

HEPATITIS C CARING AMBASSADORS PROGRAM NEWSLETTER

September 2005



IN THE NEWS.....	1
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES.....	11
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES.....	17
HIV/HCV COINFECTION.....	25
COMPLEMENTARY & ALTERNATIVE THERAPIES.....	29
MISCELLANEOUS WORKS.....	30

IN THE NEWS

AVI BioPharma Initiates Hepatitis C Clinical Trial

http://home.businesswire.com/portal/site/google/index.jsp?ndmViewId=news_view&newsId=20050928005211&newsLang=en

AVI BioPharma, Inc. today announced the initiation of an exploratory safety and efficacy clinical trial using its proprietary NEUGENE(R) antisense compound AVI-4065. The multicenter study will assess the safety, tolerability, pharmacokinetics and viral response to daily subcutaneous administration of AVI-4065 among healthy volunteers and patients with chronic active hepatitis C virus (HCV).

"There is a large, unmet medical need for effective HCV treatments, as the current treatment regimen is successful in less than half of the patients infected with genotype 1 HCV, the most common form of the virus in the U.S.," said Denis R. Burger, Ph.D., chief executive officer of AVI. "In addition, the de facto treatment regimen of nonspecific antivirals pegylated interferon and ribavirin is expensive, has a plethora of side effects, and is not well tolerated by many patients. The ability of our NEUGENE antisense to specifically target the HCV virus may offer a safer and more efficacious drug for patients."

The multicenter clinical trial will include 80 subjects: 40 healthy adult volunteers in the first phase of the study and 40 patients with chronic active HCV in the second phase. In the first phase, up to four dosage levels will be evaluated to confirm the safety of desired serum drug levels. In the second phase, 40 patients with chronic active HCV will be enrolled, including patients who are drug-naive and patients who have failed conventional interferon and ribavirin treatment. This phase of the trial will assess the safety, tolerability, pharmacokinetics, biological responses and HCV virological effects of AVI-4065 over a minimum of 14 days of treatment. Patients will be monitored following treatment to assess a sustained HCV virological response to AVI-4065.

Mark Holodniy, M.D., F.A.C.P., professor of medicine at Stanford University School of Medicine and director of the Department of Veterans Affairs Public Health Research & Consultation Program located at the Veterans Affairs Palo Alto Health Care System in Palo Alto, Calif., will serve as the principal investigator for the trial. Dr. Holodniy said, "I am pleased to participate as an investigator at one of many study sites in the rigorous clinical testing of AVI's lead compound targeted for the HCV virus. The study should provide a better understanding of the compound's safety, pharmacokinetics, and potential biological effects against HCV."

HCV is a single-stranded RNA virus. 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.

Quilt Shows Victims of Hepatitis C's Silent Onslaught

<http://www.detnews.com/2005/metro/0509/16/B01-317112.htm>

Daredevil motorcyclist Evel Knievel fought it. Actress Pamela Anderson told the world she has it. So do some 4 million other Americans, including Pam Sienkiewicz of Milford.

No, I'm not talking about the high-profile disease known as AIDS. Hepatitis C, the liver-damaging virus that Sienkiewicz, 58, caught during a Caesarean section blood transfusion in 1979, is a more low-key killer. Still, between 8,000 and 10,000 Americans die from it annually, compared with the nearly 16,000 Americans who died from AIDS in 2002.

Sometimes, hepatitis C sickens its victims quickly, and sometimes it slumbers for decades before striking. Sienkiewicz wasn't diagnosed until 2001, when she began sweating and throwing up violently and requested blood tests. Nowadays, the blood-borne virus is mostly spread by intravenous drug users sharing needles, through homemade tattoos and piercings, shared razors and possibly sex, though no one is sure how often that happens.

Yet there are people living with this virus who claim they've never used drugs and didn't get transfusions in the days before a test had been perfected to screen blood donors for the virus. This is why the quilts matter. At noon tomorrow, four rug-size hepatitis C awareness quilts will go on display in Farmington Hill's Heritage Park on Farmington Road. They'll remain there for several hours. They'll be displayed again on Sunday, Sept. 25, starting at 9 a.m. at Belleville's Lower Huron Metro Park. If you happen to see them, take a good look at the faces, names and dates of diagnosis on the patches. Some patches came from people living with hepatitis C. Others came from the relatives of those who died with it. The patches were sewn together by Marie Stern, a California woman who believes she contracted the virus in 1978 and auto-immune hepatitis several years later.

"It can be hidden for decades," she says of the disease. "You wouldn't even know it. I thought I had the flu for four months, went to a doctor and he said, 'Oh, by the way, you have chronic hepatitis C.' "Of course, my world shattered. At that time, they hardly knew anything about it and you were given a death sentence of a year and a half -- or that's how you felt. "You can have it for decades and not know it and pass it on to people without realizing it."

Stern, 56, says she's never used drugs or had a transfusion or tattoos. She believes she might have been infected during dental work performed decades ago, or even from a manicure. She and Sienkiewicz want people to get tested for hepatitis C even if they're feeling well or have only vague symptoms such as extreme fatigue, nausea, liver pain or depression. They also want as many people as possible to see the hepatitis C quilts and ponder messages of faith and courage from people who fought back.

Aethlon Medical Launches Hepatitis-C Clinical Trial

http://www.genengnews.com/news/bnitem.aspx?name=1060340XSL_NEWSML_TO_NEWSML_WEB.xml

Aethlon Medical, Inc. announced today that human clinical trials to treat patients infected with the Hepatitis-C virus (HCV) are now underway at the Apollo Hospital in New Delhi, India. The primary objective of the trial is to demonstrate the safety of Aethlon's Hemopurifier(TM) treatment technology. The secondary objective of the trial will be to obtain preliminary efficacy data related to serologic and virologic markers, including viral load measurements before and after treatment with the Hemopurifier(TM).

Aethlon Chairman and CEO, James A. Joyce, stated, "Five years ago, our vision that a device could capture circulating viruses and toxins was purely conceptual. Today, I thank the researchers, advisors, and shareholders who were instrumental in executing the development phase of our vision." Joyce continued, "As a result, we now have the opportunity to demonstrate the safety and effectiveness of our device in a clinical setting. If successful, we will provide new hope to those afflicted with Hepatitis-C and other infectious diseases."

According to the World Health Organization, Hepatitis-C (HCV) is a global disease with approximately 190 million persons infected. The infected population in India exceeds 12.5 million. In the United States, HCV is the most common blood-borne infection with approximately 3.9 million citizens infected. HCV is a leading cause for liver disease and the most common reason for liver transplantation. Unfortunately, only 50% of HCV infected respond to the current standard of Interferon and Ribavirin treatment. Interferon and Ribavirin regimens are expensive and are known to have serious side effects.

Individuals enrolled in the initial trial are HCV-infected patients that require kidney dialysis as a result of End Stage Renal Disease (ESRD). Approximately 30-35% of all ESRD patients are infected with HCV, and as a result of their condition, are unable to endure the toxicity of HCV drug treatment. Follow-on studies are planned to evaluate the ability of the Hemopurifier to improve patient response rates to Interferon and Ribavirin as a conjunctive therapy, and as a stand-alone treatment for patients who are either unable to endure or do not respond to the current standard of care. The trial will also serve as a means to obtain human safety data, which will be submitted in conjunction with planned regulatory initiatives to treat the Human Immunodeficiency Virus (HIV) and

drug and vaccine resistant Biological Weapons. Initial safety data and preliminary efficacy observations from the trial are expected to be available within the next sixty days.

Naomi Judd Finds Balance, Purpose in Hepatitis Fight

<http://www.azcentral.com/arizonarepublic/arizonaliving/articles/0929qajudd0922.html>

She's the American Liver Foundation's spokeswoman, her magazine-style show debuts Nov. 27 on the Hallmark Channel and she's preparing to talk with prospective John C. Lincoln Health Network nurses Oct. 12 in Phoenix.

But Naomi Judd - registered nurse, country music star and now health care advocate - has been happily occupied at home in recent days. Her grandkids (Wynonna Judd, her daughter and former singing partner, is their mother) just spent the night. They live about an hour from Nashville in a house on the same 1,000-acre property where Grandma lives. And her actress daughter, Ashley Judd, whose farm is up the road, needs help choosing and packing clothes for a press junket. Then there's the bounty crop of vegetables from her garden needing her attention. "I told my girlfriend, 'I'll eat what I can and can what I can't,'" Naomi Judd says by phone.

Life is full, but the pace is less stressful than in 1991, when hepatitis C forced her to retire from her singing career. She contracted the liver disease from a needle stick while working years earlier as a nurse. Today, she's cured of the disease, runs a hepatitis C education and research foundation, and advocates balance as essential to good health. And nurses, she says, occupy an invaluable role in helping patients strike that balance. [see link for interview...]

Pharmacists Able to Detect 'Hidden' Hepatitis C in Drug Users [UK]

<http://www.prnewswire.co.uk/cgi/news/release?id=154524>

New hope is on the way for intravenous drug users who are, unknowingly, suffering from the Hepatitis C Virus (HCV) according to the preliminary results of a pilot project in Lincolnshire to be launched today (Monday, 26 September 2005) at the British Pharmaceutical Conference in Manchester.

A new four month pilot project, commissioned by the Lincolnshire Drug Alcohol Action Team, offered HCV testing to all clients who attended substance misuse services in two pharmacies. The pharmacies were one setting as part of a multi-agency approach for the delivery of HCV antibody testing within different settings.

The results showed that, of those tested, more than a third (32%) tested HCV antibody positive. These clients were referred on to specialist treatment services if required. They were also offered counselling and advice on safer injecting and how to minimise self-harm.

The Hepatitis C Virus (HCV) is a highly infectious blood borne virus. Left untreated it can lead to serious liver disease including cirrhosis and liver cancer and, potentially, can lead to death(1). However, worryingly, symptoms may not present themselves until the disease develops into a chronic infection.

It is thought that the main transmission route of HCV is through the sharing of blood-contaminated drug injecting paraphernalia by intravenous drug users. Previous studies have shown a 30% prevalence rate amongst this group(2). According to the Pharmacy Based Substance Misuse Services Co-ordinator Debbie Newton, who project managed this new initiative on behalf of Lincolnshire NHS, in-pharmacy detection of HCV is vital for this 'hidden' group who may not access any other treatment services.

"Of those clients, who tested HCV positive, they all appear to have contracted the disease within the last two years," she explains. "Thanks to this new project 78% were referred to secondary services for treatment. Failing to detect and treat HCV could have had serious health consequences for these people." Mrs Newton conclude:, "This pilot project strongly suggests that it is feasible to deliver a new care pathway for HCV sufferers from a community pharmacy setting, directly into a secondary care service."

The pharmacy was just one setting as part of a multi-agency approach for the delivery of HCV antibody testing within different settings. Results are to be compared at a later date.

Project results

61 clients enquired in pharmacies about the HCV antibody testing service. 28 (46%) were tested and 9 (32%) tested HCV antibody positive. 23 (82%) returned for their results. 11 (39%) were aged 20 - 24 years, 7 (25%) aged 25 - 29

years, 9 (32%) aged 30 - 34 years and 1 aged 42 years. Of the 28 (46%) tested, 16 (57%) had previously been tested HCV antibody negative during the past 2 years and 9 (56%) of those have since tested HCV antibody positive. 4 (44%) were female and 5 (56%) were male, with 2 couples identified with both partners being infected. 7 (78%) of the 9 HCV antibody positives consented to onward referral to a specialist consultant.

Hepatitis C Suit

<http://www.wowt.com/news/headlines/1764386.html>

Doctor fled country -Jury selection is underway in a Fremont, Nebraska civil suit tied to the largest outbreak of hepatitis C in the country. Ninety nine people contracted the disease while undergoing cancer treatments three years ago. Cheryl Gentry died of liver complications. "You don't go from one patient to another and reuse a needle," said Jan Nemecek, Gentry's sister. Gentry was a patient at a Fremont clinic who contracted hepatitis C while undergoing cancer treatment. "She thought her cancer was back when she started feeling tired again," said Nemecek. "Well, that was hepatitis C. " Gentry died soon after.

Ninety eight other cancer patients also contracted hepatitis C at the same clinic. The doctor, Tahir Ali Javid, leased space in the Fremont area medical center. Javid has since gone on to improve his career, fleeing to Pakistan and becoming the acting Pakistani minister of health. This, despite having his medical license revoked by the state of Nebraska in 2003 for negligence in the hepatitis outbreak. He failed to follow basic infection control procedures and abandoned patients when he fled the country.

Javid's current position within the Pakistani health system causes many people to believe he won't be in court to face malpractice charges. His nurse, Linda Prochaska is also named in the civil suit, but Nemecek says Javid is ultimately responsible. "He's taking the easy way out and I think he needs to come back and I think he needs to at least apologize to all the people that lost loved ones or people who are affected now by this hepatitis 'c'," said Nemecek. "I would sure like to talk to him."

Reporter's question: What would you say? "What were you thinking? You have a responsibility when you received your doctorate degree that you have a responsibility to do the best that you possibly can for your patients. What were you thinking?" Prochaska is accused of using the same saline bag and syringes on multiple patients. Jury selection began Wednesday. Opening statements are scheduled to begin Monday.

Hepatitis C Trial Begins

<http://www.fremontneb.com/articles/2005/10/04/news/news1.txt>

Robert Ridder bounced back from cancer but was never the same after contracting hepatitis C, his daughter testified Monday during the opening day of the first trial stemming from the nation's largest outbreak of the disease. Ridder and his wife, Verena, of Fremont are suing former Fremont oncologist Tahir Javed and his nurse, Linda Prochaska, claiming their unsanitary medical practices resulted in Robert Ridders' contraction of hepatitis C in 2002. The Ridders are seeking unspecified damages due to damage to their marriage and loss of quality of life.

Cheryl Ridder Sudbeck, the eldest of the Ridders' four children and publisher of newspapers in Howells and North Bend, said her father farmed near Dodge until 2003, farrowing hogs, feeding cattle and raising corn and soybeans. In July 2000, Ridder was diagnosed with non-Hodgkins leukemia, received chemotherapy at the Fremont Cancer Clinic run by Javed, and was declared cancer-free. A divorced mother of two at the time of her father's cancer treatment, Sudbeck called him her "knight in shining armor."

"He was the same man he was before (the chemotherapy)," she said. "The same guy I needed when I needed someone as a single parent." In October 2002, Ridder was among 612 Fremont Cancer Clinic patients to receive letters from the Nebraska Department of Health recommending a screening test for the hepatitis C virus. Ridder learned he had the virus in November 2002. Sudbeck said the hepatitis C infection and treatments have changed her father.

"After the hepatitis C, he got weaker, he got tired," she said. "The hepatitis C robbed me of the ability to watch my dad grow old gracefully. He aged 10 years in that one year. He's never come back." Sudbeck said the diagnosis angered the whole family. "At first, we blamed the nurse," she said. "But that nurse has to answer to someone, someone you trust to cure you, not send you home with something else." In January 2003, Ridder began taking

treatments to counteract the disease. The treatments, which involved injections and oral medications, lasted six months and were directed by Omaha hepatologist Mark Mailliard.

While Ridder is considered a sustained responder, indicating the absence of live hepatitis C virus in his system, Sudbeck said Verena Ridder still worries about contracting the disease through marital relations, even though physicians agree such a transmission, although possible, is unlikely, especially with the use of a condom. "No one can tell us she absolutely will not catch hepatitis C," Sudbeck said. "She'd rather die than expose any of us." The Ridders' family practitioner, Dr. Jeffrey R. Rapp, also testified during the trial's first day.

Rapp, the Ridders' primary care physician since 1997, talked to Ridder about the virus shortly after he received the health department's letter in 2002. "I told him the hepatitis C virus would not go away on its own, that it could result in death, and that he had a long life ahead of him and should go in for treatment," Rapp said. Ronald J. Palagi, the Ridders' attorney, claimed in opening statements they face medical bills, emotional stress and "the anguish of having friends and neighbors look at you and not knowing what to do."

Attorneys Mark Christensen and Greg Thomas represent Javed and Prochaska, respectively. Javed left the United States in July 2002 and now resides in Pakistan. Prochaska attended Monday's proceedings. Both have lost their licenses to practice in Nebraska. Christensen cautioned the jury to be sensible in their deliberations. "(Palagi) wants you to be emotional about this case, to decide with your emotions rather than logic," he said. Christensen questioned whether the effects of that treatment resulted in Ridder's inability to maintain his farming operation, noting the farrowing operation had closed and the auction planned well in advance of the 2002 diagnosis. The Ridders sold their farm home and the surrounding 10 acres in 2003 and built another home in Fremont.

Budget Lacks Hepatitis C Funds for Inmates

<http://www.lsj.com/apps/pbcs.dll/article?AID=/20051003/NEWS01/510030328/1001/news>

Approved plan cuts \$1M to fight virus in prisons. Money to test and treat Michigan prisoners for hepatitis C has been eliminated in the state's new budget, effectively killing a plan to attack the potentially fatal and communicable disease festering inside the state's 42 prisons.

The 2005-06 budget, which was approved by lawmakers and Gov. Jennifer Granholm last week and took effect Saturday, cut \$1 million from the corrections department that was set aside for a new hepatitis C program. The program would have surveyed incoming inmates and tested 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. 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 Friday how many inmates are being treated now. They have said it would cost \$130 million a year to treat every infected inmate.

Biomarkers Used to Predict Recurrent Disease in Hepatitis C Transplant Patients

http://www.eurekalert.org/pub_releases/2005-10/jws-but100305.php

Two new studies on Hepatitis C (HCV) patients who underwent liver transplants examined a potential biomarker that could be used to predict who might develop hepatic fibrosis, a formation of scar-like tissue that can lead to cirrhosis. The studies found that changes in a certain type of liver cell were useful in determining those who were at the greatest risk for developing this serious complication. The results of these studies appear in the October 2005 issue of *Liver Transplantation*, the official journal of the American Association for the Study of Liver Diseases (AASLD) and the International Liver Transplantation Society (ILTS).

Hepatitis C is the leading cause of liver transplants and recurrence of the disease following transplant is a serious problem. It is estimated that up to 20 percent of HCV patients will develop fibrosis or cirrhosis within two years of undergoing a transplant. Antiviral therapy is not highly effective in transplant patients and poses additional problems for these individuals, who may have difficulty tolerating the potent drugs it involves. However, antiviral therapy might be useful for those patients likely to develop fibrosis, if they could somehow be identified. Hepatic stellate cells (HSC) normally store vitamin A in the liver, but in HCV patients these cells produce collagen and other proteins that can lead to fibrosis. Researchers tried to determine if HSC activation could help predict which

patients would later develop fibrosis by using laboratory analysis of alpha smooth muscle actin (alpha-SMA), a reliable marker for HSC activation.

In one study, led by Samer Gawrieh of the Division of Gastroenterology and Hepatology at the Mayo Clinic College of Medicine in Rochester, MN, 26 patients who underwent HCV-related liver transplants at the Mayo Clinic between April 1993 and July 1999 were included. Biopsies obtained 4 months and 1 year post-transplant were evaluated and given a score for alpha-SMA. The results showed that HSC activation of one particular type of cell (mesenchymal cells, which give rise to connective tissue) was highly reliable in predicting the development of fibrosis. "Staining early post-LT liver biopsies for alpha-SMA may help identify patients with hepatitis C at risk for severe recurrence who may benefit from early anti-HCV or anti-fibrotic therapy," the authors conclude.

In another study, led by Mark W. Russo, M.D., M.P.H. of the Division of Gastroenterology and Hepatology of the University of North Carolina in Chapel Hill, 46 patients who underwent HCV-related liver transplants at the University of Florida between 1997 and 2001 were included. Patients were divided into two groups: those who developed advanced fibrosis within 2 years of liver transplant and those who developed mild or no fibrosis in the same period. Biopsies from 4 months, 1 year and 2 years post-transplant were scored for alpha-SMA. The results showed that HSC activation was significantly higher in the 4 month biopsies for those who developed advanced fibrosis within 2 years. The authors note that alpha-SMA "is an attractive biomarker because it is determined from the organ of interest and there is biological plausibility for why increased stellate cell activity would lead to advanced fibrosis."

In an accompanying editorial by A.J Demetris and J.G. Lunz III of the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh Medical Center in Pittsburgh, the authors note that the ability of alpha-SMA to predict disease at 4 months after transplant suggests that something triggers a chain of events that begins with mesenchymal and/or HSC activation and leads to the development of fibrosis. They speculate as to what the trigger might be and how it might explain the mechanism of liver disease, examining risk factors for recurrent HCV that might offer clues, as well as substances such as viral proteins and proteins secreted by liver cells. In particular, they cite their research on p21, a protein made in the liver, which showed that progression of fibrosis was related to the effect of p21 on liver cell proliferation. "This model better fits observations about disease pathogenesis," they conclude. "It explains why any hepatocyte stressors, such as steatosis [accumulation of fat in the liver], iron, inflammation, HCV replication or spontaneously increased 21 expression, such as occurs with aging, can accelerate liver disease progression."

New Data Suggest Vertex's Oral Hepatitis C Virus Protease Inhibitor VX-950 May Reduce Liver Injury; VX-950 Clinical Milestones on Track

<http://www.newswire.ca/en/releases/archive/October2005/03/c6578.html>

MONTREAL - New data show that patients with genotype 1 hepatitis C virus (HCV) infection treated with VX-950, an investigational oral HCV protease inhibitor being developed by Vertex Pharmaceuticals Incorporated rapidly achieved substantial reductions in alanine aminotransferase (ALT) levels after 14 days of treatment. The findings were presented today by researchers at the 12th International Symposium on Hepatitis C and Related Viruses (HCV 2005) in Montreal, Canada. Vertex also provided an update on clinical development of VX-950, which is one of the most advanced of a new class of medicines in development for the treatment of chronic hepatitis C infection.

Data from a 14-day clinical study demonstrated that treatment with any one of three doses of VX-950 resulted in median serum ALT declines of 25-32 U/L in all dose groups. In the placebo group, a median 8 U/L increase was observed. Prior to treatment with VX-950, serum ALT levels were elevated in approximately 70 percent of patients in the study. In the VX-950 dose groups, 83 percent (15 of 18) of patients with elevated ALT levels at baseline (prior to treatment) had achieved normalization of ALT levels at day 14, compared to 0 percent (0 of 6) in the placebo group. Elevated ALT levels are common in HCV patients and are considered to be a marker of liver injury due to HCV infection. Mean levels of serum neopterin also were observed to decrease with VX-950 treatment in the study. Decreased neopterin levels may be a further signal of a reduction in inflammation associated with HCV infection.(1)

A study of viral isolates from patients at baseline in a 14-day clinical study, also presented at the conference, found heterogeneity among viral sequences in the HCV protease domain. In vitro analysis indicated that all

baseline viral isolates were sensitive to VX-950.(2)

"To date, data from early clinical studies have suggested that VX-950 is well-tolerated and can rapidly reduce HCV viral levels in patients over a short treatment period," said John Alam, M.D., Senior Vice President of Drug Evaluation and Approval at Vertex. "In addition, we now have evidence that treatment with VX-950 appeared to lead to a dramatic decline in markers of liver injury associated with viral infection."

Vertex affirmed today that it remains on track to achieve key milestones in its VX-950 clinical program in the fourth quarter of 2005, including initiation of a 14-day Phase Ib combination study of VX-950 and pegylated interferon in Europe and filing of an investigational new drug (IND) application in the United States to support Phase II development of VX-950. Vertex anticipates that it will initiate a 28-day, Phase II combination study of VX-950 and pegylated interferon by year-end. Vertex expects to present additional VX-950 clinical data at two more medical conferences in the fourth quarter of 2005.

Hepatitis C Drug Cost-Effective for Anemia

<http://www.sciencedaily.com/upi/index.php?feed=Science&article=UPI-1-20051003-19443500-bc-us-hepdrug.xml>

University of Los Angeles research suggests a Hepatitis C drug is cost-effective in helping patients with treatment-induced anemia. The study -- conducted with the Veterans Affairs Greater Los Angeles Healthcare System -- found that for Hepatitis C patients who develop treatment-induced anemia due to a key medication, it is more cost-effective to take an additional drug to help prevent anemia, rather than reducing or stopping treatment altogether, which has been the standard approach. Researchers said the study may lead to a new treatment standard for the one-third of Hepatitis C patients who develop treatment-induced anemia as a result of taking ribarvirin.

Hepatitis C 'Needn't be a Killer'

<http://news.bbc.co.uk/1/hi/health/4293592.stm>

Neil Hudson, 35, discovered by accident during routine health checks that he had caught hepatitis C virus from infected blood he had received while critically ill in hospital years earlier. Neil, from South London, says he is one of the lucky ones because he has since been able to get the treatment that can cure between 50-80% of those with the virus. Only 1-2% of the 466,000 people believed to be infected with hepatitis C in the UK are on such treatment, partly because six out of seven remain undiagnosed, experts estimate.

Such figures have prompted the Hepatitis C Trust, which says the UK lags behind many other European countries in its diagnosis and treatment of the disease, to call for urgent government action. Neil says it is vital that more people get tested and treated. "If you have ever had a piercing, a tattoo, if you shared any razors or toothbrushes, if you have snorted cocaine, if you have used intravenous drugs or if you have had a blood transfusion or received blood products, there is a chance that you could have hepatitis C. "That's not scaremongering. That's fact. That is how the virus is transmitted. "There could be an awful lot of people who don't know that they are infected. "If you think you are at risk, you should get tested because there is something you can do about it now rather than let it eat away at your liver and take away the standard of your life and even your life.

Since finishing a year's treatment of a drug called pegylated interferon in June 2004, Neil has had undetectable levels of the virus in his blood. Although it is not possible yet to know if he is cured, the signs are good. However, Neil said it is a struggle for many patients to get the care they need. "There is no infrastructure there which is terribly frustrating. Even six years after I was diagnosed, as a country, we are in exactly the same place. People don't know about the risks and are still finding it hard to get care." The government has launched a national framework for action on hepatitis C. The Hepatitis C Trust is calling for new screening targets, awareness campaigns and better access to treatments for the liver condition.

Hepatitis C Threatens New Generation of Egyptians

<http://www.alertnet.org/thenews/newsdesk/L05168992.htm>

CAIRO - Egyptian children face a high risk of contracting the liver disease hepatitis C from their parents, probably through the use of dirty needles in a country with one of the world's highest infection rates, a medical journal said. About 14 to 18 percent of Egyptians carry the deadly Hepatitis C (HCV) virus. The disease exploded in Egypt between 1960 and 1970, when unsterilised needles were used during a government campaign to treat the water-

borne disease bilharzia. Now the disease threatens the next generation of Egyptians, according to a study which found that parents could be passing HCV to their children.

"The strong relationship between the risk of infection in a child to the presence of (HCV) in their parents suggests transmission of HCV is occurring between family members," G. Thomas Strickland of the Maryland School of Medicine, Baltimore, said in the study, published in September's issue of the journal Hepatology. Conducted in rural areas where bilharzia is rife, the study did not find the exact routes of transmission, but said HCV could have been passed on through contact with blood or saliva. In a household environment, HCV can spread by sharing razors or toothbrushes, or by unprotected sex. But it said the practice within rural Egyptian families of sharing needles was the most probable method of transmission.

"The most common exposures (to HCV) among our subjects were frequent injections ... Usually for health purposes and often given at home by 'injectionists' who sometimes reuse their own needles and syringes or use household-provided syringes and needles in more than one person," Strickland said.

Out of the 6,734 HCV-free Egyptians who took part in the 19-month study, 67 percent of those who went on to contract HCV were under the age of 20, and of those 22 youths, the infection rate was greatest for those under the age of 10.

In his report, Strickland said that although it was difficult to draw statistical significance from the relatively small number of people who contracted HCV, further studies should be conducted into transmission within families.

"Learning the mechanisms by which HCV transmission is occurring between family members so that preventative measures can be initiated, particularly in children having HCV-infected parents, is important," he said.

Most Chronic Hepatitis C Patients Will Develop Cirrhosis in Later Life

http://www.xagenai.com/news/medicineneeds_net_news/e17aeca56fab22ce30ac615e72cc64e5.html

A study, published in the American Gastroenterological Association (AGA) journal Clinical Gastroenterology and Hepatology, showed that nearly 80 percent of chronic hepatitis C sufferers who have the disease for several decades will develop cirrhosis or end-stage liver disease later in life.

Researchers found that it is highly likely that people who are infected with hepatitis C (HCV) for more than 60 years will develop cirrhosis--the highest rate of hepatitis C-associated cirrhosis reported to date. Hepatitis C is a virus that affects the liver and is spread primarily by contact with blood and blood products in transfusions and among drug users who share needles. Other common routes of transmission are infants born to HCV-infected mothers, tattoos and body piercings and risky sexual behavior.

Of those who are infected, more than 80 percent will be chronic carriers of the disease. HCV can cause long-term scarring of the liver and usually presents with mild and non-specific symptoms, if any. They include fatigue, nausea, poor appetite and muscle and joint pain.

"Hepatitis C begins generally as a silent acute infection, with a fraction of the patients developing cirrhosis, end-stage liver disease or liver cancer," according to an editorial in the journal. "Although this is a generally accepted scenario in persons infected with HCV, there remains uncertainty about the true frequency of evolution of liver disease and its rate of progression." According to results of the study from researchers at the Queen Mary's School of Medicine and Dentistry in London, the prevalence of cirrhosis in patients with chronic HCV increases with the duration of the disease.

Nearly 80 percent of Asian patients who were infected at birth and lived with the disease for 60 years or more developed cirrhosis -- a finding that researchers say can be applied to the general population because of the similarity in the way the disease progresses in all ethnic groups. "This study suggests that prolonged infection with hepatitis C leads to cirrhosis in the majority of those who are infected," said Graham R. Foster, study author and at Queen Mary's School of Medicine and Dentistry in London. "While previous studies have found differences in disease progression in various ethnic groups, our findings confirm that fibrosis progression is the same across these groups and leads to development of cirrhosis and liver disease at the same rate in everyone."

Researchers conducted retrospective analyses of 382 patients diagnosed with hepatitis C at three hospitals in

northeast London between 1992 and 2003. Study participants were divided into two groups: Asian patients presumably infected in childhood and Caucasian patients. While the prevalence of cirrhosis in Caucasian patients was similar to the findings of previous studies, the statistics in Asians were markedly higher than previously found. The higher prevalence was partially attributed to the longer duration of HCV in the Asian patient population, those patients having suffered with the disease nearly 30 years more than the Caucasian subjects.

Linking MicroRNA to Hepatitis C -Liver-specific microRNA Facilitates Replication of the Virus, Study in Science Shows

<http://www.the-scientist.com/news/20050902/01>

There is a surprising new role for a microRNA in the accumulation of hepatitis C virus in the liver, a study in *Science* suggests. A team led by Peter Sarnow at Stanford University School of Medicine found that the liver-specific microRNA-122 (miR-122) interacts with the 5' noncoding region of the viral mRNA to enhance its replication.

While previous work has shown that microRNAs can cleave mRNA or repress its translation by binding with mRNA's 3' noncoding region, this is the first time such a molecule has been found to interact with the 5' region in an animal cell, or to positively regulate gene expression. "In the last couple of years, many people have found new and varied forms in which miRNAs can interact with the replication of animal viruses. This is a new and quite different example," said John Taylor, of the Fox Chase Cancer Center, who did not participate in the study.

The human genome contains about 800 genes that code for microRNAs. The authors chose to look at miR-122, which accounts for 70% of microRNAs found in the liver, to see if the liver-based RNA virus hepatitis C might be using the host microRNA "for its own good," said Sarnow.

To determine if miR-122 is needed to regulate hepatitis C gene expression, the researchers sequestered miR-122 by transfecting complementary oligonucleotides in Huh7 liver cell lines expressing a hepatitis C RNA replicon. They found that the amount of hepatitis C RNA was reduced by about 80% when miR-122 was inactivated. "So we knew the miRNA is important for hepatitis C abundance, [but we] didn't know whether it was a direct interaction or whether the miRNA interacts with a cellular target," said Sarnow.

They next introduced mutations into the two potential miR-122 binding sites in the noncoding region of the viral RNA genome. While mutations at the 3' noncoding region binding site had no effect on hepatitis C RNA accumulation, they found that RNA with mutations in the 5' noncoding region binding site failed to accumulate. But when they ectopically expressed miR-122 with the corresponding 5' mutations in these cells, levels of hepatitis C RNA were restored, suggesting that the putative base-to-base binding interaction between the miRNA and its mRNA target had been rescued and arguing against the possibility that the 5' mutation lowered RNA levels by causing misfolding.

From this result, which Taylor called "the most convincing evidence" in the study, Sarnow and his team concluded that there is a direct genetic interaction between miR-122 and hepatitis C that is essential for the virus to replicate. Because other miRNAs are known to reduce the translational efficiency of their mRNA targets, the researchers then evaluated amounts of core protein translated from viral RNA with and without miRNA binding sites; the results suggest that miRNA regulates viral RNA at the replication level.

The mechanism for this new miRNA role is still very much unclear, though Sarnow speculates that miR-122 may recruit the viral RNA into a replication complex or help in RNA folding. He plans to use colocalization experiments to investigate the nature of the interaction. According to the paper, hepatitis C mRNA can also replicate in non-liver cells, such as those in the kidney and cervix. "It's a puzzle that hepatitis C needs miR-122 when grown in Huh7 cells but doesn't need it when it's grown in those other cells," said Taylor. Sarnow pointed out that "that kind of makes sense" because initial infection with hepatitis C can occur through peripheral cells before the virus reaches the liver.

Scientists "could potentially design ways to manipulate this miRNA to prevent virus replication in [the] host," said Jian-Kang Zhu, at the University of California, Riverside, who did not participate in this study. Sarnow said

it will also be important to determine the normal function of the highly abundant miR-122 in the liver, particularly if the microRNA is targeted for antiviral therapies.

Sex Abuse Suspect May Have Hepatitis C

<http://www.ksl.com/?nid=148&sid=107577>

A man accused of sexually abusing several teenage boys may also have passed on hepatitis C to his victims. Blood tests were done on 39-year-old Blaine Jay Tracy to determine if he has the illness. The test was ordered after one of Tracy's alleged victims tested positive for the illness earlier this year. If Tracy tests positive the court wants to alert his other possible victims to be tested. Tracy was arrested in July on charges of forcible sex abuse and dealing in harmful material to a minor.

Surgeon Did not Know Locum had Hepatitis C Virus

http://icbirmingham.icnetwork.co.uk/0100news/0100localnews/tm_objectid=16128875&method=full&siteid=50002&headline=surgeon-did-not-know-locum-had-hepatitis-c-virus--name_page.html

A consultant surgeon at a Midland hospital had no idea his assistant in an operation was infected with the Hepatitis C virus, a disciplinary hearing heard yesterday. Urologist Ramasamy Jaganathan let junior doctor Mohammed Sarwar-Rana help out in surgery at Solihull Hospital in January 2003.

He told the General Medical Council there was a risk he could accidentally 'stab' Mr Sarwar- Rana during an operation, spilling his infected blood. The GMC has heard how the locum doctor risked exposing patients to the virus at four hospitals across the country. These included the King George Hospital in Ilford, east London, the Pilgrim Hospital in Lincolnshire, the Bradford Teaching Hospitals and the Solihull Hospital.

Mr Sarwar-Rana admits he knew he had the virus but claimed the risk was so small there was no danger to anyone. Department of Health guidelines ban anyone infected from carrying out "exposure prone procedures" such as major surgery. But Mr Jaganathan told the hearing he believed the locum should not have been involved in the operation he carried out, which involved repairing a hernia, removing a varicose vein, and a vasectomy.

Mr Jaganathan said: "I was carrying out the surgery and the assistant's job is to hold open the wound. "The cutting of the wound is done by the assistant. Although the assistant does not touch the wound he would come into contact with blood. "The surgeon's instruments can touch the assistant's hands. If that happens to be a needle or a knife in that process there could be a hole in the glove or contamination of blood from the assistant." The urologist said in his experience there was a one in 200 risk of his assistant being injured. He added: "Exposure prone procedures are defined where there could be blood contacting the surgeon or the assistant."

Asked whether he was aware Mr Sarwar-Rana was infected with Hepatitis C, he said: "No, I was not." The hearing was told Hepatitis C could cause serious illness leading to cirrhosis or even primary liver cancer. Mr Sarwar-Rana, of Woodthorpe Road, Kings Heath, Birmingham, qualified in 1981 in Pakistan but has regularly worked in the UK since becoming a fellow of the Royal College of Surgeons in Ireland in 1992. It is claimed his conduct was inappropriate, misleading, not in his patients' best interests, and a risk to the health of his patients. He denies serious professional misconduct. The hearing continues.

Flamel Technologies Announces Positive Preliminary Results of a Phase I/II Trial of IFN-alpha-XL in Patients with Chronic Hepatitis C Virus Infection

<http://www.leaddiscovery.co.uk/prlink.asp?reclink=http://www.flamel.com/pressReleases/20050923.shtml>

Flamel Technologies S.A. today announced positive preliminary Phase I/II data from a trial demonstrating the safety, tolerability, and long-acting activity of IFN-alpha-XL in patients with chronic hepatitis C virus (HCV) infection. Data also show that IFN-alpha-XL had positive effects on viral load and interferon activity biomarkers. IFN-alpha-XL utilizes Flamel's proprietary Medusa nanoparticle technology to provide a long-acting formulation of interferon alpha that may have enhanced efficacy and reduced toxicity compared with unmodified or PEG-modified interferon formulations. Flamel plans to present the full data at a medical conference.

The lead investigator of the study, Professor Christian Trepo (Hotel Dieu Hospital-Lyon), remarked, "Interferon therapy is a cornerstone in the treatment of chronic hepatitis C infection, but today its use is limited by the significant side effects associated with approved formulations of Interferon-alpha. These side effects are

debilitating and treatment limiting. The results of this first study of IFN-alpha-XL are very promising, and suggest that this novel formulation of interferon alpha may provide equivalent and possibly better therapeutic benefit with fewer side effects in comparison to existing interferon-alpha therapies. This would be a significant advance in the treatment of a disease that has reached pandemic proportions in the United States and around the world."

The dose-escalating study was conducted in 53 subjects with chronic hepatitis C. Thirty-nine participants were assigned to receive a single subcutaneous injection of one of three escalating doses of IFN-alpha-XL (12 - 14 patients per dose). The three IFN-alpha-XL groups received an injection of 9 million international units (MIU), 18 MIU, and 27 MIU, respectively. A cohort of 14 patients received three subcutaneous injections of a standard dose of Viraferon (3 MIU) over one week as a comparator. All patients completed the study, and no serious adverse events were reported.

Adverse events were similar to what has been reported in other studies of interferon therapy and were transient in duration and mild to moderate in severity. Patients receiving IFN-alpha-XL appeared to have fewer adverse events than patients receiving Viraferon, which is marketed in the U.S. as Intron® A, even when the weekly dosage of IFN-alpha-XL was at its highest level. Pharmacokinetic data demonstrate that the Medusa formulation provides sustained release of IFN-alpha-XL over one week. Significantly, post-injection serum concentrations (C_{max}) of IFN-alpha-XL were lower or equivalent than those observed for Viraferon. This is important in maintaining a concentration that provides therapeutic benefit while reducing side effects.

Dr. R. Kravtsoff, Director of preclinical and clinical development of Flamel Technologies, said: "We are very pleased with the preliminary results of this first clinical study of our long-acting Interferon alpha formulation, IFN-alpha-XL. The data demonstrate that IFN-alpha-XL was well tolerated and did not exhibit the toxicity typically observed with Interferon alpha 2b, even at the highest dose evaluated. The results indicate that reduction in viral load in these high-dose patients, including traditionally hard-to-treat genotype 1 cases, was at least equivalent to that observed in the control group. We are looking forward to sharing these results in greater detail at an upcoming medical conference."

Dr. Kravtsoff continued, "Patients with hepatitis C have significant unmet medical need, with only about half of patients treated with the current standard of care achieving a sustained, meaningful virologic response. We believe that IFN-alpha-XL may provide a new therapeutic option that would provide improved tolerance and patient compliance, leading to improved clinical outcomes."

Based on these clinical results Flamel Technologies is preparing a Phase IIa study in hepatitis C patients, while meeting with large pharmaceutical companies to explore partnership for this important program. A Phase IIa study would be designed to investigate the safety, duration of release and clinical efficacy of IFN-alpha-XL following repeated weekly administration in hepatitis C patients, compared with weekly administration of pegylated interferon alpha.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Clinical presentation of chronic hepatitis C in patients with end-stage renal disease and on hemodialysis versus those with normal renal function. Hu KQ, et al. Am J Gastroenterol. 2005 Sep;100(9):2010-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16128946&query_hl=108

BACKGROUND: The natural history of chronic hepatitis C (CHC) remains to be defined in patients with end-stage renal disease (ESRD). **AIMS:** To determine the clinical presentation of CHC and the factors associated with stage III-IV fibrosis in patients with CHC and ESRD. **METHODS:** The study included patients with CHC and ESRD (n = 91) or normal renal function (NRF, n = 159). Both groups were matched for mean age, gender, history of alcohol use, and estimated duration of hepatitis C virus (HCV) infection. **RESULTS:** Presentation of CHC and ESRD was independently associated with non-Caucasian ethnicity (OR = 3.24, p = 0.0003), a history of diabetes mellitus (DM, OR = 7.911, p < 0.0001), and lower frequencies of being obese (OR = 0.457, p = 0.035), of having hepatic steatosis (OR = 0.372, p = 0.003), and stage III-IV fibrosis (OR = 0.403, p = 0.016). After adjusting for serum levels of alpha-fetoprotein (AFP) and HCV RNA, CHC, and ESRD were independently associated with lower frequencies of elevated alanine aminotransferase (ALT, OR = 0.175, p = 0.02) and aspartate aminotransferase

(AST, OR = 0.169, p= 0.04), but higher frequencies of AST/ALT ratio >1 (OR = 7.173, p= 0.002) and hypoalbuminemia (OR = 9.567, p= 0.0007). Compared to patients with NRF and stage III-IV fibrosis, those with ESRD and stage III-IV fibrosis had a significantly higher frequency of a history of DM (OR = 8.014, p= 0.0031) and lower frequency of elevated AST (OR = 0.054, p= 0.004), which were independent of the frequencies of lower levels of ALT and albumin, and AST/ALT ratio >1. In patients with CHC and ESRD, the presence of stage III-IV fibrosis was significantly associated with hepatic steatosis (OR = 4.523, p= 0.012) and thrombocytopenia (OR = 4.884, p= 0.044), which were independent of the frequencies of a history of DM, splenomegaly, and a higher level of AST. **CONCLUSIONS:** CHC and ESRD are independently associated with a higher frequency of a history of DM, but lower frequencies of being obese, and having hepatic steatosis, stage III-IV fibrosis, and elevated transaminases. In patients with CHC and ESRD, stage III-IV fibrosis is not associated with a history of DM, but is independently associated with hepatic steatosis and thrombocytopenia.

Serum alpha-fetoprotein levels in patients with advanced hepatitis C: results from the HALT-C Trial.

Di Bisceglie AM, et al. J Hepatol. 2005 Sep;43(3):434-41.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16136646&query_hl=18

BACKGROUND/AIMS: Alpha-fetoprotein (AFP) has been useful in the diagnosis of hepatocellular carcinoma (HCC) but lacks specificity. We assessed serum AFP among patients with chronic hepatitis C and advanced fibrosis to establish predictors of AFP elevations and changes with antiviral therapy. **METHODS:** Serum AFP was measured at baseline and on therapy in patients in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C). AFP levels were correlated with patient demographic and clinical features. **RESULTS:** Baseline AFP was > or = 20 ng/mL in 191 of 1145 patients (16.6%). Mean AFP values were significantly higher in patients with cirrhosis than in those with bridging fibrosis (22.5 vs. 11.4 ng/mL, P < 0.0001). Factors independently associated with raised serum AFP in patients with cirrhosis were female gender, black race, decreased platelet count, increased serum AST/ALT ratio, serum ferritin, and Mallory bodies in liver biopsies. Serum AFP levels decreased significantly during therapy with pegylated interferon alpha-2a and ribavirin. HCC was identified in six subjects, only three of whom had AFP > 20 ng/mL. **CONCLUSIONS:** Among patients with advanced chronic hepatitis C, serum AFP values are frequently elevated, even in the absence of HCC. Factors associated with raised AFP include severity of liver disease, female gender and black race. Serum AFP levels decline during antiviral therapy.

High-dose interferon-alpha2b induction therapy in combination with ribavirin for treatment of chronic hepatitis C in patients with non-response or relapse after interferon-alpha monotherapy.

Hass HG, Kreysel C, Fischinger J, Menzel J, Kaiser S. World J Gastroenterol. 2005 Sep 14;11(34):5342-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16149143&query_hl=18

AIM: To evaluate the daily high-dose induction therapy with interferon-alpha2b (IFN-alpha2b) in combination with ribavirin for the treatment of patients who failed with interferon monotherapy and had a relapse, based on the assumption that the viral burden would decline faster, thus increasing the likelihood of higher response rates in this difficult-to-treat patient group. **METHODS:** Seventy patients were enrolled in this study. Treatment was started with 10 MU IFN-alpha2b daily for 3 wk, followed by IFN-alpha2b 5 MU/TIW in combination with ribavirin (1 000-1 200 mg/d) for 21 wk. In case of a negative HCV RNA PCR, treatment was continued until wk 48 (IFN-alpha2b 3 MU/TIW+1 000-1 200 mg ribavirin/daily). **RESULTS:** The dose of IFN-alpha2b or ribavirin was reduced in 16% of patients because of hematologic side effects, and treatment was discontinued in 7% of patients. An early viral response (EVR) was achieved in 60% of patients. Fifty percent of all patients achieved an end-of-treatment response (EOT) and 40% obtained a sustained viral response (SVR). Patients with no response had a significantly lower response rate than those with a former relapse (SVR 30% vs 53%; P = 0.049). Furthermore, lower response rates were observed in patients infected with genotype 1a/b than in patients with non-1-genotype (SVR 28% vs 74%; P = 0.001). As a significant predictive factor for a sustained response, a rapid initial decline of HCV RNA could be identified. No patient achieving a negative HCV-RNA PCR at wk 18 or later eventually eliminated the virus. **CONCLUSION:** Daily high-dose induction therapy with interferon-alpha2b is well tolerated and effective for the treatment of non-responders and relapsers, when interferon monotherapy fails. A fast decline of viral load during the first 12 wk is strongly associated with a sustained viral response.

Hepatitis C is a predictor of poorer renal survival in diabetic patients. Crook ED, Penumalee S, Gavini B, Filippova K. Diabetes Care. 2005 Sep;28(9):2187-91.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16123488&query_hl=18

OBJECTIVE: Hepatitis C virus (HCV) is highly prevalent in the U.S. and worsens renal survival in some kidney diseases. We examined the effects of HCV on renal survival in diabetic patients with renal disease. **RESEARCH DESIGN AND METHODS:** HCV and diabetes status were noted in patients seen in our nephrology clinic in 2001 and 2002. Charts of diabetic patients were reviewed for demographics, blood pressure, renal function, medicines, the presence of HCV, and other factors at the initial visit and over follow-up. The effect of HCV on renal survival was determined by Cox proportional hazards, using end-stage renal disease (ESRD) as an end point. **RESULTS:** Of 1,127 patients, prevalence rates for HCV were higher in African Americans than non-African Americans (8.09 vs. 3.93%, respectively, $P = 0.06$), with African-American men having the highest prevalence rates (12.7%). The charts of 312 diabetic patients were reviewed. Over 80% were African American, as were 23 of 24 patients with HCV. Compared with non-HCV patients, HCV patients were younger, had higher diastolic blood pressure, and had lower BMI. HCV patients had significantly worse cumulative renal survival by Kaplan-Meier. On Cox proportional hazards analysis, HCV was a significant predictor of reaching ESRD independent of initial renal function, proteinuria, blood pressure, sex, race, presence of diabetic nephropathy, age, or duration of diabetes (odds ratio 3.49, 95% CI 1.27-9.57, $P = 0.015$). **CONCLUSIONS:** HCV is common in African Americans with diabetes and renal disease and is an independent risk factor for renal survival in this population. Prospective studies are necessary to confirm these observations.

Past excessive alcohol consumption: a major determinant of severe liver disease among newly referred hepatitis C virus infected patients in hepatology reference centers, France, 2001. Delarocque-Astagneau E, et al. *Ann Epidemiol.* 2005 Sep;15(8):551-7..

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16117999&query_hl=18

PURPOSE: Our study aimed to identify factors associated with the occurrence of severe liver disease in hepatitis C virus (HCV) positive patients at first referral to hepatology reference centers in France in 2001. **METHODS:** Patients reported through the national hospital-based hepatitis C surveillance system in 2001 were included. The definition of severe liver disease was based on clinical, biological, and morphological evaluation; cirrhosis (+/- complication) and primary liver cancer were classified as severe liver disease. Patient characteristics were compared for those with and without severe liver disease. **RESULTS:** Of the 3404 newly referred patients in the 26 participating centers, 391 (11.5%) had severe liver disease. Male gender (adjusted odds ratios [aOR]=1.4; 95% confidence interval [CI], 1.0-1.9), age over 39 years at referral (aOR=3.8; 95% CI, 2.7-5.3), past excessive alcohol consumption (aOR=2.6; 95% CI, 1.9-3.5), and HIV seropositivity (aOR=1.9; 95% CI, 1.1-3.3) were each independently associated with an increased risk of severe liver disease. In the subgroup of patients with known age at time of HCV exposure, age over 39 years at time of exposure (aOR=1.6; 95% CI, 1.1-2.4), duration of HCV infection over 15 years (aOR=2.6; 95% CI, 1.8-3.7), known HBs antigen positivity (aOR=2.4; 95% CI, 1.1-5.2), and past excessive alcohol consumption (aOR=2.7; 95% CI, 1.8-3.9) were each associated with increased risk of severe liver disease. **CONCLUSIONS:** Our findings underscore the important role of past excessive alcohol consumption on the development of severe liver disease for HCV patients.

Gamma-glutamyl transferase (GGT) as an independent predictive factor of sustained virologic response in patients with hepatitis C treated with interferon-alpha and ribavirin. Villela-Nogueira CA, et al. *J Clin Gastroenterol.* 2005 Sep;39(8):728-30.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16082285&query_hl=18

BACKGROUND: Recently, gamma-glutamyl transferase (GGT) has been investigated as a predictive factor for therapy response in hepatitis C patients, but so far its value in pretreatment screening has not been established. Therefore, this study aimed at evaluating GGT as an independent predictive factor for the response to treatment with interferon-alpha and ribavirin in hepatitis C virus (HCV)-infected patients. **METHODS:** Naive chronic hepatitis C patients undergoing a 6-month follow-up after interferon-alpha and ribavirin therapy had their sustained virologic response (SVR) analyzed according to age, sex, body mass index, GGT levels, genotype, and liver histology by use of a multivariate logistic regression model. **RESULTS:** Of the 211 patients studied with a mean age of 48+/-10 years, 125 (59%) were males. Overweight was detected in 47% of patients. Genotype 1 was detected in 141 (75%) of the 187 patients tested. Cirrhosis was present in 67 (32%). A high pretreatment GGT level was observed in 134 (63%). SVR was obtained in 84 (40%) patients. In the final logistic regression model, the variables

independently associated with SVR were GGT ($P < 0.001$), genotype ($P < 0.001$), and liver histology ($P < 0.001$).

CONCLUSION: A normal GGT level is an independent predictive factor for SVR in HCV-infected patients and should be considered for pretreatment screening.

Liver enzyme values in injection drug users with chronic hepatitis C. Mehta SH, Dig Liver Dis. 2005 Sep;37(9):674-80.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15951255&query_hl=18

BACKGROUND: Liver enzymes fluctuate in chronic hepatitis C virus infection. However, the range that can be attributed to the course of hepatitis C virus (versus an intercurrent cause of hepatitis) is unknown. **AIMS:** To characterise the range of liver enzyme values as a function of the upper limit of normal (ULN) of the assay among persons chronically infected with hepatitis C virus. **PATIENTS:** One thousand and fifty-nine hepatitis C virus chronically infected individuals with $> \text{ or } = 5$ semi-annual evaluations. **METHODS:** Alanine aminotransferase and aspartate aminotransferase levels were prospectively obtained. Potential causes of elevations were examined using serologic testing. **RESULTS:** Among 1059 individuals, 11,463 enzyme measurements were obtained over 6.5 years, of which 63.5% were $< 1.25 \times \text{ULN}$, 26.5% were $1.25\text{-}2.5 \times \text{ULN}$, 8.3% were $2.5\text{-}5 \times \text{ULN}$, and 1.6% were $5\text{-}10 \times \text{ULN}$; only 0.2% were $> 10 \times \text{ULN}$. Elevations $> 10 \times \text{ULN}$ were transient, the alanine aminotransferase/aspartate aminotransferase ratio tended to be different at the time of the elevation compared to before and after and 24% were associated with acute viral hepatitis. On the other hand, subjects with elevations $5\text{-}10 \times \text{ULN}$ tended to have elevated levels throughout follow-up and only 8% were associated with acute viral hepatitis. **CONCLUSIONS:** Liver enzymes fluctuate up to $5 \times \text{ULN}$ in most hepatitis C virus-infected persons; clinicians should seek alternate explanations for those with higher alanine aminotransferase or aspartate aminotransferase levels, especially among hepatitis C virus-infected persons with greater than 10-fold elevations.

Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. Ferenci P, et al. J Hepatol. 2005 Sep;43(3):425-33.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15990196&query_hl=18

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 (40 KD) 180 microg/week plus placebo or ribavirin (1000/1200 mg/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 (40 KD)/ribavirin with early virological responses (HCV RNA negative or $> \text{ or } = 2 \log_{10}$ decrease) at week 12 had SVRs at week 72 (HCV RNA $< 50 \text{ IU/mL}$). 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 $> \text{ or } = 80\%$ 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 $> \text{ or } = 2 \log_{10}$ reduction in HCV RNA after 12 weeks.

Hepatitis C virus RNA kinetics during the initial 12 weeks treatment with pegylated interferon-alpha 2a and ribavirin according to virological response. Carlsson T, et al. J Viral Hepat. 2005 Sep;12(5):473-80.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108761&query_hl=18

SUMMARY: To optimize treatment of chronic hepatitis C early identification of patients who will not achieve a sustained virological response (SVR) is desirable. We investigated hepatitis C virus (HCV) RNA kinetics at day 1 (in 15 patients; genotypes 1 and non-1, 9 and 6 respectively) at weeks 1, 4 and 12 (in 53 patients; genotypes 1 and non-1, 19 and 34, respectively) during treatment with pegylated interferon alpha-2a and ribavirin. Patients with SVR had a significantly more pronounced mean \log_{10} decline from baseline in HCV RNA levels at weeks 1 and 4 compared with patients who failed to achieve SVR (1.99 vs 0.85 at week 1, $P = 0.0003$ and 2.89 vs 1.72 at week 4, $P = 0.0159$), whereas no difference was noted after day 1. For patients with a 2- \log_{10} decrease in HCV RNA levels at day 7, the positive predictive value (PPV) for a SVR was 92%, whereas week 12 was the best time point for predicting a later nonresponse [negative predictive value (NPV) 92%] in patients failing to achieve a 2- \log_{10} drop.

For patients with genotype non-1 and a 2-log₁₀ decrease in HCV RNA levels the PPV for a SVR was 89% week 1, and 79% weeks 4 and 12. The corresponding NPV for patients with genotype non-1 were 43, 40 and 100% respectively. During treatment with pegylated interferon alpha-2a plus ribavirin the HCV RNA decline at week 1 was an accurate predictor of SVR in patients who had achieved a 2-log₁₀ drop in HCV RNA levels, whereas the lack of such decline week 12 was an accurate marker of a nonresponse.

Weight loss during pegylated interferon and ribavirin treatment of chronic hepatitis C*.

Seyam MS, et al. J Viral Hepat. 2005 Sep;12(5):531-5.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108770&query_hl=18

SUMMARY: Treatment of hepatitis C virus (HCV) infection with interferon (IFN)-alpha, as monotherapy or in combination with ribavirin, is associated with significant side-effects including weight loss. The aim of our study was to describe the evolution of body weight during combination antiviral treatment and to examine the possible determinants of weight loss. This was a retrospective analysis of 126 patients who received combination therapy of pegylated IFN-alpha-2b and ribavirin at our unit. Body weight was recorded at each outpatient attendance during treatment and follow-up, and was expressed as a percentage of baseline value. We observed a decline of body weight during treatment. Median (range) weight values at 4, 12, 24, and 48 weeks (expressed as percentage of baseline weight) were 97.7 (91.5-110.2), 95.4 (84.4-109.4), 93.7 (80.8-106.5), and 91.1 (80.1-103.6) respectively. There was no significant association of increased weight loss with age, gender, pretreatment weight, ethnicity, pretreatment histological stage, cumulative IFN dose (adjusted for body weight), HCV genotype or treatment outcome. Median body weight returned to baseline within 6 months of stopping treatment. Patients experience significant weight loss during combination therapy. Those experiencing greater weight losses during therapy did not benefit from improved antiviral response.

Humoral immune response in acute hepatitis C virus infection. Netski DM, et al. Clin Infect Dis. 2005 Sep 1;41(5):667-75. Epub 2005 Jul 22.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16080089&query_hl=18

BACKGROUND: There is little information on the timing, magnitude, specificity, and clinical relevance of the antibody response to acute hepatitis C virus (HCV) infection. We investigated the specificity, titer, and neutralizing potential of antibody responses to acute infection by examining 12 injection drug users before, during, and after infection. **METHODS:** Seroconversion was defined as incident detection of HCV-specific antibodies by using a commercially available enzyme-linked immunosorbent assay (ELISA). HCV protein-specific antibody responses were measured using recombinant antigens in an ELISA. For neutralization assays, plasma was incubated with human immunodeficiency virus (HIV)-HCV H77 or control HIV-murine leukemia virus (MLV) pseudotype virus and then allowed to infect Hep3B hepatoma cells. **RESULTS:** The mean time to HCV seroconversion was 6 weeks after the onset of viremia. Antibody responses to nonstructural proteins were detected before responses to the structural proteins, and antibodies to both were primarily restricted to the immunoglobulin G1 (IgG1) subclass. The maximum median end point titers for antibody responses to structural and nonstructural proteins were 1 : 600 and 1 : 6400, respectively. Antibodies that neutralized a retroviral pseudotype bearing HCV 1a envelope glycoproteins were detected at seroconversion in only 1 subject and at 6-8 months after seroconversion in 3 subjects. The delayed appearance of neutralizing antibodies was consistent with the late development of antibodies specific for the viral envelope glycoproteins, which are believed to mediate virus neutralization. **CONCLUSION:** The humoral immune response to acute HCV infection is of relatively low titer, is restricted primarily to the IgG1 subclass, and is delayed. A better understanding of why production of neutralizing antibody is delayed may improve efforts to prevent HCV infection.

Higher doses of peginterferon alpha-2b administered twice weekly improve sustained virological response in difficult-to-treat patients with chronic hepatitis C: results of a pilot randomized study. Lodato F, et al. J Viral Hepat. 2005 Sep;12(5):536-42.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108771&query_hl=18

SUMMARY: Beside substantial progress in treatment of chronic hepatitis C (CHC) particular patients (genotype 1/4, high viral load, previous nonresponse, cirrhosis) remain difficult to treat. The aim of our pilot randomized study was to compare efficacy and tolerability of standard doses of Peginterferon alpha-2b + ribavirin with higher

doses of Peginterferon alpha-2b administered twice weekly + ribavirin. Sixty-five outpatients with CHC were subsequently enrolled. Group A (n = 22) received recommended doses of Peginterferon alpha-2b and group B (n = 43), received high doses twice weekly. Groups were comparable for baseline characteristics. All genotype 1/4 patients had high baseline viraemia. Sustained virological response (SVR) was significantly higher in group B among naive patients (72%vs 25%, P = 0.024). A significantly higher rate of SVR was observed in group B both considering only genotype 1/4 patients, (46%vs 13%, P = 0.03) and grouping together genotype 1/4 naive and relapsers (57%vs 11%, P = 0.039). Discontinuation rate was 32% (7 of 22) in group A and 19% (8 of 43) in group B. Our response rates are the highest reported for genotype 1/4 with high viraemia. Our pilot study supports the need of randomized studies to evaluate both viral kinetics and efficacy of high dose and twice weekly administration of Peginterferon alpha-2b in genotype 1/4 patients with high viraemia who may need personalized treatment schedules.

Hepatitis C virus infection facilitates gallstone formation. Chang TS, et al. J Gastroenterol Hepatol. 2005

Sep;20(9):1416-21.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16105130&query_hl=18

BACKGROUND: Bile duct damage and hepatic steatosis are two characteristic histological findings in hepatitis C virus infection; and high prevalence of hepatitis C antibody is noted in patients with cholangiocarcinoma. The purpose of the present study was to examine the relationship between biliary diseases and hepatitis C virus infection. **METHODS:** Persons who received a general checkup in Chang Gung Memorial Hospital between 2000 and 2002 were included. All of them had hemogram, serum biochemistry, hepatitis B surface antigen, hepatitis C antibody and ultrasonography studies. The prevalence of gallbladder stone, bile duct stone and gallbladder polyp/cholesterolosis were compared in different viral infection groups. **RESULTS:** Of the 28 486 persons, 22 967 were negative for both hepatitis B surface antigen and hepatitis C antibody (group NBNC), 4152 were hepatitis B surface antigen carriers (group B), 1195 were positive for hepatitis C antibody (group C), and 172 were positive for both markers. The 379 persons (1.3%) having had cholecystectomy were considered to have gallbladder stone at the time when cholecystectomy was done. Gallbladder stone was found in 6.0% persons of group NBNC, 5.4% in group B and 11.7% in group C. The prevalence of gallbladder stone in group C was found especially high for age groups 31-40 years and 61-70 years. The prevalence of bile duct stone was higher in group C (0.4%) than in group NBNC or B (both 0.1%). Stepwise logistic regression analysis showed that age, liver cirrhosis, body mass index, hepatitis C virus infection and gender were independent factors associated with gallbladder stone.

CONCLUSIONS: Hepatitis C virus infection facilitates gallstone formation.

Rationale and design of the REPEAT study: a phase III, randomized, clinical trial of peginterferon alfa-2a (40 kDa) plus ribavirin in non-responders to peginterferon alfa-2b (12 kDa) plus ribavirin. Jensen DM,

Marcellin P. Eur J Gastroenterol Hepatol. 2005 Sep;17(9):899-904

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16093865&query_hl=18

OBJECTIVE: The retreatment with PEGasys in patients not responding to prior peginterferon alfa-2b (12 kDa)/ribavirin combination therapy (REPEAT) study is a phase III, randomized, parallel group, multinational clinical trial. The main objective is to compare the efficacy and safety of 48 and 72 weeks of treatment with peginterferon alfa-2a (40 kDa) (PEGASYS) plus ribavirin (COPEGUS) in patients who did not respond to previous peginterferon alfa-2b (12 kDa) plus ribavirin therapy. **STUDY DESIGN:** Patients will be randomized to one of four treatment groups: two groups will receive peginterferon alfa-2a (40 kDa) at the standard dose of 180 mug once weekly for 48 or 72 weeks. The other two groups will receive a 12-week high-dose induction regimen with peginterferon alfa-2a (40 kDa) 360 mug once-weekly followed by 60 or 36 weeks of peginterferon alfa-2a (40 kDa) 180 mug once weekly. All patients will receive the standard dose of ribavirin (1000 or 1200 mg/day) throughout treatment. The primary efficacy variable is the rate of sustained virological response, defined as non-detectable hepatitis C virus (HCV) RNA (<50 IU/ml) 24 weeks after the end of treatment. Secondary variables include the percentage of patients with non-detectable HCV RNA at the end of treatment, the percentage of patients with at least a 2-log₁₀ decrease in serum HCV RNA at weeks 12 and 24 of treatment, and the percentage of patients with non-detectable HCV RNA at treatment weeks 12, 24 and 48. Safety data will be recorded and analysed throughout the entire course of the study with the assistance of a Safety Review Board.

Pegylated interferon and ribavirin therapy for chronic hepatitis C virus genotype 4 infection.

Legrand-Abravanel F, et al. J Med Virol. 2005 Sep;77(1):66-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16032749&query_hl=18

Hepatitis C Virus (HCV) is classified into six genotypes. Genotype 4 is now spreading in Europe, especially among drug users, who are often infected with both HCV and the human immunodeficiency virus (HIV). Previous studies have shown that HCV-4 responds poorly to interferon. Pegylated interferon (peg-IFN) associated with ribavirin is now the most effective treatment for eradicating the virus. We have now studied the response of HCV-4 to peg-IFN and ribavirin and investigated the influence of HIV infection on anti-HCV therapy. Twenty-eight patients infected with HCV-4 were given peg-IFN plus ribavirin for 48 weeks. Patients infected with HCV alone tended to have a better initial response (66%) than patients infected with both HCV and HIV (30%, $P = 0.06$) and eradication was better (50%) than in doubly infected patients (15%, $P = 0.06$). After controlling for major factors influencing virus response, the virus response 12 weeks after the beginning of treatment in patients infected with HCV-4 (50%) was similar to that of patients infected with genotype 1 (53%) and lower than that of patients infected with genotypes 2 or 3 (82%, $P < 0.05$). The response 24 weeks after the end of therapy in patients infected with HCV-4 (32%) was similar to that of patients infected with HCV-1 (28%) and lower than that of patients with HCV-2 or HCV-3 (62% $P < 0.05$). These results indicate that HCV-4 patients should be considered to be difficult-to-treat.

Antiviral activity and safety of 873140, a novel CCR5 antagonist, during short-term monotherapy in HIV-infected adults. Lalezari J, et al. AIDS. 2005 Sep 23;19(14):1443-1448.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16135896&query_hl=18

OBJECTIVE: 873140 is a spirodiketopiperazine CCR5 antagonist with prolonged receptor binding and potent antiviral activity in vitro. This study evaluated plasma HIV RNA, safety, and pharmacokinetics following short-term monotherapy in HIV-infected adults. **DESIGN::** Double-blind, randomized, placebo-controlled multi-center trial. **METHODS:** Treatment-naive or experienced HIV-infected subjects with R5-tropic virus, CD4 cell count nadir $> 200 \times 10^6$ cells/l, viral load > 5000 copies/ml and not receiving antiretroviral therapy for the preceding 12 weeks were enrolled. Forty subjects were randomized to one of four cohorts (200 mg QD, 200 mg BID, 400 mg QD, 600 mg BID) with 10 subjects (eight active, two placebo) in each cohort, and received treatment for 10 days. Serial HIV RNA, pharmacokinetics, and safety evaluations were performed through day 24. **RESULTS:** Of the 40 subjects, 21 were treatment-experienced; 35 were male, 20 were non-white, and eight were coinfecting with hepatitis C virus. Median baseline HIV RNA ranged from 4.26 log₁₀ to 4.46 log₁₀. 873140 was generally well tolerated with no drug-related discontinuations. The most common adverse events were grade 1 gastrointestinal complaints that generally resolved within 1-3 days on therapy. No clinically significant abnormalities were observed on electrocardiogram or in laboratory parameters. Mean log changes in HIV RNA at nadir, and the percentage of subjects with > 1 log₁₀ decrease were -0.12 (0%) for placebo, -0.46 (17%) for 200 mg once daily, -1.23 (75%) for 200 mg twice daily, -1.03 (63%) for 400 mg once daily, and -1.66 (100%) for 600 mg twice daily. An Emax relationship was observed between the area under the 873140 plasma concentration-time curve and change in HIV RNA. **CONCLUSIONS:** 873140 demonstrated potent antiretroviral activity and was well tolerated. These results support further evaluation in Phase 2b/3 studies.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Patterns of expression of cytochrome P450 genes in progression of hepatitis C virus-associated hepatocellular carcinoma. Tsunedomi R, et al. Int J Oncol. 2005 Sep;27(3):661-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16077914&query_hl=18

Cytochrome P450 (CYP) genes are involved in the pathogenesis of hepatocellular carcinoma (HCC). To examine changes in expression of CYPs in HCC arising from hepatitis C virus (HCV)-infected liver, we used oligonucleotide array data of 27 CYPs from samples of 50 HCV-associated HCCs, five HCV-infected non-tumorous livers, and six HCV-negative normal livers. Progression of primary HCC can be characterized by decrease in the grade of tumor differentiation, increased frequency of venous invasion and increased tumor size. On the basis of tumor differentiation, the self-organizing map (SOM) classified the 27 CYPs into four groups. The first group contained 11 CYPs, including the CYP2C and CYP4F families, that showed decreased expression in parallel with progression of HCV-infected liver to HCC with less differentiation. The second group contained CYP-IID,

CYP3A7 and CYP27A1, genes that showed high levels of expression specific to well differentiated HCC. The third group contained 5 sterol-metabolizing CYPs with levels lower in HCV-infected livers than in HCV-uninfected livers. The last group included the CYP2E1 and CYP3A families. Among the 27 CYPs, levels of 7 (CYP2B6, CYP-IIC, CYP2C9, CYP2C19, CYP3A5, CYP4F3 and CYP27A1) were significantly lower and levels of 2 (CYP2E1 and CYP4F2) were slightly lower in HCC with venous invasion than in HCC without venous invasion. Levels of CYP-IIC and CYP2C9 were inversely associated with tumor size. In contrast, levels of CYP51A1 were positively associated with tumor size. **Our present study revealed** that expression of specific CYPs was altered in conjunction with progression of HCV-associated HCC. These CYPs may serve as markers of progression and molecular targets for treatment of HCV-associated HCC.

Telomerase reverse transcriptase mRNA expression in peripheral lymphocytes of patients with chronic HBV and HCV infections. Satra M, et al. J Viral Hepat. 2005 Sep;12(5):488-93

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108763&query_hl=18

SUMMARY: Telomerase activity is present at low levels in peripheral lymphocytes (PL) and is upregulated upon activation, possibly protecting PL from telomere shortening. As decreased telomere length is considered a sign of cellular senescence, telomerase may, therefore, play an important role on immune function, organ regeneration and carcinogenesis. So far, quantification of human telomerase reverse transcriptase levels (hTERT) in PL, has not been reported. We determined hTERT mRNA levels in PL of hepatitis B virus (HBV) and hepatitis C virus (HCV) patients, in an attempt to address whether hTERT transcripts in PL are altered in these viral diseases, which are characterized by immune dysfunction and increased incidence of hepatocarcinogenesis. hTERT mRNA levels in PL of HBV (n = 17), HCV (n = 24) patients and healthy controls (n = 22) were quantified by real-time polymerase chain reaction. We observed significantly lower hTERT mRNA levels in HBV and HCV patients compared with healthy individuals ($P < 0.05$). hTERT mRNA levels were not associated with the patients' clinical status (inactive, hepatitis and cirrhosis). Also no correlation was observed between hTERT mRNA expression, and HBV and HCV replicative activity. In the inactive group (n = 18) we observed a negative correlation between hTERT mRNA expression and disease duration ($r_s = -0.52$, $P < 0.03$). We performed for the first time an accurate quantification of hTERT mRNA expression in PL of HBV and HCV patients. The observed low levels of hTERT mRNA expression in the above patients may suggest its involvement in the immunopathogenesis of chronic viral hepatitis.

Interferon-alpha suppresses liver cell proliferation in patients with chronic hepatitis C virus infection.

Donato MF, et al. J Viral Hepat. 2005 Sep;12(5):499-506

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108765&query_hl=18

SUMMARY: Interferon (IFN) therapy has been shown to reduce the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C, including virological nonresponders (NR). Whether IFN suppresses liver cell proliferation, i.e. the relevant risk factor for HCC, is unknown. The aim of the study was to evaluate the effect of IFN therapy on liver cell proliferation in chronic hepatitis C. The proliferating cell nuclear antigen-labelling index (PCNA-LI) was assessed prior to and at the end of therapy in the liver of 29 patients with chronic hepatitis C who received 3 MU IFN-alpha2b thrice weekly for 24-48 weeks. Overall, the median value of PCNA-LI was significantly reduced from 2.6% to 1.1% at the end of therapy ($P < 0.0001$). At baseline, PCNA-LI median values were similar in the 15 virological responders compared with the 14 NRs (2.3%vs 3.4%, $P = 0.121$) and at the end of therapy, median changes of PCNA-LI (-1.4%vs-1.1%, $P = 0.089$) were also similar although there was a higher decline of the proliferation index in responders with respect to NRs at the end of therapy (0.7%vs 1.6%, $P = 0.004$). In the two groups, the rate of fibrosis score reduction was also similar (7%vs 20%, $P = 0.326$). In contrast, the histological activity index was more often reduced in responders than in NRs both at the ≥ 2 and ≥ 4 points reduction level (80%vs 36%, $P = 0.02$ and 53%vs 14%, $P = 0.03$, respectively). **The study showed** a significant suppression of liver cell proliferation in IFN-treated patients with chronic hepatitis C. Although the strongest IFN effect was observed in virological responders, a reduction of proliferative activity was also seen in virological NRs.

Polymorphisms of the renin-angiotensin system and the severity of fibrosis in chronic hepatitis C virus infection. Forrest EH, et al. J Viral Hepat. 2005 Sep;12(5):519-24

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108768&query_hl=18

SUMMARY: Patients with chronic hepatitis C virus (HCV) infection vary in their rates of fibrosis progression.

The renin-angiotensin system (RAS) regulates fibrosis. Polymorphisms in the genes of the RAS may contribute to the outcome of renal and cardiovascular disease. We studied four RAS gene polymorphisms in 195 patients with chronic HCV infection. Patients were grouped by Ishak stage of fibrosis on liver biopsy: group 1 (fibrosis score 0 or 1; n = 97), group 2 (fibrosis score 2 or 3; n = 73) and group 3 (fibrosis score 4-6; n = 25). Polymorphisms of the angiotensinogen (AGT) gene (M235T and AT-6), the angiotensin I converting enzyme gene and the type 1 angiotensin II receptor gene were assayed. There was no difference in the distribution of these polymorphisms of the RAS between the fibrosis groups. There did not appear to be any increased prevalence of fibrosis if two or even three of the polymorphisms associated with increased RAS effect were present. On multivariate analysis factors significantly associated with fibrosis were necroinflammatory activity ($P < 0.001$) and age ($P < 0.001$). No association was identified between these four RAS polymorphisms and fibrosis in chronic HCV infection.

Hepatitis C virus-specific reactivity of CD4+-lymphocytes in children born from HCV-infected women.

Della Bella S, et al. *J Hepatol.* 2005 Sep;43(3):394-402

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16023248&query_hl=18

BACKGROUND/AIMS: T-lymphocyte reactivity against viral antigens may represent the only immunological marker of host contact with a virus. Aim of the present study was to investigate whether vertical exposure to hepatitis C virus (HCV) could activate HCV-specific T-cell responses that may represent a biomarker of previous contact with the virus, and possibly contribute to the low rate of vertical HCV transmission. **METHODS:** We studied 28 children born from chronically HCV-infected mothers. HCV-specific activation and proliferation of CD4+-lymphocytes and cytokine production were evaluated in cultures of peripheral blood mononuclear cells (PBMCs) stimulated in vitro with HCV-peptides. **RESULTS:** HCV-specific CD4+-cell reactivity was observed in 20 out of the 28 children (71%). The proliferation of HCV-specific CD4+-cells was more frequent and vigorous in children than in their mothers. In children, but not in the mothers, activation of CD4+-cells upon stimulation with HCV-peptides was directly correlated with proliferation. Early upon stimulation with HCV-peptides, lymphocytes from children produced lower levels of IL-10 than lymphocytes from the mothers. **CONCLUSIONS:** Vertical exposure to HCV induces the development of viral-specific CD4+-cell-mediated immune responses, possibly endowed with protective function against infection, which may contribute to the low rate of vertical HCV transmission.

Cytokine profile of peripheral blood mononuclear cells from patients with different outcomes of hepatitis C virus infection.

Gramenzi A, et al. *J Viral Hepat.* 2005 Sep;12(5):525-30.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108769&query_hl=18

SUMMARY: The relationship between the balance of helper T-cell type 1 (Th1) or type 2 (Th2) cytokines and the clinical course of hepatitis C virus (HCV) infection is unclear. We evaluated Th1 [interleukin (IL)-2, interferon-gamma (IFN-gamma)] and Th2 cytokine (IL-4, IL-10) and 2,5-oligoadenylate synthetase (OAS, an IFN-induced antiviral protein) production by peripheral blood mononuclear cells from 10 healthy anti-HCV-positive individuals (group A), 10 HCV-RNA-positive with persistently normal alanine aminotransferase (ALT) levels (group B), 10 HCV-RNA-positive with abnormal ALT (group C) and 10 uninfected healthy controls. IL-2 production was significantly increased in group B when compared with all the other groups. No difference was found for IFN-gamma. IL-4 was significantly higher in group C than in both group B ($P = 0.0006$) and controls ($P = 0.004$). Compared with controls, IL-10 was significantly decreased in group A ($P = 0.013$) and B ($P = 0.004$). The production of 2,5-OAS was significantly higher in group B than in A ($P = 0.04$) and in C ($P = 0.004$). Finally, in all HCV-RNA-positive patients, a significant correlation was found between ALT and both IL-2 ($r = -0.78$; $P = 0.0008$) and IL-4 ($r = 0.75$; $P = 0.0008$). In conclusion: (i) subjects who cleared HCV showed a cytokine profile similar to controls; (ii) a preferential shift towards a Th1 profile seems associated with a more favourable clinical outcome in chronic hepatitis C; and (iii) a prevalent Th2 profile seems implicated in HCV pathogenesis and severity of liver disease.

GNB3 C825T polymorphism and response to interferon-alfa/ribavirin treatment in patients with hepatitis C virus genotype 1 (HCV-1) infection.

Sarrazin C, et al. *J Hepatol.* 2005 Sep;43(3):388-93.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16019105&query_hl=18

BACKGROUND/AIMS: The outcome of infection with the hepatitis C virus (HCV) has been shown to be

influenced by genetic host factors. The G protein beta3 subunit (GNB3) C825T polymorphism has been shown to determine immune cell functions in vitro. We investigated the association of GNB3 genotypes with treatment response in HCV-infected patients. **METHODS:** We genotyped 1781 HCV-free blood donors and 232 HCV-infected patients treated with interferon-alfa/ribavirin. Sustained virologic response (SVR) was defined by undetectable HCV-RNA 24 weeks after discontinuation of therapy. Non-response (NR) was defined by positive HCV-RNA at the end of at least 24 weeks of treatment. GNB3 genotypes were determined by DNA restriction enzyme analyses. **RESULTS:** Genotype distribution was not significantly different in healthy controls and HCV-infected patients. Only in HCV genotype 1-infected patients a significant correlation between GNB3 CC genotype and NR could be observed (6 TT, 42 TC, 54 CC) versus SVR (11 TT, 25 TC, 19 CC) patients ($P = 0.004$). In a logistic regression analysis including biochemical and virologic characteristics, only GNB3 CC genotype was significantly associated with NR (OR 4.9; 95% CI = 1.4-16.5; $P = 0.011$). **CONCLUSIONS:** The GNB3 825 CC genotype is associated with NR in HCV-1-infected patients.

Accumulation of 8-nitroguanine in the liver of patients with chronic hepatitis C. Horiike S, et al. *J Hepatol.* 2005 Sep;43(3):403-10.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16023246&query_hl=18

BACKGROUND/AIMS: Nucleic acid damage by reactive nitrogen and oxygen species may contribute to inflammation-related carcinogenesis. To investigate the extent of nucleic acid damage in hepatitis C virus infection and its change after interferon treatment, we measured 8-nitroguanine and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in the liver of patients with chronic hepatitis C (CHC) before and after interferon therapy. **METHODS:** Hepatic accumulation of 8-nitroguanine and 8-OHdG was immunohistochemically evaluated in 20 CHC patients and 7 control patients with non-alcoholic fatty liver. **RESULTS:** Immunoreactivities of 8-nitroguanine and 8-OHdG were strongly detected in the liver from patients with CHC, but not in control livers. 8-Nitroguanine accumulation was found not only in infiltrating inflammatory cells, but also hepatocytes particularly in the periportal area. The accumulation of 8-nitroguanine and 8-OHdG increased with inflammatory grade (8-nitroguanine; $P = 0.0019$, 8-OHdG; $P = 0.0009$). In the sustained virological responder group after interferon therapy, 8-nitroguanine and 8-OHdG accumulation were markedly decreased in the liver (8-nitroguanine; $P = 0.018$, 8-OHdG; $P = 0.018$). **CONCLUSIONS:** In this study, we demonstrated for the first time that 8-nitroguanine accumulated in the liver of patients with CHC. 8-Nitroguanine is a useful biomarker to evaluate the severity of HCV-induced chronic inflammation in relation to hepatocellular carcinoma.

Hepatitis C Virus Genotype 1a NS5A Pretreatment Sequence Variation and Viral Kinetics in African American and White Patients. Layden-Almer JE, et al. *J Infect Dis.* 2005 Sep 15;192(6):1078-87. Epub 2005 Aug 12..

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16107963&query_hl=18

In hepatitis C virus (HCV) infection, race is a determinant of treatment response and interferon (IFN) effectiveness. Here, we investigated whether there were differences in the pretreatment viral strains between African American patients and white patients and whether these differences correlated with viral kinetics. IFN effectiveness was calculated using a viral kinetic model. The HCV NS5A region from 21 treated patients with HCV genotype 1a was sequenced and analyzed. White patients displayed more mutations in the V3 region (mean \pm SD, 4.5 \pm 1.4 vs. 2.9 \pm 1.6; $P = .016$), and treatment responders tended to have more mutations in this region than did nonresponders. There was a significant positive correlation between IFN effectiveness and the number of mutations in the V3 region ($P = .03$). There was no clustering of strains by race, treatment response, or IFN effectiveness in phylogenetic analyses. **The results of this study**, in conjunction with those of a previous study illustrating the impaired IFN effectiveness in African Americans, suggest a role for host-related factors.

Interdomain communication in hepatitis C virus polymerase abolished by small molecule inhibitors bound to a novel allosteric site. Di Marco S, et al. *J Biol Chem.* 2005 Aug 19;280(33):29765-70. Epub 2005 Jun 13.

<http://www.jbc.org/cgi/content/abstract/280/33/29765>

The hepatitis C virus (HCV) polymerase is required for replication of the viral genome and is a key target for therapeutic intervention against HCV. We have determined the crystal structures of the HCV polymerase complexed with two indole-based allosteric inhibitors at 2.3- and 2.4-Angstroms resolution. The structures show that these inhibitors bind to a site on the surface of the thumb domain. A cyclohexyl and phenyl ring substituents,

bridged by an indole moiety, fill two closely spaced pockets, whereas a carboxylate substituent forms a salt bridge with an exposed arginine side chain. Interestingly, in the apoenzyme, the inhibitor binding site is occupied by a small alpha-helix at the tip of the N-terminal loop that connects the fingers and thumb domains. Thus, these molecules inhibit the enzyme by preventing formation of intramolecular contacts between these two domains and consequently precluding their coordinated movements during RNA synthesis. Our structures identify a novel mechanism by which a new class of allosteric inhibitors inhibits the HCV polymerase and open the way to the development of novel antiviral agents against this clinically relevant human pathogen.

Serum KL-6 as a novel tumor marker for hepatocellular carcinoma in hepatitis C virus infected patients.

Kurosaki M, et al. Hepatol Res. 2005 Sep 29; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16202647&query_hl=5

The up-regulation of MUC1 protein is associated with malignant phenotype of cancer. We investigated the significance of KL-6, one of the MUC1 antigens, as a tumor marker in hepatitis C virus positive hepatocellular carcinoma (HCC). Serum KL-6 was determined in 203 patients with chronic hepatitis (CH), 47 patients with liver cirrhosis (LC) and 78 patients with HCC. KL-6 was higher in HCC compared to non-HCC ($p=0.0005$) and was higher in patients with multiple HCC nodules compared to a single nodule ($p=0.02$). There was no correlation between KL-6 and existent tumor markers for HCC such as alpha-fetoprotein, lens culinaris agglutinin-reactive alpha-fetoprotein or des-gamma-carboxyprothrombin. In the prospective analysis, the cumulative incidence of HCC was significantly greater in CH and LC patients with high initial KL-6 (above 400U/ml) compared to the others ($p=0.02$). Moreover, in the prospective observation of 25 patients whose HCC was completely cured by radiofrequency ablation therapy, the cumulative incidence of distant recurrences was significantly greater in patients with high initial KL-6 compared to the others ($p=0.005$). **These results suggest** that serum KL-6 could be a novel tumor marker in the diagnosis and the prediction of prognosis of HCC that may have additive value to the existent markers.

Novel type I interferon IL-28A suppresses hepatitis C viral RNA replication. Zhu H, Butera M, Nelson DR, Liu C. Virol J. 2005 Sep 7;2:80.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16146571&query_hl=18

Interferon alpha (IFN-alpha)-based therapy is the currently approved treatment for chronic hepatitis C viral infection. The sustained antiviral response rate is approximately 50% for genotype-1 infection. The major challenge to the HCV community is to improve antiviral efficacy and to reduce the side effects typically seen in IFNalpha-based therapy. One of the strategies is to identify new interferons, which may have better efficacy and less undesirable side effects. In this report, we examined the role of IL-28A (IFN lambda2), a novel type I IFN, in suppression of human hepatitis C viral RNA replication. We have cloned both the human genomic DNA and cDNA of IL-28A, and evaluated their biological activity using HCV RNA replicon cell culture system. The results show that IL-28A effectively inhibits HCV subgenomic RNA replication in a dose-dependent manner. Treatment of human hepatoma cells with IL-28A activates the JAK-STAT signaling pathway and induces the expression of some interferon-stimulated genes (ISGs), such as 6-16 and 1-8U. We also demonstrate that IL-28A induces expression of HLA class I antigens in human hepatoma cells. Moreover, IL-28A appears to specifically suppress HCV IRES-mediated translation. Although IL-28A receptor shares one subunit with the IL-10 receptor, IL-10 treatment has no detectable effect on IL-28A-induced antiviral activity. Interestingly, IL-28A can synergistically enhance IFNalpha antiviral efficacy. **Our results suggest** that IL-28A antiviral activity is associated with the activation of the JAK-STAT signaling pathway and expression of ISGs. The effectiveness of IL-28A antiviral activity and its synergistic effect on IFN-alpha indicate that IL-28A may be potentially used to treat HCV chronic infection.

Involvement of chemokines and type 1 cytokines in the pathogenesis of hepatitis C virus-associated mixed cryoglobulinemia vasculitis neuropathy. Saadoun D, et al. Arthritis Rheum. 2005 Sep;52(9):2917-25.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16142759&query_hl=18

OBJECTIVE: To examine the expression profiles of a large number of genes within typical vasculitic nerve lesions in patients with mixed cryoglobulinemia (MC) vasculitis in order to better characterize the molecules involved in cellular tissue activation and trafficking. **METHODS:** The quantitative expression of 19 genes coding for cytokines, chemokines, and their receptors in the nerve lesions of 9 patients with hepatitis C virus (HCV)-

associated MC vasculitis, 7 with idiopathic polyarteritis nodosa (PAN) (rheumatic disease controls), and 8 patients with noninflammatory idiopathic neuropathy (noninflammatory neuropathy controls) was assessed using a real-time reverse transcriptase-polymerase chain reaction procedure. **RESULTS:** Compared with the noninflammatory controls, HCV-MC vasculitis patients had a significantly higher expression of Th1 cytokines in vasculitic nerve lesions (mean +/- SEM fold increase 33.7 +/- 11.6 for interferon-gamma and 7.2 +/- 1.9 for tumor necrosis factor alpha), whereas Th2 cytokines were absent (interleukin-4 [IL-4], IL-5, and IL-13) or were not significantly different (IL-10). Chemokines involved in T cell and monocyte trafficking were also significantly up-regulated in the HCV-MC vasculitis patients (mean +/- SEM fold increase 27.4 +/- 8.3 for macrophage inflammatory protein 1alpha [MIP-1alpha], 19.9 +/- 5.7 for MIP-1beta, and 7.2 +/- 1.5 for CXCR3). Compared with patients with idiopathic PAN, there was a trend toward higher expression of MIP-1alpha and CXCR3 in HCV-MC vasculitis patients (mean +/- SEM fold increase 27.4 +/- 8.3 versus 5.3 +/- 3.4 for MIP-1alpha and 7.2 +/- 1.5 versus 2.5 +/- 0.9 for CXCR3). **CONCLUSION:** This study is the first to demonstrate a role of cellular immunity and Th1 lymphocytes in the pathogenesis of HCV-MC vasculitic nerve lesions.

Suppression of hepatitis C virus replication by cyclosporin a is mediated by blockade of cyclophilins.

Nakagawa M, et al. Gastroenterology. 2005 Sep;129(3):1031-41.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16143140&query_hl=18

BACKGROUND & AIMS: Cyclosporin A specifically suppresses hepatitis C virus (HCV) replication in vitro at clinically achievable concentrations. In this study, we investigated the mechanisms of action of cyclosporin A against HCV replication. **METHODS:** The in vitro effects of cyclosporin A on HCV replication were analyzed using an HCV replicon system that expresses chimeric luciferase reporter protein. **RESULTS:** The significant effects of cyclosporin A on expression of an HCV replicon and the absence of such effects of FK506, which shares mechanisms of action with cyclosporin A, suggested the involvement of intracellular ligands of cyclosporin A, the cyclophilins. Transient and stable knockdown of the expression of cytoplasmic cyclophilins A, B, and C by short hairpin RNA-expressing vectors suppressed HCV replication significantly. A cyclosporin analogue, cyclosporin D, which lacks immunosuppressive activity but exhibits cyclophilin binding, induced a similar suppression of HCV replication. Furthermore, cyclosporin A treatment of Huh7 cells induced an unfolded protein response exemplified by expression of cellular BiP/GRP78. Treatment of cells with thapsigargin and mercaptoethanol, which induce the unfolded protein responses, suppressed HCV replication, suggesting that the cyclosporin-induced unfolded protein responses might contribute to the suppression of HCV protein processing and replication. **CONCLUSIONS:** The anti-HCV activity of cyclosporin A is mediated through a specific blockade of cyclophilins, and these molecules may constitute novel targets for anti-HCV therapeutics.

Mutations in the NS5B region of the hepatitis C virus genome correlate with clinical outcomes of interferon-alpha plus ribavirin combination therapy.

Hamano K, et al. J Gastroenterol Hepatol. 2005 Sep;20(9):1401-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16105128&query_hl=18

BACKGROUND AND AIM: Combination treatments of interferon-alpha (IFN) and ribavirin (RBV) are more effective than those of IFN alone in hepatitis C virus (HCV) infection. However, mechanisms of the action of the combination regimen are not well understood. To elucidate the viral genetic basis of IFN plus RBV combination therapy, genetic variabilities of HCV-1b were analyzed. **METHODS:** We performed pair-wise comparisons of full-length HCV genomic sequences in three patients' sera before and after initiation of IFN plus RBV treatment. Subsequently, we analyzed amino acid sequences of the NS5B region, which codes for the viral RNA-dependent RNA polymerase, and compared these with the outcomes of the therapy in 81 patients. **RESULTS:** Analysis of the entire HCV sequence in patients who received IFN plus RBV therapy did not show consistent amino acid changes between before and after the initiation of the therapy. NS5B sequence analyses revealed that mutations at positions 300-358 of NS5B, including polymerase motif B to E, occurred more frequently in a group of patients exhibiting a sustained viral response (SVR) or an end-of-treatment response (ETR) compared with a group of patients exhibiting a non-response (NR). Closer examination revealed that mutations at aa 309, 333, 338 and 355 of NS5B occurred significantly more frequently in the SVR plus ETR group than in the NR group (P = 0.0004). Multivariate analysis showed that the number of mutations at these four sites was an independent predictor of SVR plus ETR versus NR. **CONCLUSIONS:** Particular amino acid changes in the NS5B region of HCV may correlate with outcomes of IFN plus RBV combination therapy.

Broad Repertoire of the CD4+ Th Cell Response in Spontaneously Controlled Hepatitis C Virus Infection Includes Dominant and Highly Promiscuous Epitopes. Schulze Zur Wiesch J, et al., J Immunol. 2005 Sep 15;175(6):3603-13.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16148104&query_hl=18

A vigorous hepatitis C virus (HCV)-specific Th cell response is regarded as essential to the immunological control of HCV viremia. The aim of this study was to comprehensively define the breadth and specificity of dominant HCV-specific CD4(+) T cell epitopes in large cohorts of subjects with chronic and spontaneously resolved HCV viremia. Following in vitro stimulation of PBMC, HCV-specific cell cultures from each subject were screened with an overlapping panel of synthetic 20-mer peptides spanning the entire HCV polyprotein. Of 22 subjects who spontaneously controlled HCV viremia, all recognized at least one of a group of six epitopes situated within the nonstructural (NS) proteins NS3, NS4, and NS5, each of which was detected by >30% of subjects, but most subjects recognized additional, more heterogeneous specificities. In contrast, none of the most frequently targeted epitopes was detected by >5% of persons with chronic infection. The most frequently recognized peptides showed promiscuous binding to multiple HLA-DR molecules in in vitro binding assays and were restricted by different HLA-DR molecules in functional assays in different persons. **These data demonstrate** that predominant CD4(+) T cell epitopes in persons with resolved HCV infection are preferentially located in the nonstructural proteins and are immunogenic in the context of multiple class II molecules. This comprehensive characterization of CD4(+) T cell epitopes in resolved HCV infection provides important information to facilitate studies of immunopathogenesis and HCV vaccine design and evaluation.

Cryoglobulin-associated uptake of hepatitis C virus into human hepatocytes. Hilgard P, et al. Hepatogastroenterology. 2005 Sep-Oct;52(65):1534-40.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16201113&query_hl=5

AIMS: The mechanisms of binding and uptake of hepatitis C-virus (HCV) are critical determinants of the infection-reinfection cycle but due to ongoing absence of a robust cell culture system, these mechanisms are still largely hypothetical. Cryoglobulins are atypical immunoglobulins, present in 40% of HCV patients. The aim of this study was to determine the role of these HCV-containing cryoglobulins as carrier molecules for viral uptake into primary human hepatocytes. **METHODOLOGY:** Cryoglobulins were precipitated from serum of chronically HCV-infected patients, labeled with biotin and incubated with freshly prepared hepatocytes from human liver tissue. Binding and endocytosis of HCV-cryoglobulins were studied by specific assays, ligand blot analysis and electron microscopy on hepatocellular plasma membranes. **RESULTS:** Biotinylated HCV-cryoglobulins specifically bound to hepatocytes and inhibitors of homotypic endosomal fusion reduced their uptake and intracellular trafficking. Ligand-blot and electron microscopy analysis revealed adhesion to hepatocellular plasma membranes. Inoculation of human hepatocytes with HCV-cryoglobulins but not serum from the same patients induced HCV infection in vitro. **CONCLUSIONS:** HCV may enter hepatocytes in conjunction with cryoglobulins via immunoglobulin or related receptors. We hypothesize, that this mechanism plays a role in chronic hepatitis to support the infection-reinfection cycle of the virus.

Positive selection of cytotoxic T lymphocyte escape variants during acute hepatitis C virus infection.

Guglietta S, et al. Eur J Immunol. 2005 Sep;35(9):2627-37..

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16114108&query_hl=18

Cellular immune responses are induced during hepatitis C virus (HCV) infection and acute-phase CD8+ T cells are supposed to play an important role in controlling viral replication. In chimpanzees, failure of CD8+ T cells to control HCV replication has been associated with acquisition of mutations in MHC class I-restricted epitopes. In humans, although selection of escape mutations in an immunodominant CTL epitope has been recently described, the overall impact of immune escape during acute HCV infection is unclear. Here, by performing an in depth analysis of the relationship between early cellular immune responses and viral evolution in a chronically evolving HCV acutely infected individual, we demonstrate: (i) the presence of a potent and focused CD8+ T cell response against a novel epitope in the NS3 protein, (ii) the elimination of the quasi-species harboring the original amino acid sequence within this epitope, and (iii) the selection for a virus population bearing amino acid changes at a single residue within the cytotoxic T cell epitope that strongly diminished T cell recognition. **These results**

support the view that acute-phase CD8+ T cell responses exert a biologically relevant pressure on HCV replication and that viruses escaping this host response could have a significant survival advantage.

In vitro studies of cross-resistance mutations against two hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061. Lin C, et al. J Biol Chem. 2005 Sep 12; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16087668&query_hl=18

VX-950 is a potent, small-molecule, peptidomimetic inhibitor of the hepatitis C virus (HCV) NS3*4A serine protease, which has recently demonstrated antiviral efficacy in a phase I trial in patients chronically infected with genotype 1 HCV. In a previous study, we described in vitro resistance mutations against either VX-950 or another HCV NS3*4A protease inhibitor, BILN 2061, which has also demonstrated antiviral activity in phase I clinical trials in hepatitis C patients. Single amino acid substitutions were identified in the HCV NS3 serine protease domain that conferred drug resistance, distinct for either inhibitor. The dominant resistance mutation against VX-950, A156S, remains sensitive to BILN 2061. The major BILN 2061-resistant mutations, D168V and D168A, are fully susceptible to VX-950. Modeling analysis suggested that there are different mechanisms of resistance for these mutations, induced by VX-950 or BILN 2061, respectively. In the current study, we identified mutations that are cross-resistant to both HCV protease inhibitors. The cross-resistance conferred by substitutions of Ala¹⁵⁶ with either Val or Thr was confirmed by characterization of the purified enzymes and reconstituted replicon cells that contain the single amino acid substitution, A156V or A156T. Both cross-resistance mutations, A156V and A156T, displayed significantly diminished fitness (or replication capacity) in a transient replicon cell system.

LKM1 autoantibodies in chronic hepatitis C infection: a case of molecular mimicry? Marceau G, et al. Hepatology. 2005 Sep;42(3):675-82.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16037945&query_hl=18

Anti-liver-kidney microsomal type 1 (LKM1) autoantibodies directed against the cytochrome P450 2D6 (CYP2D6) are considered specific markers of type 2 autoimmune hepatitis, but are also found in 5% of sera from patients chronically infected by hepatitis C virus (HCV). Molecular mimicry between HCV proteins and CYP2D6 has been proposed to explain the emergence of these autoantibodies. Anti-LKM1 autoantibodies from hepatitis C-infected patients were affinity-purified against immobilized CYP2D6 protein and used to screen a phage display library. CYP2D6 conformational epitopes were identified using phage display analysis and the identification of statistically significant pairs (SSPs). Cross-reactivity between CYP2D6 and HCV protein candidates was tested by immunoprecipitation. Nineteen different clones were isolated, and their sequencing resulted in the mapping of a conformational epitope to the region of amino acids 254-288 of CYP2D6. Candidate HCV proteins for molecular mimicry included: core, E2, NS3 and NS5a. Affinity-purified autoantibodies from HCV+/LKM1+ patients immunoprecipitated either NS3, NS5a, or both, and these reactivities were specifically inhibited by immobilized CYP2D6. **In conclusion**, HCV+/LKM1+ sera recognize a specific conformational epitope on CYP2D6 between amino acids 254 to 288, the region that contains the major linear epitope in type 2 autoimmune hepatitis patients. Cross-reactivity due to molecular mimicry at the B-cell level was shown between the CYP2D6 and the HCV NS3 and NS5a proteins and could explain the presence of anti-LKM1 in patients chronically infected with HCV. Further investigation of the role played by this molecular mimicry in HCV-infected patients may lead to more specific strategies for diagnosis and treatment.

Chronic liver injury in rat and man upregulates the novel enzyme angiotensin converting enzyme II.

Paizis G, et al. Gut. 2005 Sep 15; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16166274&query_hl=18

BACKGROUND: Angiotensin converting enzyme (ACE) 2, is a recently identified homolog of ACE that may counter-regulate the actions of angiotensin (Ang) II by facilitating its breakdown to Ang 1-7. The renin angiotensin system (RAS) has been implicated in the pathogenesis of cirrhosis, but the role of ACE2 in liver disease is not known. **AIMS:** This study examined the effects of liver injury on ACE2 expression and activity in experimental hepatic fibrosis and human cirrhosis, and the effects of Ang 1-7 on vascular tone in cirrhotic rat aorta. **METHODS:** In sham operated and bile duct ligated (BDL) rats, QRT-PCR was used to assess hepatic ACE2 mRNA, and Western blotting and immunohistochemistry to quantify and localize ACE2 protein. ACE2 activity was quantified

by quenched fluorescent substrate assay. Similar studies were performed in normal human liver and in hepatitis C cirrhosis. **RESULTS:** ACE2 mRNA was detectable at low levels in rat liver and increased following BDL (363-fold, $P < 0.01$). ACE2 protein increased after BDL (23.5-fold, $P < 0.05$) as did ACE2 activity (4-fold, $P < 0.05$). In human cirrhotic liver, gene (>30-fold), protein expression (97-fold) and activity of ACE2 (2.4 fold) were increased compared to control (all $P < 0.01$). In healthy livers ACE2 was confined to endothelial cells, occasional bile ducts and perivenular hepatocytes, however, in both BDL and human cirrhosis, there was widespread parenchymal expression of ACE2 protein. Exposure of cultured human hepatocytes to hypoxia lead to increased ACE2 expression. In precontracted rat aorta Ang 1-7 alone did not affect vascular tone, but it significantly enhanced acetylcholine mediated vasodilatation in cirrhotic vessels. **CONCLUSIONS:** ACE2 expression is significantly increased in liver injury in both man and rat, possibly in response to increasing hepatocellular hypoxia, and may modulate RAS activity in cirrhosis.

The concentration of sFasL, ICE and IL-1beta in the serum and the liver tissue of chronic HCV infected patients. Lapinski TW, Hepatogastroenterology. 2005 Sep-Oct;52(65):1479-83.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16201101&query_hl=5

BACKGROUND/AIMS: In HCV infected patients HCV, apoptosis is as important as cytotoxicity. The aim of the present study was to estimate the activity of apoptosis in patients infected with hepatitis C before and during antiviral treatment. **METHODOLOGY:** 23 patients with hepatitis C were treated with Rebetron for 12 months. The concentration of IL-1beta, ICE and sFasL in the serum and liver tissue was analyzed before treatment was begun. The concentrations of IL-1beta, ICE and sFasL after 2 and 12 weeks of treatment were also analyzed. The concentrations of IL-1beta, ICE and sFasL in the liver tissue of patients with hepatitis C were compared with the concentrations in liver tissue of patients with alcohol related liver damage, but not HBV or HCV infected. **RESULTS:** Only 35% of the patients eliminated HCV-RNA from the blood six months after treatment had ended. The concentration of ICE and IL-1beta in the liver tissue of patients with hepatitis C was compared to concentrations in the liver tissue of patients with alcohol related liver damage. The concentration of sFasL in the liver tissue was twice as high among patients with alcohol related liver damage in comparison to the patients with infected hepatitis C. In the control group sFasL and ICE were not confirmed in the serum. After antiviral therapy the number of patients with sFas ligand in the blood increased (before beginning treatment 1 patient, after 12 weeks 8 patients). The high concentrations of ICE and IL-1beta in the serum showed a tendency to decrease during 12 weeks of therapy in the successfully treated patients. **CONCLUSIONS:** The HCV seems to be a mild stimulator of apoptosis. There was only a slight correlation between the morphology changes in the liver tissue and apoptosis in patients with HCV. There was no correlation between the success of the therapy and the apoptosis activity.

HIV/HCV COINFECTION

Transmission of Hepatitis C Virus Among HIV-Positive Homosexual Men and Response to a 24-Week Course of Pegylated Interferon and Ribavirin. Gilleece YC, et al. J Acquir Immune Defic Syndr. 2005 Sep 1;40(1):41-46.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16123680&query_hl=18

OBJECTIVE: To evaluate treatment outcome of acute hepatitis C virus (HCV) in HIV-positive individuals. **DESIGN:** Open-label, prospective study conducted in London, January 1997-December 2003. **METHODS:** Patients in whom acute HCV infection had been diagnosed had sequential HCV RNA levels measured at 0, 4, 12, 24, 32, and 48 weeks. If HCV RNA positive at 12 weeks, patients were offered pegylated interferon alpha-2b 1.5 mug/kg/wk and ribavirin 800-1200 mg/d for 24 weeks. Patients with increasing HCV RNA titers were offered treatment earlier. **RESULTS:** Fifty male homosexuals with a mean age 37 years were identified: 44 from abnormal liver function test results, 4 from sexual contact with an HCV-positive partner, and 2 at HIV seroconversion. Overall, 12 individuals became HCV RNA negative spontaneously. This was significantly associated with high baseline median CD4 count ($P = 0.029$), CD4 count >500 cells/mm ($P = 0.017$), and lower HCV RNA titers ($P = 0.017$). Only 27 patients accepted treatment, 16 (59%) of whom reached sustained virologic response. This was associated with higher peak mean alanine aminotransferase ($P < 0.001$) and higher baseline CD4% ($P = 0.041$). **CONCLUSIONS:** Sustained virologic response rates in HIV-positive patients treated for acute HCV infection are

lower than in HIV-negative subjects. Because a high percentage of individuals seroconvert spontaneously, treatment should be delayed until after 12 weeks.

Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. Miller MF, et al. Clin Infect Dis. 2005 Sep 1;41(5):713-20. Epub 2005 Jul 22.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16080095&query_hl=18

BACKGROUND: There are conflicting data in the medical literature regarding the degree of immune restoration (as measured by CD4 cell count) in patients who commence highly active antiretroviral therapy (HAART) when coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), compared with those with HIV infection alone. **METHODS:** We performed a meta-analysis that compared CD4 cell count increases after HAART initiation in HCV-negative and HCV-positive patients who were infected with HIV. Published studies in the English-language medical literature that involved cohorts of HCV-negative and HCV-positive patients who were coinfecting with HIV were obtained by searching the Medline, Embase Drugs and Pharmacology, and EBM Review-Cochrane Central Register of Controlled Trials databases. Data were extracted independently from relevant studies by 3 investigators and were used in a fixed-effects meta-analysis to determine the mean difference in the expected CD4 count change in the 2 groups. **RESULTS:** Eight trials involving 6216 patients were analyzed. Patients with HIV-HCV coinfection had a mean increase in the CD4 cell count that was 33.4 cells/mm³ (95% CI, 23.5-43.3 cells/mm³) less than that for HIV-infected patients without HCV infection. The results of the meta-analysis were independent of any one study and were not influenced by the year in which HAART was started. **CONCLUSIONS:** This meta-analysis shows that patients with HIV-HCV coinfection do, in fact, have less immune reconstitution, as determined by CD4 cell count after 48 weeks of HAART, than do patients with HCV infection alone. Future research should examine whether an impaired immunologic response corresponds with meaningful virologic and clinical outcomes.

Influence of Hepatitis C Virus Infection on HIV-1 Disease Progression and Response to Highly Active Antiretroviral Therapy. Rockstroh JK, et al. J Infect Dis. 2005 Sep 15;192(6):992-1002. Epub 2005 Aug 11.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16107951&query_hl=18

OBJECTIVE: To assess hepatitis C virus (HCV) antibody prevalence in the EuroSIDA cohort, along with survival, human immunodeficiency virus (HIV)-1 disease progression, virologic response (plasma HIV-1 RNA load of <500 copies/mL), and CD4 cell count recovery by HCV serostatus in patients initiating highly active antiretroviral therapy (HAART). **RESULTS:** HCV serostatus at or before enrollment was available for 5957 patients; 1960 (33%) and 3997 (67%) were HCV seropositive and seronegative, respectively. No association between an increased incidence of acquired immunodeficiency syndrome-defining illnesses or death and HCV serostatus was seen after adjustment for other prognostic risk factors known at baseline (adjusted incidence rate ratio [IRR], 0.97 [95% confidence interval {CI}, 0.81-1.16]). However, there was a large increase in the incidence of liver disease-related deaths in HCV-seropositive patients in adjusted models (IRR, 11.71 [95% CI, 6.42-21.34]). Among 2260 patients of known HCV serostatus initiating HAART, after adjustment, there was no significant difference between HCV-seropositive and -seronegative patients with respect to virologic response (relative hazard [RH], 1.13 [95% CI, 0.84-1.51]) and immunologic response, whether measured as a $\geq 50\%$ increase (RH, 0.94 [95% CI, 0.77-1.16]) or a ≥ 50 cells/ μ L increase (RH, 0.92 [95% CI, 0.77-1.11]) in CD4 cell count after HAART initiation. **Conclusions.** HCV serostatus did not affect the risk of HIV-1 disease progression, but the risk of liver disease-related deaths was markedly increased in HCV-seropositive patients. The overall virologic and immunologic responses to HAART were not affected by HCV serostatus.

Impact of Chronic Viral Hepatitis on Health-Related Quality of Life in HIV: Results from a Nationally Representative Sample. Kanwal F, et al. Am J Gastroenterol. 2005 Sep;100(9):1984-94.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16128943&query_hl=18

BACKGROUND: Little is known about the health burden of chronic viral hepatitis in HIV-infected patients. We compared health-related quality of life (HRQOL) of patients with HIV and hepatitis C virus (HCV) or HIV and hepatitis B virus (HBV) coinfection to those with HIV monoinfection. **METHODS:** Using a nationally representative sample of 1,874 adults with HIV who completed a baseline and two follow-up interviews, we

identified those with HIV monoinfection (n = 1,493), HIV-HCV coinfection (n = 279), and HIV-HBV coinfection (n = 122). We measured baseline and change over time scores for physical and mental health (PHS, MHS), overall quality of life (QOL), overall health, and disability days. To identify the independent effect of coinfection, we adjusted for demographic and clinical predictors of HRQOL using multivariable regression. **RESULTS:** Despite significant differences in socio-demographic characteristics between groups, there were no differences in the baseline scores for PHS, MHS, overall QOL, overall health, or disability days between groups. The HRQOL did not decline significantly over time for the HIV patients with or without HCV or HBV coinfection. All groups reported similar longitudinal changes in the HRQOL scores for all measures. **CONCLUSIONS:** We found no significant differences in disease burden as assessed by a generic HRQOL instrument between patients with HIV monoinfection and HIV-HCV or HIV-HBV coinfection. These data are relevant in counseling coinfecting patients regarding the impact of coinfection on HRQOL, and are important in designing clinical trials and conducting cost-effectiveness analyses including this vulnerable cohort.

Prevalence of hepatitis B and C in pregnant women who are infected with human immunodeficiency virus.

Santiago-Munoz P, et al. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 2):1270-3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16157150&query_hl=18

OBJECTIVE: The purpose of this study was to evaluate the prevalence of hepatitis B and hepatitis C virus coinfection among pregnant women who are infected by human immunodeficiency virus and who attend an obstetric complications prenatal clinic. **STUDY DESIGN:** A de-identified research obstetric human immunodeficiency virus database was reviewed regarding patient demographic characteristics, risk factors for infection, history of sexually transmitted diseases, and initial CD4 count. **RESULTS:** Four hundred fifty-five women who are infected with human immunodeficiency virus with 572 pregnancies were delivered over 11 years. The overall prevalence of human immunodeficiency virus and hepatitis B or C virus coinfection in our population was 6.3%. More specifically, 1.5% was co-infected with hepatitis B virus, and 4.9% was co-infected with hepatitis C virus. Patients with hepatitis virus were more likely to use intravenous drugs (52% vs 18%; P < .01) and alcohol (38% vs 5%; P < .01). Co-infected patients were older (28 vs 25.6 years; P=.04), but there were no racial differences. Median baseline CD4 counts in hepatitis B virus co-infected patients were significantly lower (310 cells/mm³) than those in either hepatitis C virus co-infected patients (453 cells/mm³) or patients who were not co-infected with human immunodeficiency virus (414 cells/mm³). **CONCLUSION:** One of 16 pregnant women who were infected with human immunodeficiency virus was co-infected with hepatitis B or hepatitis C virus. Hepatitis B co-infections appear to be associated with more compromised immune status in our cohort.

Liver injury and changes in hepatitis C Virus (HCV) RNA load associated with protease inhibitor-based antiretroviral therapy for treatment-naïve HCV-HIV-coinfecting patients: lopinavir-ritonavir versus nelfinavir.

Sherman KE, et al. Clin Infect Dis. 2005 Oct 15;41(8):1186-95. Epub 2005 Sep 13.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16163639&query_hl=18

BACKGROUND: Highly active antiretroviral therapy (HAART) initiation in patients coinfecting with human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) has been associated with transaminase and HCV viral load flares. Previous studies have included highly variable antiretroviral regimens. We compared effects of 2 protease inhibitor-based regimens on alanine aminotransferase (ALT) levels and HCV loads in HCV-HIV-coinfecting patients initiating HAART. **METHODS:** Seventy HIV-infected patients with positive baseline results of HCV enzyme-linked immunosorbent assay from a treatment trial comparing lopinavir-ritonavir with nelfinavir were evaluated during a 48-week period. HCV and HIV titers were analyzed at baseline, at weeks 24 and 48 of treatment, and during flares in the ALT level of >5 times the upper limit of normal. **RESULTS:** A total of 57 of 70 patients tested positive for HCV RNA at baseline. HCV titers for patients in lopinavir-ritonavir and nelfinavir groups, respectively, were as follows: baseline, 6.07 and 6.22 log IU/mL; week 24 of treatment, 6.68 and 6.48 log IU/mL; and week 48 of treatment, 6.32 and 6.44 log IU/mL. Of patients with a CD4⁺ cell count of <100 cells/mm³ at baseline, 5 of 11 in the nelfinavir group and 0 of 10 in the lopinavir-ritonavir group had an increase in the HCV load of >0.5 log IU/mL from baseline to week 48. The mean ALT level increased by 45 U/L at 24 weeks and 18 U/L at 48 weeks in the nelfinavir group but decreased by 18 U/L at 24 weeks and 7 U/L at 48 weeks in the lopinavir-ritonavir group. Eight patients in the nelfinavir group and 2 patients in the lopinavir-ritonavir group had grade 3 or 4 flares in the ALT level. **CONCLUSIONS:** HAART initiation is associated with increased HCV loads and ALT levels. A low baseline CD4⁺ cell count is associated with persistent increases in the HCV RNA load in

nelfinavir-treated patients. These results warrant careful interpretation of abnormalities in the ALT load after HAART initiation in HCV-HIV-coinfected patients to prevent premature discontinuation of treatment.

Increased Hepatocyte Fas Expression and Apoptosis in HIV and Hepatitis C Virus Coinfection.

Macias J, et al. J Infect Dis. 2005 Nov 1;192(9):1566-76. Epub 2005 Sep 29.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16206071&query_hl=5

BACKGROUND: Chronic hepatitis C disease (CHC) follows an accelerated course in human immunodeficiency virus (HIV) coinfection. The reasons for this are unclear. Fas-mediated hepatocyte apoptosis is involved in the pathogenesis of hepatitis C virus (HCV) infection. We sought to compare the expression of Fas on hepatocytes and irreversible apoptosis of hepatocytes among patients with CHC with and without HCV/HIV coinfection. **Methods:** Fas-immunostained hepatocytes were semiquantified, and apoptotic hepatocytes were detected by staining caspase-cleaved cytokeratin 18 filaments and counted across the entire section of liver-biopsy specimens from HCV-infected patients with and without HCV/HIV coinfection. **Results:** One hundred thirty-four HCV/HIV-coinfected and 100 HCV-infected patients were included. HCV/HIV coinfection was associated with both diffuse distribution of Fas-stained hepatocytes (adjusted odds ratio [AOR], 7.4 [95% confidence interval {CI}, 3.8-14.4]) and with apoptotic hepatocyte counts greater than the median (AOR, 2.5 [95% CI, 1.5-4.5]). In HCV/HIV-coinfected patients, CD4(+) cell nadir <200 cells/mL was associated with both Fas expression (AOR, 2.9 [95% CI, 1.3-6.8]) and hepatocyte apoptosis (AOR, 2.3 [95% CI, 1.1-4.9]). **CONCLUSION:** HCV/HIV-coinfected patients show higher levels of hepatocytes expressing Fas and undergoing irreversible apoptosis than do HCV-infected patients. However, low CD4(+) cell nadirs in coinfecting patients are associated with hepatocyte Fas expression and apoptosis.

Presence of Hepatitis C Virus (HCV) RNA in the Genital Tracts of HCV/HIV-1-Coinfected Women.

Nowicki MJ, et al. J Infect Dis. 2005 Nov 1;192(9):1557-65. Epub 2005 Sep 29.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16206070&query_hl=5

BACKGROUND: Hepatitis C virus (HCV)-infected women--in particular, those coinfecting with human immunodeficiency virus type 1 (HIV-1)--can transmit infection to their children and sex partners. **METHODS:** The present study was conducted to analyze the presence of HCV RNA in cervicovaginal lavage (CVL) fluid from 71 women (58 HCV/HIV-1-coinfected women and 13 HCV-infected, HIV-1-uninfected women) enrolled in the Women's Interagency HIV Study. **RESULTS:** HCV RNA was detected (by a commercial polymerase chain reaction assay) in CVL fluid from 18 (29%) of the HIV-1-infected women and from none of the HIV-1-uninfected women ($P < .05$). Multivariate analysis revealed that risk factors for the presence of HCV RNA in CVL fluid were HCV viremia (odds ratio [OR], 16.81; $P = .02$) and HIV-1 RNA in CVL fluid (OR, 19.87; $P = .02$). This observation suggests local interactions between HIV-1 and HCV in the genital tract compartment. There was no correlation between HCV RNA in CVL fluid and CD4, CD8, or CD3 cell counts, HIV-1 RNA viremia, the number of leukocytes in CVL fluid, or HIV-1 therapy. Furthermore, in 3 of 5 analyzed patients who had a detectable CVL HCV RNA load, we found viral variants differing in the 5' untranslated region that were present neither in plasma nor in peripheral-blood mononuclear cells. **CONCLUSIONS:** Our observations point to the importance of the genital tract compartment, in which local HCV replication could be facilitated by local HIV-1 replication.

Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy.

Brau N, et al. J Hepatol. 2005 Sep 20; [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16182404&query_hl=2

BACKGROUND/AIMS: HIV/HCV-coinfected patients reportedly have a faster fibrosis progression rate (FPR) than HCV-monoinfected patients. This study examined whether HIV suppression through highly active antiretroviral therapy (HAART) attenuates this accelerated fibrosis progression. **METHODS:** In two hepatitis C centers, a retrospective analysis identified 656 consecutive treatment-naive HCV-infected patients who had undergone a liver biopsy, had a presumed date of HCV infection, and had been tested for HIV, 274 of them HIV-positive (95.2% on HAART) and 382 HIV-negative. The primary outcome measure was the FPR, defined as Ishak fibrosis score [0-6] over estimated duration of HCV infection. **RESULTS:** Among HIV/HCV-coinfected patients, 51.2% had undetectable HIV RNA (<400 copies/mL). There was no difference in FPR between HIV/HCV-coinfected and HCV-monoinfected patients (0.136 vs. 0.128 Ishak fibrosis units/year, $P = 0.29$). However,

HIV/HCV-coinfected patients with any detectable HIV viral load >400copies/mL had a faster FPR (0.151) than HCV-monoinfected patients (0.128, P=0.015) and than HIV/HCV-coinfected patients with undetectable plasma HIV RNA (0.122, P=0.013) who in turn had the same FPR as HCV-monoinfected subjects (0.128, P=0.52). An accelerated FPR in HIV viremic patients was seen with CD4+ cells <500/mm³ (0.162 vs. 0.123, undetectable HIV RNA, P=0.005) but not with CD4+ cells >500/mm³ (0.118 vs. 0.121, P=0.89). In multivariable linear regression analysis of HIV/HCV-coinfected patients, log₁₀ HIV RNA level, necroinflammation, and age at HCV infection were independently correlated to FPR, but not alcohol use or CD4+ cell count (r²=0.45 for model). **CONCLUSIONS:** HIV/HCV-coinfected patients with undetectable HIV RNA through HAART have a slower FPR than those with any HIV RNA level and an FPR similar to HCV-monoinfected individuals.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Treatment of chronic hepatitis C virus infection via antioxidants: results of a phase I clinical trial.

Melhem A, et al. J Clin Gastroenterol. 2005 Sep;39(8):737-42. Liver Unit, Department of Medicine, Hebrew http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16082287&query_hl=18

BACKGROUND: The pathogenesis of chronic hepatitis C virus (HCV) infection is associated with a defective host antiviral immune response and intrahepatic oxidative stress. Oxidative stress and lipid peroxidation play major roles in the fatty liver accumulation (steatosis) that leads to necro-inflammation and necrosis of hepatic cells. Previous trials suggested that antioxidative therapy may have a beneficial effect on patients with chronic HCV infection. **AIMS:** To determine the safety and efficacy of treatment of chronic HCV patients via a combination of antioxidants. **METHODS:** Fifty chronic HCV patients were treated orally on a daily basis for 20 weeks with seven antioxidative oral preparations (glycyrrhizin, schisandra, silymarin, ascorbic acid, lipoic acid, L-glutathione, and alpha-tocopherol), along with four different intravenous preparations (glycyrrhizin, ascorbic acid, L-glutathione, B-complex) twice weekly for the first 10 weeks, and followed up for an additional 20 weeks. Patients were monitored for HCV-RNA levels, liver enzymes, and liver histology. Assessment of quality of life was performed using the SF-36 questionnaire. **RESULTS:** In one of the tested parameters (eg, liver enzymes, HCV RNA levels, or liver biopsy score), a combination of antioxidants induced a favorable response in 48% of the patients (24). Normalization of liver enzymes occurred in 44% of patients who had elevated pretreatment ALT levels (15 of 34). ALT levels remained normal throughout follow-up period in 72.7% (8 of 11). A decrease in viral load (one log or more) was observed in 25% of the patients (12). Histologic improvement (2-point reduction in the HAI score) was noted in 36.1% of the patients. The SF-36 score improved in 26 of 45 patients throughout the course of the trial (58% of the patients). Treatment was well tolerated by all patients. No major adverse reactions were noted. **CONCLUSIONS:** These data suggest that multi antioxidative treatment in chronic HCV patients is well tolerated and may have a beneficial effect on necro-inflammatory variables. A combination of antiviral and antioxidative therapies may enhance the overall response rate of these patients.

Chinese Herbal Medicine and Chemotherapy in the Treatment of Hepatocellular Carcinoma: A Meta-analysis of Randomized Controlled Trials . Xiaojuan Shu, MPH et al. Integrative Cancer Therapies, Vol. 4, No. 3, 219-229 (2005)

<http://ict.sagepub.com/cgi/content/abstract/4/3/219>

BACKGROUND: Hepatocellular carcinoma (HCC), one of the most common malignancies worldwide, is highly resistant to standard therapy. It is unclear whether chemotherapy, arterial embolization, or arterial chemoembolization improve survival advantage enough to justify their high toxicity. Treatment with Chinese herbal medicine has been explored, combining herbs that stimulate host immune response with those that have cytotoxic activity against HCC cells. The authors sought to evaluate the effectiveness of Chinese herbal medicine combined with chemotherapy. The hypothesis was that Chinese herbal medicine added to chemotherapy for the treatment of HCC would improve survival and tumor response, when compared to treatment with chemotherapy alone.

METHODS: The authors searched the databases TCMLARS, PubMed, and EMBASE as well as the bibliographies of studies identified in the systematic search for potentially relevant titles or abstracts of studies in any language. They retained those that (1) treated only HCC patients, (2) were described as randomized or reported that there was no statistical difference between treatment groups, (3) gave patients either Chinese herbal medicine therapy combined with chemotherapy in the treatment group or chemotherapy alone in the control group, and (4) provided data on the number of enrolled subjects and responders and nonresponders for tumor response and survival. The

authors used random effects meta-analysis to combine data. **RESULTS:** Twenty-six studies representing 2079 patients met the inclusion criteria. Chinese herbal medicine combined with chemotherapy, compared to chemotherapy alone, improved survival at 12 months (relative risk [RR], 1.55; 95% confidence interval [CI], 1.39-1.72; $P < .000$), 24 months (RR, 2.15; 95% CI, 1.75-2.64; $P < .000$), and 36 months (RR, 2.76; 95% CI, 1.95-3.91; $P < .000$). Tumor response increased (RR, 1.39; 95% CI, 1.24-1.56; $P < .000$). **CONCLUSION:** These findings provide promising evidence that combining Chinese herbal medicine with chemotherapy may benefit patients with HCC. Because of the low quality of these studies, these findings should be confirmed through conducting high-quality, rigorously controlled trials.

MISCELLANEOUS WORKS

Susceptibility to hepatitis A in patients with chronic liver disease due to hepatitis C virus infection: missed opportunities for vaccination. Shim M, et al. *Hepatology*. 2005 Sep;42(3):688-95.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16104047&query_hl=18

Hepatitis A virus (HAV) superinfection is associated with a high risk of liver failure and death in patients with underlying chronic liver disease. Although HAV vaccination is recommended for all patients with chronic hepatitis C virus (HCV) infection, little is known about adherence to these recommendations in clinical practice. The aims of this study were to determine the frequency of HAV testing and vaccination among patients with chronic HCV infection. We conducted a retrospective cohort study of 1,193 patients diagnosed with chronic HCV infection over a 1-year period. During 1,646 person-years of follow-up, patients were seen by their primary care provider a median of 10.0 times (interquartile range, 4.0-20.0). HAV antibody testing was performed in 640 subjects (53.6%), and 317 (49.5%) of those tested were susceptible (HAV antibody negative). Only 94 of the 1,193 patients (7.9%) received the HAV vaccine, including 26.8% of the 317 susceptible patients, 0.9% of the 323 patients who were already immune to HAV, and 1.1% of the 553 subjects who were never tested. Among the 94 vaccinated patients, 45 received only one dose of the vaccine. Three of the unvaccinated patients developed acute HAV infection during follow-up, and 1 of them died of acute liver failure. **In conclusion,** despite published recommendations to vaccinate against HAV in patients with chronic HCV infection, we found that HAV testing and vaccination rates were low in clinical practice. Public health programs to increase awareness about HAV vaccination in patients with chronic liver disease are needed.

Irritability rather than depression during interferon treatment is linked to increased tryptophan catabolism.

Russo S, et al. *Psychosom Med*. 2005 Sep-Oct;67(5):773-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16204437&query_hl=5

OBJECTIVE: Treatment with recombinant interferon is associated with high rates of psychiatric comorbidity. We investigated the relation between catabolism of the essential amino acid tryptophan, being rate-limiting of peripheral and cerebral serotonin formation, and psychiatric symptoms in patients undergoing combination treatment with interferon-alpha and ribavirin. **PATIENTS AND METHODS:** Eighteen patients with viral hepatitis C who received interferon were included. A psychiatrist screened patients before and while on interferon-alpha treatment for 2 months, using a structured diagnostic interview. Fasting plasma tryptophan and platelet serotonin levels were measured at each visit. **RESULTS:** At baseline no evident psychopathology was observed. After 2 months of interferon treatment, 10 patients experienced increased irritability. No other structural psychopathology was observed. Decreased plasma tryptophan level correlated with the presence of irritability ($p = .047$). Platelet serotonin levels were found to be decreased during treatment ($p = .002$). **CONCLUSIONS:** Aggressive impulse dysregulation is highly prevalent in patients receiving interferon treatment. This is associated with decreased plasma tryptophan levels which may lead to attenuated peripheral and central serotonergic neurotransmission.

Description of a new hepatitis C risk assessment tool. Nguyen MT, et al. *Arch Intern Med*. 2005 Sep 26;165(17):2013-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16186472&query_hl=18

BACKGROUND: Because of the low prevalence of hepatitis C virus (HCV) infection in the general population, mass screening would be expensive and of low yield. Some researchers advocate targeted screening of persons at

elevated HCV risk. **METHODS:** This cross-sectional study aimed to develop a patient-administered tool to assess HCV infection risk. Two hundred seven patients with unknown HCV status from a general medicine practice and 222 HCV-positive patients from a hepatology practice completed a 72-item survey about demographic, social, and clinical risk factors for HCV infection. General medicine patients also underwent HCV serologic testing.

RESULTS: Three (1.5%) of 207 general medicine patients had positive HCV antibody test results. These patients plus the 222 hepatology patients were significantly more likely than HCV-negative patients to report an array of factors. In a multivariable model, 7 factors remained significantly associated with HCV infection: sex with a prostitute or an injecting drug user, exposure to blood products, refusal as a blood donor or as a life insurance applicant, witnessing illicit drug use, and self-reported HBV infection. A simplified model that assigned 1 point for each factor present predicted HCV infection as well as a weighted model (based on chi(2) testing and receiver operating characteristic curve comparison). In a population with a 2% prevalence of HCV infection, people who identified 2 risk factors had a 10% chance of HCV infection, whereas those with 4 or more risk factors had a 50% chance. **CONCLUSIONS:** A self-administered 72-item questionnaire can stratify patients into HCV risk groups. If validated in other primary care populations, this instrument could help target HCV screening.

Demographic, HIV risk behavior, and health status characteristics of "crack" cocaine injectors compared to other injection drug users in three New England cities. Buchanan D, et al. *Drug Alcohol Depend.* 2005 Sep 16; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16171952&query_hl=18

OBJECTIVES: To compare demographic, HIV risk behaviors, and health status characteristics of injection drug users (IDUs) who have injected "crack" cocaine with IDUs who have not. **METHODS:** Nine hundred and eighty-nine IDUs were recruited in New Haven, CT, Hartford, CT and Springfield, MA from January 2000 to May 2002. Participants were administered a modified version of the National Institute on Drug Abuse Risk Behavior Assessment Questionnaire. **RESULTS:** Nine percent (n=89) of participants reported "ever" injecting crack cocaine and 4.2% (n=42) reported injecting crack in the past 30 days. Lifetime and current crack injectors did not differ significantly on any demographic characteristics. Lifetime and current crack injectors did not differ on gender, age or marital status from IDUs who have never injected crack. Significant differences were found on race, education, employment and residence, with crack injectors more likely to be white, employed, better educated and living in New Haven than IDUs who have never injected crack. After adjusting for current (past 30 day) speedball and powder cocaine injection, crack injectors reported higher rates of risky drug use behaviors and female crack injectors reported higher rates of risky sexual behaviors. Crack injectors reported higher rates of abscesses, mental illness and Hepatitis C infection, but not Hepatitis B or HIV infection. **CONCLUSIONS:** The emergence of crack cocaine injection requires urgent attention, as this new drug use behavior is associated with elevated rates of high risk behaviors.

When Does Mother to Child Transmission of Hepatitis C Virus Occur? Mok J, et al. *Obstet Gynecol Surv.* 2005 Sep;60(9):572-574.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16121099&query_hl=18

Mother-to-child transmission of hepatitis C virus (HCV) has been reported in up to 10% of cases and is much more likely to occur when the mother is also infected by HIV. Although women with HCV viremia are especially likely to transmit infection, the precise time when transmission takes place is not known. Transmission of HCV was examined in a prospective cohort study using data from the European Pediatric Hepatitis C Network. Fifty-four HCV-infected children were tested by the HCV RNA polymerase chain reaction technique within 3 days of birth. Nearly one third (31%) of newborn infants tested in the first 3 days of life had positive results. Transmission was more likely if the mother was coinfecting by HIV, but the difference was not statistically significant. Mode of delivery, gender, and gestational age failed to predict the polymerase chain reaction (PCR) findings. Mean birth weight was significantly lower in infected children, but there was no significant difference when low-birth-weight infants were compared with normal-weight neonates. Breast-fed infants were marginally less likely than formula-fed infants to be PCR-positive. Four of 10 infants born to mothers who tested positive 4 weeks before delivery were themselves PCR-positive, but this was not the case for any of 4 infants born to PCR-negative women. A positive association between PCR positivity in the first 3 days of life and infection by genotype 1 remained significant after adjusting for several possible confounding factors. In 36 infants who were PCR-negative when born, the mean age at the first positive test was 3.9 months. Late intrauterine or intrapartum transmission was considered to be most

likely for 27 infants who were PCR-negative at birth but -positive by age 3 months. Peripartum transmission seemed likely for 9 infants who were PCR-negative at birth and PCR-positive for the first time after 3 months. It appears that at least one third of HCV-infected infants, and possibly as many as half of them, acquire infection before birth. Should effective treatment be developed that is safer for pregnant women than are interferon-alpha and ribavirin, treatment optimally would begin early in pregnancy.

Physical and psychosocial contributors to quality of life in veterans with hepatitis C not on antiviral therapy.

Rowan PJ, et al. *J Clin Gastroenterol*. 2005 Sep;39(8):731-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16082286&query_hl=18

BACKGROUND AND AIMS: Treatment-naive hepatitis C virus (HCV)-infected patients report impaired health-related quality of life (HRQOL), although causes are unclear. Psychosocial factors may be major determinants of HRQOL. **METHODS:** We administered a general (Short Form-36; SF-36) and a liver-specific (Chronic Liver Disease Questionnaire; CLDQ) HRQOL measure to 62 HCV-infected veterans being considered for antiviral therapy. Psychosocial assessment included the Structured Clinical Interview for DSM-IV Axis I Disorders/Non-Patient (SCID-I/NP), Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), Abbreviated Cook-Medley (ACM) anger measure, and Medical Outcomes Study Social Support Measure (SSM). We examined the potential determinants of HRQOL, including psychosocial measures, demographic measures (age, sex, race/ethnicity), clinical measures (presence of cirrhosis, comorbid medical conditions), and viral data (quantitative PCR). **RESULTS:** SF-36 scores were significantly lower in HCV-infected patients than published U.S. population norms but similar to those reported by previous studies of HCV-infected samples. CLDQ scores were very similar to those reported by previous studies. Demographic, clinical, and viral indicators were not statistically associated with HRQOL, and neither was the presence of a substance abuse or psychotic disorder. Lower BDI-II and BAI scores were associated with better general and disease-specific HRQOL. Lower SSM scores were associated with lower scores on SF-36 but not CLDQ; however, this effect did not persist in multiple linear regression analyses. In these, BDI-II was the strongest independent predictor of both SF-36 and CLDQ. **CONCLUSIONS:** Psychosocial factors, especially depression, are strong indicators of impaired HRQOL for HCV-infected veterans not receiving antiviral therapy. Screening and treatment of psychosocial factors is recommended.

Ethical challenges in the care of persons with hepatitis C infection: a pilot study to enhance informed consent with veterans. Geppert CM, Dettmer E, Jakiche A. *Psychosomatics*. 2005 Sep-Oct;46(5):392-401.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16145183&query_hl=18

Psychiatric and addictive disorders are often considered contraindications to hepatitis C virus (HCV) treatment. In this pilot study, the ability of 30 veterans to provide informed consent for combined antiviral HCV therapy was examined with a mental health assessment protocol specifically geared to evaluate capacity in this area. The results showed that subjects lacked essential knowledge regarding the course of the disease and the nature of antiviral treatment despite receiving prior counseling. Informed consent assessments of candidates for HCV treatment may identify deficits that are responsive to intervention, thereby allowing patients with comorbid psychiatric and addictive disorders to receive effective HCV treatment.

Comparison of characteristics of treated and non-treated patients with Hepatitis C infection.

Hare CB, et al. *Pharmacoepidemiol Drug Saf*. 2005 Sep 1; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16136612&query_hl=18

OBJECTIVES: This study compares the characteristics of treated and non-treated patients with Hepatitis C (HCV) infection. **METHODS:** Information on patient demographics, clinical data, and treatment regimens were collected from a retrospective medical record review of 998 patients diagnosed with HCV, representing a diverse geographic sample of 200 U.S. physicians including 130 gastroenterologists, 50 infectious disease physicians, and 20 hepatologists. A total of 551 patients were randomly selected and 447 were provided as an augmented sample in an intent-to-treat analysis based on treatment decisions. Pretreatment factors examined included age, gender, race, weight, HCV genotype, HCV viral load, serum ALT levels, liver biopsy results, cirrhosis, HIV co-infection, HBV co-infection, IV drug use, and insurance status. Univariate analyses were performed using Chi-squared or ANOVA tests. Factors that were significant in univariate analyses were entered into a multivariate logistic regression model with HCV treatment as the outcome variable. **RESULTS:** Of the 998 patients reviewed, 778 were treated for HCV

and 220 were not treated. In univariate analyses, non-treated patients were more likely to be African American, HBV co-infected, HIV co-infected, IDUs, alcoholics, Medicaid insured, and were less likely to have had biopsies. The multivariate regression analysis demonstrated that performance of a liver biopsy, treatment with psychiatric medications (antidepressants and anxiolytics), and patient weight were independently associated with treatment, while Medicaid insurance and HIV co-infection were independently associated with a decreased likelihood of receiving HCV therapy. **CONCLUSION:** This study suggests that it is not the clinical stage of HCV infection but the patient's demographic characteristics and co-morbid conditions that impact the decision to initiate HCV therapy.

Changes in epidemiological patterns of HCV infection and their impact on liver disease over the last 20 years in Greece. Savvas SP, et al. *J Viral Hepat.* 2005 Sep;12(5):551-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108773&query_hl=18

SUMMARY: The aim of this study was to investigate the relative frequency of hepatitis C virus (HCV) genotypes in Greek patients with chronic infection as well as possible secular changes in their distribution in relation to modes of transmission, age and time at acquisition of the infection and other variables. We evaluated 434 unselected patients, 241 males and 193 females with a median age of 46.2 years (18-75), with chronic HCV infection presenting during the period 1996-2000. HCV infection was confirmed by the detection of HCV-RNA by polymerase chain reaction (PCR), while HCV genotyping was performed by the Inno-LiPA assay. Liver biopsies were evaluated according to Ishak's scoring system. Of 434 patients, 167 had a history of blood transfusion [post-transfusion hepatitis (PTH)], 80 were i.v. drug users and in 187 the route of infection remained unknown. The overall distribution of HCV genotypes 1, 2, 3 and 4 was 47, 8.3, 27 and 15.2%, respectively. Genotype 3 was common in younger adults and i.v. drug users, whereas genotype 1 predominated in older people and PTH patients ($P < 0.001$ for both). Infection acquired before 1981 (group A) was related to transfusion and genotype 1, while after 1981 (group B) with i.v. drug use and genotype 3 ($P < 0.01$). Biopsy was available in 369 (85%) patients, of whom 22.5% had cirrhosis; 29.8% in group A and 9.9% in group B. In a multivariate analysis, cirrhosis was strongly associated with the duration of infection ($P = 0.013$). Our study revealed a change of HCV genotype distribution in the last 20 years among Greek patients with chronic HCV infection as a result of epidemiological changes in HCV transmission. The presence of cirrhosis was associated only with the duration of infection. These observations have impact both on prevention and treatment.

Future trends of HCV-related cirrhosis and hepatocellular carcinoma under the currently available treatments. Sypsa V, et al. *J Viral Hepat.* 2005 Sep;12(5):543-50.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108772&query_hl=18

SUMMARY: The epidemic of hepatitis C virus (HCV) infection is a major public health issue. We conducted a comprehensive analysis to estimate future HCV-related morbidity and mortality, using a model which is the first to take into account currently available treatments. We reconstructed the incident infections per year in the past that progressed to chronic hepatitis C (CHC) in Greece. Then, the natural history of the disease was simulated in subcohorts of newly infected subjects in the presence or absence of treatment using yearly estimates of the number of treated patients obtained from national databases. Annual estimates of the incidence and prevalence of CHC by fibrosis stage, hepatocellular carcinoma (HCC) and mortality were obtained up to 2030. The current proportion of naive CHC patients receiving treatment in Greece is 1.2% per year. Treatment of 1.2-10% of naive CHC patients per year would reduce the cumulative number of incident cirrhosis and HCC cases from 2002 to 2030 by 10.8-39.4% and 12.8-39.8%, respectively and decrease the number of prevalent cirrhosis and HCC cases in 2030 by approximately 17-48% compared with the number estimated under the assumption of no treatment. Approximately 17 cirrhosis cases or six HCC cases or 10 premature deaths would be prevented for every 100 treated patients. However, the prevalent cirrhotic/HCC cases because of HCV and HCV-related deaths would not plateau until 2030. Despite the introduction of effective treatment, HCV-related morbidity and mortality will likely increase during the next 20-30 years in Greece. Intensive primary prevention efforts coupled with increased access to the currently available treatments are necessary to control the chronic consequences of HCV epidemic.