tissue, or antiretroviral therapy containing d4T or protease inhibitors. **CONCLUSIONS:** 12% of HIV/HCV-coinfected patients receiving IFN plus RBV concomitantly with highly active antiretroviral therapy developed laboratory markers of MT. Although most of cases were asymptomatic, our study suggests that concomitant use of RBV plus ddl should be avoided, and that routine monitoring of lactate and pancreatic enzymes may be recommended.

Continuous release of hepatitis C virus (HCV) by peripheral blood mononuclear cells and B-lymphoblastoid cell-line cultures derived from HCV-infected patients. Bare P, et al. *J Gen Virol.* 2005 Jun;86(Pt 6):1717-27. PMID: 15914850 [PubMed - in process]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15914850&query_hl=5

In order to investigate hepatitis C virus (HCV) persistence and replication in peripheral blood mononuclear cells (PBMC) from a group of haemophilic individuals, HCV production and release to PBMC culture supernatants (SNs) from HCV singly infected patients and HIV/HCV co-infected patients was studied. HCV RNA+ SNs were found more frequently from HIV/HCV co-infected individuals (89.5 %) with poor reconstitution of their immune status than from singly HCV-infected patients (57 %) or from HIV/HCV co-infected individuals with a good response to highly active anti-retroviral therapy (50 %). The presence of the HCV genome in culture SNs was associated with lower CD4+ T-cell counts and with a more severe clinical picture of HIV infection. In spite of prolonged negative HCV viraemia, PBMC from HIV/HCV co-infected patients released the HCV genome after culture. HCV permissive PBMC allowed generation of HCV productive B cell lines with continuous HCV replication. **These findings** add further weight to the involvement of PBMCs in persistence of HCV infection and emphasize the role of B lymphocytes as HCV reservoirs.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Effects of a new pharmacological complex (silybin+vitamin E+phospholipids) on some markers of metabolic syndrome and of a liver fibrosis in patients with non-alcoholic fatty liver disease: a preliminary open pilot study. Trappoliere M, et al. *Gastroenterol Dietol.* 2005 Jun;51(2):193-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15990709&query_hl=9

AIM: This open preliminary pilot study was aimed to evaluate the effect of a new pharmaceutical complex (silybin+vitamin E+phospholipids - RealSIL-IBI-Lorenzini Pharmaceutical, Italy) on some parameters of metabolic syndrome and of liver fibrosis in patients with non alcoholic fatty liver disease (NAFLD) with or without the contemporaneous presence of hepatitis C virus (HCV)-related chronic hepatitis. **METHODS:** Eighty five patients were consecutively enrolled in the study and divided in 2 groups; the first group was represented by 59

patients affected by NAFLD, negative for other known causes of chronic liver damage (M/F= 39/20; median age and range: 44 years, 22-76, group A); the second group was represented by 26 patients (M/F=19/7; median age and range 51 years, 20-75, group B) with HCV-related chronic hepatitis associated to NAFLD. Adverse events and drop-outs were absent in all group and compliance at the study was absolute. **RESULTS:** This open preliminary study shows that the new compound silybin+vitamin E+ phospholipids is active, in vivo, and produces some therapeutic effects in patients with different forms of chronic liver damage. In particular, it improves insulin resistance and plasma levels of markers of liver fibrosis in patients in whom these parameters are particularly altered. **CONCLUSIONS:** Our data have a role of suggestion to further evaluate, through a controlled trial, a possible therapeutic use of this new compound in the management of patients with NAFLD.

Inhibition effect of Chinese herbal medicine on transcription of hepatitis C virus structural gene in vitro.

Dou J, Chen Q, Wang J. World J Gastroenterol. 2005 Jun 21;11(23):3619-22.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15962388&query_hl=12

AIM: To investigate the inhibitory effect of Chinese herbal medicine on the transcription of hepatitis C virus (HCV) structural gene in Hela D cells. **METHODS:** Hela cell line was transfected with recombinant pBK-CMV-HCV containing HCV structural gene by Lipofec-tamine. RT-nested-PCR and Western blot assay were used to testify the HCV gene expression in Hela cells. The Hela cells expressing HCV structural protein were named Hela D cells. Prescriptions of Xiao chaihu Decoction (XCHD), Fufang Huangqi (FFHQ) and Bingganling (BGL) were respectively added to Hela D cells in various concentrations. Semi-quantitative RT-nested-PCR product analysis was performed according to the fluorescent density between HCV DNA band and GAPDH DNA band in gel electrophoresis after screened. **RESULTS:** Recombinant pBK-CMV-HCV could correctly express the HCV structural gene in Hela D cells. After co-culture of Hela D cells with three prescriptive different concentrations for 48 h respectively, the transcription of HCV gene decreased with increasing of the concentration of each prescription. The lightness ratio of HCV product bands to GAPDH product bands was 0.24, 0.10 and 0.12 in Hela D cells incubated with 0.1 g/mL of XCHD, FFHQ and BGL respectively and the lightness ratio HCV product bands to GAPDH product bands was 0.75, 0.67 and 0.61 respectively in the control cells. **CONCLUSION:** The prescriptions of XCHD, FFHQ and BGL partly inhibit the transcription of HCV structural gene in Hela D cells.

Herbal medicine Ninjinyoeito ameliorates ribavirin-induced anemia in chronic hepatitis C: A randomized controlled trial.

Motoo Y, et al. World J Gastroenterol. 2005 Jul 14;11(26):4013-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15996025&query_hl=1

AIM: Ribavirin (RBV) shows a strong antiviral effect on hepatitis C virus when used in combination with interferon. However, RBV-induced anemia is a major problem in this therapy. It would be of great clinical importance to ameliorate the anemia without reducing the RBV dose. We report here that, Ninjinyoeito (NYT), a herbal medicine can reduce the RBV-induced anemia. **METHODS:** Twenty-three patients with chronic hepatitis C were treated with interferon alpha 2b plus RBV with (NYT group) or without (control group) NYT by a randomized selection. Eighteen patients completed the treatment schedule, and hemato-biochemical and virological effects were evaluated. **RESULTS:** There was no significant difference in biochemical and virological responses between the two groups. However, anemia was significantly reduced in the NYT group compared with the control group. The maximal decrease of Hb in the NYT group (2.59+/-1.10 g/dL) was significantly (P = 0.026) smaller than that in the control group (3.71+/-0.97 g/dL). There was no significant difference in serum glutathione peroxidase activity, serum RBV concentration, and Th1/Th2 balance between the two groups. There was no specific adverse effect in NYT administration. **CONCLUSION:** These results suggest that NYT could be used as a supportive remedy to reduce the RBV-induced anemia in the treatment of chronic hepatitis C.

MISCELLANEOUS WORKS

Evolution over a 10 year period of the epidemiological profile of 1,726 newly diagnosed HCV patients in Belgium.

Gerard C, et al. J Med Virol. 2005 Aug;76(4):503-10.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15977247&query_hl=1

In order to evaluate the future burden of hepatitis C, there is a need to quantify the evolution with time of some crucial parameters such as disease frequency and age, modes of infection and infecting genotypes of patients presenting for the first time at consultation. The yearly evolution of these parameters was analyzed retrospectively

in a cohort of 1,726 patients living in Belgium, who were diagnosed as hepatitis C virus (HCV) carriers by polymerase chain reaction (PCR) between 1992 and 2002. The epidemiological profile of HCV patients showed significant changes during this period. The number of new patients increased with time. The proportion of patients under 50 increased linearly at a rate of 3% per year. The rate of newly presenting patients infected by transfusion before 1990 decreased, but only by 2.7% per year. The proportion of intravenous (IV) drug users increased by 2.5% per year. Patients presenting "undefined" risk factors increased by 2.1% per year. Nosocomial acquisition of HCV infection exhibited a disturbing relative stability in time whereas dialysis tended to disappear as a cause of infection. There was a significant linear annual decrease of 2.3% in the frequency of genotype 1b, which was counterbalanced by a significant increase of 0.7% for genotype 1a and 1.1% for genotype 4. Genotypes 2 and 3 did not vary significantly with time. Such figures are useful for evaluating the epidemiological changes of C virus infection and for anticipating the future economical cost of hepatitis C treatment in the next few years.

Knowledge of hepatitis among active drug injectors at a syringe exchange program. Carey J, et al. *J Subst Abuse Treat.* 2005 Jul;29(1):47-53.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15979531&query_hl=1

Injecting drug users (IDUs) are at high risk for contracting and spreading viral hepatitis through nonsterile injection practices, unprotected sexual contact, and unsanitary living conditions. We sought to characterize hepatitis knowledge, prior testing, and vaccination history among IDUs at a New York City syringe exchange program (SEP). IDU subjects generally had a poor understanding of viral hepatitis transmission and prevention. We also found low vaccination rates: only 8% reported receiving hepatitis A vaccine and 11%, hepatitis B vaccine. Educating IDUs about risky behaviors and medical preventive interventions, such as vaccines for hepatitis A and B and treatment for hepatitis C, may help prevent disease and reduce transmission. Stronger linkages between health-care centers and SEPs, drug treatment programs, and other service delivery centers where IDUs are encountered may promote hepatitis education and vaccination.

Hepatitis C virus infection among prisoners in the California state correctional system. Fox RK, et al. *Clin Infect Dis.* 2005 Jul 15;41(2):177-86.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15983913&query_hl=1

BACKGROUND: Incarcerated populations are at high risk for hepatitis C virus (HCV) infection, yet prisoners are not routinely screened or treated for HCV infection. Understanding the risk factors of HCV infection among prisoners could help improve HCV interventions. **METHODS:** Prevalence and risk of HCV infection among 469 prisoners entering California State correctional facilities were assessed using HCV antibody screening, HCV RNA measurement, and structured interviews. Multivariate logistic regression analysis was used to identify independent correlates of HCV infection. **RESULTS:** The prevalence of HCV infection was 34.3% overall (95% confidence interval [CI], 30%-38%) and was 65.7% among those with a history of injection drug use (IDU), compared with 10.2% among those with no history of IDU (odds ratio [OR], 17.24; 95% CI, 10.52-28.25). Significant differences in HCV antibody positivity were found in association with age at first detention but not with the nature of the crime. Independent correlates of HCV infection included age, history of IDU, cumulative time of incarceration, biological sex (OR for females subjects compared with males subjects, 0.35; 95% CI, 0.13-0.96), and a history of having sex with a male IDU (OR, 4.42; 95% CI, 1.46-13.37). We identified significant differences in risk factors between male and female subjects--notably, that the risk of HCV infection was significantly elevated among female non-IDUs who reported having sexual partners with a history of IDU. Among non-IDUs, correlates of HCV infection included history of receipt of blood products and cumulative years of incarceration. **CONCLUSIONS:** HCV infection is pervasive among the California prison population, including prisoners who are non-IDUs and women with high-risk sexual behavior. These results should promote consideration of routine HCV antibody screening and behavioral interventions among incarcerated men and women.

Changing of hepatitis C virus genotype patterns in France at the beginning of the third millenium: The GEMHEP GenoCII Study. Payan C, et al. *J Viral Hepat.* 2005 Jul;12(4):405-13.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15985012&query_hl=1

This cross-sectional study aimed to investigate, during a short period between 2000 and 2001, in a large population of patients with chronic hepatitis C, the epidemiological characteristics of hepatitis C virus (HCV) genotypes in

France. Data from 26 referral centres, corresponding to 1769 patients with chronic hepatitis C were collected consecutively during a 6-month period. HCV genotyping in the 5'-non-coding region (NCR) was performed in each center using the line probe assay (LiPA, in 63% of cases), sequencing (25%) or primer-specific polymerase chain reaction (PCR) (12%). HCV genotypes 1a, 1b, 2, 3, 4, 5, non-subtyped 1 and mixed infection were found in 18, 27, 9, 21, 9, 3, 11 and 1% of our population, respectively. HCV genotype distribution was associated with gender, age, source and duration of infection, alanine aminotransferase (ALT) levels, cirrhosis, alcohol consumption, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfection. In multivariate analysis, only the source of infection was the independent factor significantly associated with genotype ($P = 0.0001$). **In conclusion**, this study shows a changing pattern of HCV genotypes in France, with i.v. drug abuse as the major risk factor, an increase of genotype 4, and to a lesser extent 1a and 5, and a decrease of genotypes 1b and 2. The modification of the HCV genotype pattern in France in the next 10 years may require new therapeutic strategies, and further survey studies.

Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. Lok AS, et al. *Hepatology*. 2005 Jun 28; [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15986415&query_hl=1

Knowledge of the presence of cirrhosis is important for the management of patients with chronic hepatitis C (CHC). Most models for predicting cirrhosis were derived from small numbers of patients and included subjective variables or laboratory tests that are not readily available. The aim of this study was to develop a predictive model of cirrhosis in patients with CHC based on standard laboratory tests. Data from 1,141 CHC patients including 429 with cirrhosis were analyzed. All biopsies were read by a panel of pathologists (blinded to clinical features), and fibrosis stage was determined by consensus. The cohort was divided into a training set ($n = 783$) and a validation set ($n = 358$). Variables that were significantly different between patients with and without cirrhosis in univariate analysis were entered into logistic regression models, and the performance of each model was compared. The area under the receiver-operating characteristic curve of the final model comprising platelet count, AST/ALT ratio, and INR in the training and validation sets was 0.78 and 0.81, respectively. A cutoff of less than 0.2 to exclude cirrhosis would misclassify only 7.8% of patients with cirrhosis, while a cutoff of greater than 0.5 to confirm cirrhosis would misclassify 14.8% of patients without cirrhosis. The model performed equally well in fragmented and nonfragmented biopsies and in biopsies of varying lengths. Use of this model might obviate the requirement for a liver biopsy in 50% of patients with CHC. **In conclusion**, a model based on standard laboratory test results can be used to predict histological cirrhosis with a high degree of accuracy in 50% of patients with CHC.

Cost-effectiveness of interferon {alpha} or peginterferon {alpha} with ribavirin for histologically mild chronic hepatitis C. Grieve R, et al. *Gut*. 2005 Jun 30; [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15994216&query_hl=1

BACKGROUND: For patients with mild chronic hepatitis C the cost-effectiveness of antiviral therapy is unknown. **AIMS:** To assess whether anti-viral therapy (either interferon alpha or peginterferon alpha combined with ribavirin) is cost-effective at a mild stage compared to waiting and only treating those cases who progress to moderate disease. **PATIENTS:** Cases with mild chronic hepatitis C. **METHODS:** A cost-effectiveness model estimates long- term costs and outcomes for patients with mild chronic hepatitis C. The model uses effectiveness and cost data from the UK mild hepatitis C RCT, combined with estimates of disease progression and cost from observational studies. **RESULTS:** For patients with genotype non-1 antiviral treatment at a mild rather than a moderate stage improved outcomes measured by Quality Adjusted Life Years (QALYs) gained. The mean cost per QALY gained from antiviral treatment with interferon alpha-2b and ribavirin, compared to no treatment, was pound5,285 (\$8,284). For these patients treatment at a mild stage with peginterferon alpha-2b and ribavirin rather than interferon alpha-2b and ribavirin, led to further additional QALYS; the average cost per QALY gained was pound21,155 (\$33,158). For patients with genotype 1, interferon alpha-2b and ribavirin treatment for mild disease only led to a sustained virological response (SVR) for 18% of cases and was not cost-effective. **CONCLUSIONS:** For patients with chronic hepatitis C and genotype non-1, antiviral treatment compared to no treatment at a mild stage, is cost-effective. For patients with genotype 1, antiviral therapy at a mild disease stage is not cost-effective.

Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Lackner C, et al. *Hepatology*. 2005 Jun;41(6):1376-82.PMID: 15915455 [PubMed - in process]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15915455&query_hl=1

[query_hl=12](#)

Liver biopsy is recommended before antiviral treatment, particularly for patients with hepatitis C virus (HCV) genotype 1 infection, but it may cause complications and is limited by sampling error. Several non-invasive tests comprising routine laboratory parameters (simple fibrosis tests) have been proposed to predict fibrosis in chronic HCV. The aim of the current study was to validate and compare the diagnostic accuracies of the simple fibrosis tests, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR), cirrhosis discriminant score (CDS), age-platelet (AP) index, Pohl score, AST-to-platelet ratio index (APRI), and platelet count per se. Staging was performed in liver biopsy specimens of 194 treatment-naïve patients with chronic HCV according to Ishak et al. by two independent pathologists. Receiver operating characteristic curve analysis showed comparable diagnostic accuracies of CDS, AP index, APRI, and platelet count for prediction of significant fibrosis (F3-F6) (area under the ROC curve [AUROC], 0.71, 0.74, 0.80, and 0.71, respectively; pathologist A) and for prediction of cirrhosis (F5-F6) (AUROC, 0.91, 0.91, 0.90, and 0.89, respectively; pathologist A). Diagnostic accuracy of APRI for prediction of significant fibrosis was superior to that of AAR ($P < .05$). Significant fibrosis was reliably predicted by $APRI > \text{or} = 1.5$ and platelet count $< 150 \times 10^9/L$ in 24% and 22% of the patients, respectively, whereas cirrhosis was reliably excluded by $APRI < 2.0$ and platelet count $> \text{or} = 150 \times 10^9/L$ in 85% and 78% of the patients, respectively. **In conclusion**, simple fibrosis tests may render liver biopsy unnecessary only in a minority of patients with chronic HCV. Improved serum fibrosis markers with greater sensitivity for severe fibrosis or cirrhosis are needed.

Comparison of Qualitative (COBAS AMPLICOR HCV 2.0 versus VERSANT HCV RNA) and Quantitative (COBAS AMPLICOR HCV Monitor 2.0 versus VERSANT HCV RNA 3.0) Assays for Hepatitis C Virus (HCV) RNA Detection and Quantification: Impact on Diagnosis and Treatment of HCV Infections.

Desombere I, et al. J Clin Microbiol. 2005 Jun;43(6):2590-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15956369&query_hl=12

Quantitative measurements of serum hepatitis C virus (HCV) RNA are becoming increasingly important in the management of HCV-infected patients. Here we compared two quantitative assays, the COBAS AMPLICOR HCV Monitor 2.0 assay (Roche Diagnostics) and the branched DNA-based VERSANT HCV RNA 3.0 assay (Bayer Diagnostics) for HCV RNA measurement in 344 samples derived from 120 patients with chronic genotype 1 HCV infection. The overall concordance between the results of the two tests was 95%, and the HCV RNA titers within the dynamic ranges of the assays correlated very well ($r(2) = 0.86$). Furthermore, both tests performed equally well in determining an early viral response at week 1 or 4 during antiviral therapy. We also compared two qualitative HCV RNA detection assays: the COBAS AMPLICOR HCV 2.0 assay versus the transcription-mediated amplification (TMA)-based VERSANT HCV RNA qualitative assay. Stored samples from sustained responders to interferon-ribavirin therapy were retested by the HCV TMA assay and were found to contain no detectable HCV RNA, demonstrating complete concordance between the results of PCR and TMA. However, HCV RNA was detected by the TMA assay in end-of-treatment (ETR) samples from 33% of patients with relapses who were HCV RNA negative according to the COBAS AMPLICOR assay. This observation suggests that a TMA assay can lead to a more correct definition of the ETR response.

Prediction of viremia for cases of hepatitis C virus (HCV) infection using a third-generation anti-HCV enzyme immunoassay test. Huang WS, et al. Hepatogastroenterology. 2005 May-Jun;52(63):893-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15966227&query_hl=8

BACKGROUND/AIMS: Positive results for anti-hepatitis C virus (HCV) testing reveal subjects are infected by HCV, with presence of HCV RNA indicating persistent infection. In this study, we attempted to evaluate the validity of the HCV viremia using a commercially available, third-generation anti-HCV test. **METHODOLOGY:** Sample rate/cut-off rate (S/CO) ratios for 1,907 anti-HCV-positive tests ($S/CO > 1$, AxSYM HCV 3.0; Abbott, IL, USA), which had been performed during the last three years, were retrospectively analyzed. Cases with S/CO values between 1 and 100 were divided into 20 groups according to S/CO range (in increments of 10) and ALT (normal or elevated). Ten random cases were obtained for each of the 20 groups. If cases in any group numbered $< \text{or} = 10$, all were recruited. Totally, 193 cases were enrolled for HCV RNA detection (COBAS Amplicor; Roche Diagnostics, NJ, USA). **RESULTS:** The S/CO distribution was biphasic, with two S/CO peaks in the ranges 1-10 (10.7%) and 81-90 (24.2%). Regardless of the ALT level, all samples with S/COs $< \text{or} = 10$ were negative for HCV RNA. Of the samples with S/CO values > 10 , the optimal cut-off was 40 with sensitivity and specificity for both of

81%. In conclusion, subjects with S/CO values ≤ 10 (10.7%) were more likely to be cases of past infection or of non-specific reaction. Most (90%, 108/120) of the subjects with S/COs >40 represent current or persistent infection. To predict viremia in subjects with S/COs between 10 and 40, 6.7% of all anti-HCV-positive subjects was invalid by a cross-sectional observation. **CONCLUSIONS:** Follow-up or further study is recommended. The third-generation EIA test plays a semiquantitative role for the prediction of viremia in HCV infection.

Cancer history and other personal factors affect quality of life in patients with Hepatitis C.

Olson SH, et al. Qual Life Outcomes. 2005 Jun 16;3(1):39 [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15960844&query_hl=13

BACKGROUND: Although patients with chronic hepatitis C (CHC) have been found to have reduced quality of life, little is known about how other characteristics affect their quality of life. The purpose of this study was to investigate the effect of other characteristics, including history of cancer, on quality of life in patients with CHC. **METHODS:** One hundred forty patients from clinics at three hospitals in New York City completed a detailed epidemiologic interview about demographic and lifestyle characteristics and the SF-36 measuring health-related quality of life. We compared results from our patients to normative data using t-tests of differences between means. We used multivariate analyses to determine other personal and health-related factors associated with quality of life outcomes. **RESULTS:** Compared to normative data, these patients had reduced quality of life, particularly on physical functioning. The summary Physical Component Score (PCS) was 45.4 ± 10.6 and the Mental Component Score (MCS) was 48.2 ± 11.1 , vs norms of 50 ± 10.0 ; p-values were <0.0001 and <0.05 , respectively. In multivariate analyses, the PCS was significantly lower among those with cancer history, [greater than or equal to] 2 other chronic conditions, less education, low physical activity, and higher alanine aminotransferase (ALT) levels. Cancer was more important for men, while other chronic conditions and depression were more important for women. On the MCS, history of depression, low physical activity, alcohol use, and female gender were independently associated with poorer scores. **CONCLUSIONS:** Several health and lifestyle factors independently influence quality of life in CHC patients. Different factors are important for men and women.

Hepatitis C and health-related quality of life among patients with hemophilia. Posthouwer D, et al.

Haematologica. 2005 Jun;90(6):846-50.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15951299&query_hl=12

Hepatitis C has a negative effect on health-related quality of life (HRQoL). It is not clear whether hepatitis C affects HRQoL of patients with hemophilia. The objective of this study was to assess the effect of hepatitis C virus (HCV) infection on HRQoL in patients with hemophilia. A cross-sectional study was performed among all registered hemophilia patients in the Netherlands. HRQoL was determined by using the self-administered SF-36 questionnaire. Patients were eligible for the study if they completed the SF-36, had been treated with clotting factor products before 1992, and had reported their hepatitis C status. Data on the severity of hemophilia were obtained from the hemophilia treatment centers. The validity of the self-reported data on hepatitis C status was verified in a random sample of 92 (15%) patients; 92% reported their hepatitis C status correctly. Fifty-five percent (333/602) of the study population had a current HCV infection. All eight domains of the SF-36 were lower in patients with a current HCV infection than they were in patients who had never been infected with HCV. After adjustment for age, severity of hemophilia, human immunodeficiency virus (HIV) status, employment status, and joint limitations, hepatitis C infection was associated with a decrease of HRQoL on the domains of general health (difference 6.9 [95% confidence interval (C.I.) 2.7 to 11.2]) and vitality (3.8 [95% C.I. 0.1 to 7.7]). Hemophilia patients infected with HCV scored lower on the HRQoL domains of general health and vitality than hemophilia patients who had never been infected with HCV.

Medical students' knowledge of sharps injuries. Elliott SK, Keeton A, Holt A., Clinical Microbiology, J Hosp Infect. 2005 Jun 1; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15936114&query_hl=12

Healthcare workers (HCWs) including medical students are at risk of occupational exposure to blood-borne viruses following sharps incidents including needlestick injuries. The recent Department of Health guidelines recommend that all HCWs entering a career involving exposure-prone procedures should be tested for hepatitis C, making preventative strategies even more relevant. A survey of current medical students' knowledge regarding prevention of sharps injuries in Birmingham, UK was carried out to determine their awareness of these risks and to compare the findings with an earlier cohort of students. Two hundred and fifty-six medical students were enrolled into the study. Their knowledge of needlestick injury, prevention and management had significantly improved compared

with the previous study. This demonstrates that intensive teaching and self-learning programmes can improve the knowledge of HCWs and reduce the number of needlestick injuries.

Results of a hepatitis C general transfusion lookback program for patients who received blood products before July 1992. Williams JL, et al. *Transfusion*. 2005 Jun;45(6):1020-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15935002&query_hl=12

BACKGROUND: The Centers for Disease Control and Prevention recommend hepatitis C virus (HCV) antibody (anti-HCV) screening for persons who received blood products before July 1992. A general transfusion lookback program was implemented to identify, counsel, and screen persons who received transfusions at the Alaska Native Medical Center between January 1980 and July 1992. **STUDY DESIGN AND METHODS:** Hard-copy transfusion records data were entered, and available databases were queried to identify deceased patients and the mailing address of those living. Patients were notified by letter of their HCV risk and encouraged to seek counseling and testing. Serum samples were screened for anti-HCV and HCV RNA, and program costs were estimated. **RESULTS:** Overall, 3169 transfusion recipients were identified, with 1356 (43%) living and targeted for notification. Of 764 patients notified and screened by this program, 41 (5%) were anti-HCV-positive and 19 (2%) were HCV RNA-positive. There was a higher probability of detecting anti-HCV with each subsequent increase of a transfusion event. Among 298 lookback patients, 33 percent were unaware of having received a blood transfusion. The estimated cost per person sent notification was US\$57 and to detect an anti-HCV-positive case it was US\$3146. **CONCLUSION:** This general transfusion lookback program successfully notified and screened patients at a reasonable cost. Further investigation would be helpful in determining the role these programs or other measures could play in promoting HCV screening in persons receiving transfusions before July 1992, especially among those who are unaware of their transfusion history.