

HEPATITIS C CARING AMBASSADORS PROGRAM NEWSLETTER

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IN THE NEWS.....	1
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES.....	13
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES.....	18
HIV/HCV COINFECTION.....	23
COMPLEMENTARY & ALTERNATIVE THERAPIES.....	26
MISCELLANEOUS WORKS.....	27

IN THE NEWS

Old View Slows Hepatitis C Fight (New Zealand)

http://www.rednova.com/news/health/192556/old_view_slows_hepatitis_c_fight/

Carriers of hepatitis C are going undiagnosed and missing new treatments because of ignorance and stigma, says a medical researcher. Dr Ian Sheerin, of the Christchurch School of Medicine and Health Sciences, said general practitioners did not actively offer testing, and some patients preferred not to know.

"There seems to be an old view that there's nothing you can do about it, but there are some very good treatments now," he said. Last year, Pharmac began funding a new combination therapy medication for hepatitis C, called pegylated interferon. Treatment had a success rate as high as 80 per cent for some types of hepatitis C infection.

As many as 30,000 New Zealanders are thought to have the disease, spread by contact with infected blood. It is known as the "silent epidemic" because some never develop symptoms and it is thought fewer than 30% have been diagnosed. Sheerin said there was a need for specialised GP clinics to test people and provide follow-up education, support and ongoing laboratory testing for liver function. He cited a successful example in Wellington that ran in conjunction with the needle- exchange programme.

Because up to 80% of infections were associated with injecting- drug use, many affected people felt marginalised from society and did not like to go to a regular GP, he said. Hepatitis Foundation chief executive John Hornell said all GPs should offer testing, so infected people could be monitored and treated. Some people would have forgotten about illicit drug use in their past, he said. "A lot of professional people did it in the 1970s when heroin came in, and I know of people who've got hep C who only injected once."

Bill Jang, 50, had hepatitis C for 25 years before he was diagnosed. His symptoms were "subtle and non- specific". "There's nothing that hits you like a tonne of bricks. You put a lot of it -- tiredness, intolerance to alcohol -- down to the effects of ageing. I thought maybe I just need my cholesterol checking." Jang said he had injected drugs as a teenager. Although clean now, his condition was worsened by heavy drinking in his 20s and 30s. After two courses of treatment in his 40s, he was clear of the virus.

Jang, who is manager of the Hepatitis C Resource Centre in central Christchurch, said people needed to realise the infection was more of a problem than many thought. "A lot of people my age have almost forgotten they put themselves at risk in the '70s and '80s," he said. "We also need to upskill doctors a lot better so they can learn to monitor it." Jang said the resource centre needed more resources to employ paid educators.

About 4000 people are affected by hepatitis C in Christchurch. The city has the most injecting-drug users per capita in the country.

4 Million People in Bangladesh Suffering From Hepatitis C Virus

http://www.rednova.com/news/health/194403/4_million_people_in_bangladesh_suffering_from_hepatitis_c_virus/

Some 4 million people or 3 percent of the total population of Bangladesh are suffering from the Hepatitis C virus (HCV), New Age reported on Monday. The daily quoted Health and Family Welfare Minister Dr Khandaker Mosharraf Hossain as saying that more than 170 million people across the world are suffering from HCV, of which 30 million are in India, 14 million in Egypt, 11 million in Pakistan and 4 million in the United States.

The yearly increase of HCV patients across the world is 3 to 4 million, the minister said at a seminar on "Mass Awareness to Prevent Hepatitis-C in Bangladesh" organized by Sandhani Central Committee (FCC). General Secretary of FCC Mamun Shiblee was quoted as saying that due to a mass awareness program, people are much more aware of Hepatitis-B than of HCV, which is why they do not take necessary precautionary measures to prevent its spread. He underscored the necessity of mass awareness campaign to save people from HCV as no

vaccine has yet been invented to counteract its effects. He said that blood screening for HCV is not routinely carried out in most cases in Bangladesh.

FCC adviser Dr Mani Lal Aich Litu also said on the seminar that blood transfusion without proper screening, being shaved in men's saloons where the blades are used over and over, and intravenous drug using are the main sources of HCV infection. He said that 25 percent of intravenous drug users and 1.2 percent of blood donors suffer from Hepatitis-C, which leads to liver cirrhosis and cancer resulting in death. He advised the use of disposable syringes during blood tests, compulsory blood screening and avoiding men's salons.

Genelabs Drug Discovery Team Advances Compounds Against the Hepatitis C Virus in Preclinical Development

<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/08-04-2005/0004082446&EDATE=>

REDWOOD CITY, Calif., Aug. 4 -- Genelabs Technologies, Inc. today announced that a non-nucleoside compound from its internal Hepatitis C virus (HCV) drug discovery program has advanced into preclinical development. The compound, designated GL60667, is the second Genelabs non-nucleoside compound to advance into preclinical development. Genelabs also announced that the company has further advanced GL59728, its first non-nucleoside preclinical development candidate. Genelabs plans to initiate Good Laboratory Practices (GLP) preclinical studies on GL59728 which, if successful, would enable the company to file an Investigational New Drug Application (IND) for the compound. Genelabs retains all commercial rights to its non-nucleoside compounds.

Genelabs based its decision to advance compound GL60667 on rigorous pre-determined standards, including various measures of potency, metabolism, pharmacokinetics and toxicity. Genelabs believes that compounds meeting these criteria should hold a competitive advantage over other non-nucleoside HCV inhibitors described in the scientific literature. GL60667 has demonstrated the following properties in in vitro assays:

- potency of approximately 40 nanomolar against an HCV replicon
- potency of approximately 20 nanomolar for inhibition of the HCV polymerase.
- potency against the major genotypes of HCV, including genotype 1, the most common genotype in the United States and western Europe

The concentration of GL60667 that is effective in reducing HCV replication is more than 100 times lower than the concentration that causes toxicity to various human cell lines, as demonstrated in a battery of tests conducted by Genelabs. Genelabs also has profiled the metabolic and pharmacokinetic properties of GL60667 in several different animal species. Extrapolating from this data, Genelabs believes the compound should be suitable for once-a-day dosing.

Separately, Genelabs advanced its first non-nucleoside preclinical candidate, GL59728, into IND-enabling studies based on favorable results from 1-day and 7-day toxicology studies in two animal species. Selection of a vendor for process development and large-scale synthesis is underway. "The preclinical results generated to date from our hepatitis C virus drug discovery efforts demonstrate the depth and breadth of our research programs in this important and growing therapeutic area," stated James A.D. Smith, president and chief executive officer. "We know of only a handful of HCV drug discovery programs targeting the polymerase that have moved into preclinical development, and we believe ours has produced the most exciting results thus far. I am very pleased with the progress we have demonstrated towards our goal of developing best-in-class compounds targeting the hepatitis C virus."

In addition to its non-nucleoside HCV drug discovery program, Genelabs also has an HCV drug discovery program using nucleoside compounds under a September 2004 research collaboration and license agreement with Gilead Sciences, Inc. Apart from the nucleoside and non-nucleoside HCV polymerase drug discovery programs, in 2004 Genelabs initiated a third HCV drug discovery program focusing on another target essential for HCV replication. This target is encoded by the region of the HCV genome known as NS5a. Genelabs believes compounds targeted at NS5a could lead to drugs that inhibit HCV by a novel mechanism. As such, these compounds may be particularly attractive for combination treatment regimens in HCV. In preliminary studies, Genelabs' small molecule compounds in this program can inhibit the HCV replicon with minimal toxicity to human cell lines. The company has generated initial lead compounds which are in the process of optimization.

While Hep C infections climb dramatically, a downtown Hep C clinic struggles to find funding

http://www.zwire.com/site/news.cfm?newsid=14972579&BRD=2318&PAG=461&dept_id=484045&rfti=6

San Antonio, TX - The Metropolitan Health District estimates there are 20,000 cases of Hepatitis C in San Antonio, yet less than 25 percent know they're infected, and a clinic that could treat thousands of patients is understaffed and underfunded. Hep C is a bloodborne virus that attacks the liver and, untreated, can cause liver disease, cancer, and failure. In Bexar County, about 4,000 new cases are reported annually.

The caseload overwhelmed gastroenterology clinics at the University Health Center, prompting the need for a clinic devoted solely to treating Hep C. In 2000, it opened the Hepatitis Clinic, one of the few clinics that treats exclusively Hep C in South Texas, and the only one that treats low-income people and people without health insurance. Each month, the Hepatitis Clinic, staffed with two doctors - one full and one part-time - two physician assistants, and a clinic coordinator, sees 500-600 Medicare, Medicaid, and CareLink patients from all over the state (CareLink is Bexar County's insurance program for people who don't have health insurance and aren't eligible for Medicare or Medicaid).

Hep C treatments are expensive and intense, sometimes requiring patients to visit the clinic weekly, which is difficult, says Anastacio Hoyumpa, director of the Hepatitis Clinic, because the clinic is chronically underfunded and understaffed. In order to provide care for the high volume of patients it sees, the clinic relies on the tenuous goodwill of pharmaceutical companies and annual grants. The clinic is working on outreach to get people at risk for Hep C to come in for testing. This year the clinic participated in National AIDS testing day, providing free Hep C rapid tests in conjunction with the San Antonio AIDS Foundation. "We don't talk about who has Hepatitis C, but who should be screened," says Hoyumpa. "In most cases, Hep C is discovered incidentally, when a patient comes in for some other procedure, such as a blood test."

According to the National Liver Foundation, at-risk groups for Hep C are diverse: from health-care workers exposed to Hep C-positive blood to people who received tattoos with unsterile needles to anyone who ever used intravenous drugs, even once. "It's a big mistake to think that this is a disease of drug users or a fringe element," says Bob Madison, a spokesman for the National Liver Association. "Soccer moms and CEOs are just as likely to have it as a rock 'n' roll freako with a tongue piercing and multiple tattoos." Prior to 1996, it was common practice to vaccinate a group of soldiers using a jetgun without sterilizing it between patients. "The medics would move through a whole line of guys - by the time they got to guy 10, he was getting injected with the blood of nine guys," says Madison.

... The most successful treatment is a mixture of two drugs, pegylated interferon, an injection administered weekly, and ribavirin pills, which is generally prescribed for six months to a year. According to the National Liver Foundation, combination therapy costs \$6,000-8,000 per patient, per year. While CareLink covers office visits and lab work, it does not pay for prescriptions; the Hepatitis Clinic works with three pharmaceutical companies that donate drugs. "The minute the drug companies say, We have given enough to the clinic," says Hoyumpa, "that will be the day that we close the clinic, because we can't treat any of those patients."

Follow-up visits comprise the bulk of the clinic's patient load. Patients are seen in the clinic once a week during the first two months of treatment. Even those who respond well experience difficult side effects: flu-like symptoms, fatigue, depression, and bouts of intense emotion...

The Hepatitis Clinic also offers a monthly support group, which provides yoga classes and emotional support, as well as lectures on issues such as social services and labor rights. "There are a lot of stigmas associated with Hep C," says Kashi. "Some people have lost their jobs; they are fired because they are too sick to work during treatment. Some of our patients are shunned by their family members."

Today, the Hepatitis Clinic is funded through the University Physicians Group, which provides for the current staff level. Anything above that is funded through grants. According to Hoyumpa, who also works half-time at a similar clinic at the Veterans Administration Hospital, the clinic should have at least three physician assistants, but it recently lost one when a grant ended, which could result in patients waiting longer for appointments; at times the wait has been as long as six months. "We are looking for more grants," he says, "but the clinic sees so many patients that to be able to plan our programming and provide good care, we need stable salaries not dependent on grant money."

Hoyumpa has appealed to the city's elected officials for more funding. "We have approached the City Council and the county commissioners, but we haven't gotten anywhere. We have already saved the City millions in prevention, but the City would rather fund a soccer team." Yet, if Hoyumpa is cynical about the future funding of the clinic, he is optimistic where the disease is concerned. "Ten to 15 years ago there were no treatments. Patients came to us with the feeling they were going to die," he says. "Today Hepatitis C is not a death sentence. There are effective

treatments, and new drugs are coming on board. [Hep C treatments] are the subject of intense study. There is reason to hope.

Tarvacin(TM) starts with Phase I study against Hepatitis C Virus

http://www.rxpnews.com/research/pharmacology/article_2010.shtml

Peregrine Pharmaceuticals, Inc. announced today the initiation of a phase I anti-viral study of Tarvacin(TM), the Company's first Anti-Phospholipid Therapy candidate. The phase I study is an open-label, dose-escalation study in up to 32 adult patients with chronic hepatitis C virus (HCV) infection who either no longer respond to or failed standard therapy with pegylated interferon and ribavirin combination therapy.

The objectives of the trial are to evaluate safety, pharmacokinetics and viral load following a single intravenous infusion. The study is being conducted at Bach and Godofsky Infectious Diseases, the largest private infectious disease practice specializing in the treatment of viral hepatitis in the United States. Bach & Godofsky is located in Bradenton, FL.

"Tarcavin(TM) is truly a novel approach to treating HCV and we are eager to offer patients the opportunity to participate in this trial," stated Eliot W. Godofsky, M.D., Principal Investigator and clinical assistant professor of medicine at the University of South Florida in Tampa. "This study is an important step for our Tarcavin(TM) antiviral program," said Joseph Shan, Peregrine's senior director of clinical and regulatory affairs. "Meanwhile, we are continuing our Tarcavin(TM) development efforts for other viral diseases."

Anadys Pharmaceuticals Announces Publication of Clinical Study of Isatoribine in Chronic Hepatitis C Demonstrating Proof of Concept

<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/08-23-2005/0004092747&EDATE=>

SAN DIEGO, Aug. 23 -- Anadys Pharmaceuticals, Inc. reported the publication of the results of a Phase IB clinical trial of isatoribine (ANA245) in HEPATOLOGY(1), the official journal of the American Association for the Study of Liver Disease (<http://www3.interscience.wiley.com/cgi-bin/abstract/111081950/ABSTRACT>). This peer-reviewed publication concluded that isatoribine treatment resulted in biological activity and a statistically significant antiviral effect with relatively few and mild side effects.

"The manuscript describes the encouraging combination of good tolerability with desirable immunologic and anti-HCV activity that we observed for isatoribine," said Yves Horsmans, M.D., Professor at Cliniques Universitaires St. Luc in Brussels and Principal Investigator of the study. "These results create strong interest in clinical evaluation of ANA975, the oral prodrug form of isatoribine that now is being jointly developed by Anadys and Novartis."

The Phase IB clinical trial was designed to test the safety and tolerability of isatoribine in patients chronically infected with HCV. The study was a dose-escalating, open-label evaluation of isatoribine administered intravenously at 200 mg, 400 mg, 600 mg and 800 mg doses to 32 adults, most of whom received once daily dosing for seven days. The trial was conducted at two clinical centers in Western Europe. Patients participating in the study were either HCV-treatment naive or were partial responders to or relapsed from interferon-alpha, a component of the current standard of treatment. Study results showed that isatoribine demonstrated dose-dependent changes in immunologic biomarkers. The amount of HCV in the bloodstream, or plasma viral load, was significantly reduced in patients receiving 800 mg once daily for seven days. Of the 12 patients in this 800 mg dose group, 10 were infected with HCV genotype 1, which is considered difficult-to-treat with current therapies. Isatoribine treatment was safe and well tolerated in the study, with no serious adverse events and a low frequency of side effects, although definitive conclusions regarding product safety cannot be made until the results of future clinical trials of longer duration in more patients are known. No patient altered isatoribine treatment or withdrew from the study due to adverse events or clinical laboratory abnormalities.

Star's fight for life

<http://entertainment.news.com.au/story/0,10221,16367055-7485,00.html>

AMERICAN Pie star Natasha Lyonne is fighting for her life after being diagnosed with hepatitis C, a heart infection and a collapsed lung. But it has been rumoured she's also fighting a battle with heroin. Lyonne, 26, is reportedly in intensive care at New York's Beth Israel Hospital. Her father, Aaron Braunstein, believes she may have picked up the liver virus while shooting a movie abroad three years ago. But the primary mode of transmission of hepatitis C is via contaminated blood through needles shared by drug users or through blood

transfusions. Braunstein said he was taking legal action against the hospital after an employee leaked information about his daughter's critical condition.

Pamela Anderson plans to beat Hepatitis C

http://people.monstersandcritics.com/article_1044179.php/Pamela_Anderson_plans_to_beat_Hepatitis_C

Busty babe Pamela Anderson is determined to up her daily work-out regime and quit drinking because she is desperate to stay off hepatitis C treatment for as long as possible. The champagne-loving star was diagnosed with the blood disorder two years ago (03) and has since come to terms with the fact that if she takes care of herself she'll be able to live with it.

She says, "My doctor has told me because of my health problems that I should work out an hour a day and I'm not doing anything close to that. "I'm not on any medication yet because my doctor says my liver is in such good shape. The only thing that I really need to do is to quit drinking... I'm going to stop."

Reuse of syringes to withdraw saline from a common bag resulted in a massive outbreak of 99 new HCV infections at an independent hematology/oncology clinic in Nebraska

http://www.clinicaloptions.com/hep/news/news_imed_392.asp

August 16, 2005 — Reuse of syringes to withdraw saline from a common bag resulted in a massive outbreak of 99 new HCV infections at an independent hematology/oncology clinic in Nebraska, according to a recent epidemiologic investigation. Health-care associated transmission of HCV has been previously documented, and such cases are usually due to aseptic technique. Here, Oliveira and colleagues reported an outbreak of HCV at a hematology/oncology clinic that was traced back to a single founder patient and to a single nurse who failed to use sterile needles and syringes to withdraw saline from a common saline bag.

The clinic was an independent facility located on the grounds of a hospital complex in Nebraska. In September 2002, a gastroenterologist not affiliated with the clinic notified the Nebraska Health and Human Services office that 4 patients, all of whom had been seen at the clinic, had been diagnosed with HCV genotype 3a infection. In addition, it was reported that a single nurse had been dismissed in December 2001 due to breaches in infection control practices. The investigators therefore contacted all of the 613 living clinic patients who had been treated in 2000 and 2001 and offered them HCV testing. A total of 473 patients were tested, 103 of whom had been enrolled in the clinic after the dismissal of the nurse in 2001. Because none of the post-2001 patients were infected, the investigators focused on the remaining 391 patients, 99 of whom tested positive for HCV without any pre-existing signs of the infection. A total of 95 of the 99 HCV-positive patients were infected with genotype 3a, and the remaining 5 had samples that could not be tested. The overall attack rate was 27%.

Two patients were identified who had pre-existing signs of HCV infection. One visited the clinic only once in 2001. The presumed source of the outbreak was the second patient, who had enrolled at the clinic in 2000. This source patient was infected with HCV genotype 3a with a viral load of greater than 200,000 copies/mL; a central venous catheter was implanted upon his enrollment at the clinic. In a bivariate analysis of risk factors, having a central venous catheter, having the catheter flushed with saline at least once, biological sex, underlying diagnosis, exposure to subcutaneous injections and the number of clinic visits were all significantly associated with HCV infection. In the multivariate analysis, only the number of saline flushes to a central venous catheter remained significant. Patient records indicated that all 99 infected patients had visited the clinic and received a saline flush on one of the days that the presumed source patient had also visited the clinic.

On investigation, it was found that the one nurse at the facility was responsible for all catheter care, medication infusion, and blood specimen collection. Patient interviews revealed that this nurse reused disposable syringes to withdraw saline solution from common 500 mL bags after using the syringes to withdraw blood from central venous catheters. The same bag was used to flush the catheters of subsequent patients.

In February 2001, 3 patients reported the nurse to the hospital's infection control committee, but the hospital replied that the clinic was independently owned and operated. However, the committee forwarded the complaints to the clinic's oncologist, but no action was taken. In April 2001, the clinic underwent a certification process to become a cancer research center, and during this process a number of infection-control breaches were documented. In July 2001, the oncologist dismissed the nurse responsible for these breaches. Unfortunately, the infection-control breaches were not reported to state authorities. The oncologist's and nurse's professional licenses were revoked only in 2004.

The investigators wrote, "Despite the high attack rate, the fact that our investigation started only after an alert gastroenterologist's report illustrates the difficulty in identifying HCV outbreaks and the need for improved HCV surveillance, such as targeted follow-up by public health authorities of infected persons perceived to be at low-risk for HCV infection." For example, the investigators cite persons over 60 years of age as low risk. They strongly suggested that single-use, pre-filled syringes or single-use vials of saline be used instead of large common bags of saline due to the risk of contamination. [Reference: Macedo de Oliveira A, White KL, Leschinsky DP, et al. An outbreak of hepatitis C virus infections among outpatients at a hematology/oncology clinic. *Ann Intern Med*. 2005;142:898-902.]

High-risk behaviors and increasing time of incarceration contribute to high prevalence of HCV infection in the prison population

http://www.clinicaloptions.com/hep/news/news_imed_391.asp

August 12, 2005 — High-risk behaviors such as illicit intravenous drug use (IDU) as well as increasing time in the prison environment itself contribute to the extremely high rates of HCV infection among the incarcerated population, highlighting the need for systematic screening and HCV education, according to a large study of inmates in the California state correctional system.

Studies of HCV infection in incarcerated populations have found prevalence rates between 22% and 40%, compared to a rate of less than 2% in the general United States population. While exposures such as IDU and high-risk sexual behavior are thought to be more common among persons entering the prison system, it has been suggested that the prison environment itself may pose a risk for infection. Understanding the sources of risk for prisoners would allow for more appropriate screening, prevention, and care. In order to determine the prevalence and risk factors associated with HCV infection, Fox and colleagues studied people entering the California correctional system.

The study sample consisted of 467 inmates entering 3 California state correctional facilities. Inmates were interviewed to collect demographic, medical, behavioral, and incarceration-related information. The medical data collected included history of blood transfusion or receipt of blood products, abnormal liver test results, psychiatric illnesses, and prior testing for bloodborne pathogens. Behavioral information included the duration, quantity, and frequency of alcohol consumption, illegal drug use, tattooing, and body piercing. Inmates were also asked about being assaulted, ritualistic cutting, acupuncture, "gassing" (ie, having a collection of bodily fluids thrown between individuals as a method of assault), and history of use of shared toothbrush, razor, or clippers. Sexual behavior data were collected on the duration, quantity, and frequency of having sex with opposite- or same-sex partners, having transactional sex, having sex with IDUs, having nonconsensual sex, and having sex with partners who were known to have hepatitis or risk factors for bloodborne pathogens. The total lifetime length of time incarcerated, number of times incarcerated, type of incarceration, age at first incarceration, and the type of criminal charges related to the current incarceration were also recorded. Serum samples were taken from each inmate and were tested for HCV antibodies and HCV RNA.

The percentage of inmates with HCV infection was 34.3%. The study sample was representative of the California inmate population at large. The median age was 35 years, 72% were male, 26% were white, 23% were African American, and 37% were Hispanic. About 43% of inmates reported a history of IDU, with one third of these being active users in the past 6 months. The investigators first conducted bivariate analyses to find variables significantly associated with HCV infection. Significant demographic variables included older age, white race, and homosexual or bisexual orientation. HCV infection was also significantly associated with the following behavioral factors: IDU, history of blood transfusion, and history of previous incarceration. Significant sexual variables included having same-sex sexual partners, having sex partners who were IDUs, and having sex with commercial sex workers. The investigators also looked at factors related to incarceration and found that HCV prevalence increased significantly with cumulative years of incarceration, younger age at first incarceration, and a history of juvenile detention.

To isolate independent risk factors, the investigators entered the above significant variables into a backward stepwise logistic regression model. Variables that were significantly and independently associated with HCV infection included sex, history of IDU, cumulative time of incarceration, and age. Each year in the prison system increased risk by 10%. When corrected for age and cumulative time of incarceration, IDUs were nearly 13 times more likely to be infected with HCV than were nonusers. In addition, women who reported having sex with an IDU had a 14-fold increased risk of HCV, but this variable was not significant for men.

The investigators concluded that factors in place before incarceration as well as the prison environment itself both contribute to the soaring rates of HCV infection in the prison population. They urged systematic screening of all inmates. They wrote, "Although a large proportion of individuals may not medically be candidates for antiviral treatments, they are likely to benefit from HCV education and counseling. . . . Inmates frequently cycle between correctional and community environments and are likely to engage in high-risk behaviors in the community, potentially increasing transmission of the virus." [Reference: Fox RK, Currie SL, Evans J, et al. Hepatitis C virus infection among prisoners in the California state correctional system. *Clin Infect Dis*. 2005;41:177-186.]

Most chronic hepatitis C sufferers will develop cirrhosis in later life. Study suggests cirrhosis and liver disease nearly inevitable for people with hep C

http://www.eurekalert.org/pub_releases/2005-09/aga-mch083105.php

Bethesda, Maryland (Sept. 1, 2005) – 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, according to a study published today in the American Gastroenterological Association (AGA) journal *Clinical Gastroenterology and Hepatology*. 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. It is estimated that more than 4 million Americans are now infected with HCV (more than 170 million people worldwide) and nearly 10,000 Americans die from the disease each year.

"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 appearing in this month's 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, PhD, FRCP, study author and professor of hepatology 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.

A study examines the incidence and risk factors associated with Hepatitis C infection in rural Egypt.

<http://i-newswire.com/pr44319.html>

The prevalence of antibodies to Hepatitis C Virus (HCV) in Egypt is among the highest in the world. From the 1950s until 1982 hundreds of thousands were infected during mass campaigns to control schistosomiasis (a parasitic disease) using mass therapy with intravenous antimony compounds, but little is known about current risk factors and rates of transmission. Studies of high risk populations, such as intravenous drug users, shed little light on HCV transmission in Egypt where this high risk behavior is rare.

In a study led by G. Thomas Strickland, M.D. of the Department of Epidemiology and Preventive Medicine at the University of Maryland School of Medicine in Baltimore, MD and published in the September 2005 issue of *Hepatology*, Egyptian and American researchers surveyed rates of HCV infection in two rural communities having a prevalence of antibody to HCV of 24 and 9 percent. A total of 10,112 HCV negative individuals were identified

during an annual survey in 1997, with follow-up performed on an average of 1.6 years later in 6,738 subjects. Of these, 33 developed HCV antibodies, an incidence of 3.1/1000 person-years (PY), and 6.8/1000 PY in the 28 subjects in the village having the 24 percent prevalence of HCV. None of the 33 individuals was diagnosed with viral hepatitis or reported symptoms of acute hepatitis. An analysis of risk factors showed the strongest predictor of infection with HCV was having an anti-HCV positive family member. Among those that did, incidence was 5.8/1000 PY, compared to 1.0/1000 PY; 27/33 incident cases had an anti-HCV positive family member. Parenteral exposures increased the risk of HCV, but were not statistically significant; 67 percent of seroconverters were less than 20 years old, and the highest incidence rate (14.1/1000 PY) was in children under 10 living in households with an anti-HCV positive parent in the village with the high prevalence of HCV antibodies. The infection rate was also increased (13.1/1000 PY) in men married to an HCV positive woman.

"We believe HCV exposures in rural Egyptian communities are usually less intense than those in individuals infected by contaminated blood, either from transfusion of blood or a blood product, or from abuse of intravenous drugs," the authors state. Although not statistically proven to be a risk in this study, they cite frequent injections, usually given at home for health purposes with syringes and needles sometimes used for more than one person, as the most common parenteral exposure route. The strong relationship between the risk of infection in children and the presence of HCV antibodies in their parents suggests that transmission of HCV is occurring between family members, possibly by exposure to infectious blood or saliva, or by sharing needles. In the past, mass treatment campaigns for schistosomiasis involving multiple injections may have caused numerous HCV infections in families, but this would not account for current infection rates, other than placing younger members of families living with those who contracted HCV in this way at higher risk.

The authors conclude: "It is exceedingly important to learn the mechanisms by which HCV transmission is occurring between family members so that preventive measures can be initiated, particularly in children having HCV-infected parents."

Study: Injection Drug Use is Main HCV Risk in HIV

http://www.hepatitisneighborhood.com/content/in_the_news/archive_2484.aspx

It appears injection drug use is the most common way hepatitis C is transmitted among those infected with HIV, the virus that causes AIDS, says a recent study from a group of Swiss researchers. Scant Data on HCV Prevalence in HIV. Information on how hepatitis C is spread among people infected with HIV is "sparse", wrote the team of researchers at University Hospital Berne in Switzerland. Additionally, facts about whether HCV is transmitted by unprotected sexual intercourse in this population, and how often, are "controversial", they wrote.

"The impetus [for this study] was the stories among researchers about HCV—mini-epidemics among HIV-infected men who have sex with men, and the availability of the respective prospective data in our cohort," explained study leader Hansjakob Furrer, MD, in the hospital's division of Infectious Diseases. In hopes of helping to increase knowledge about this aspect of hepatitis C, the research team pulled records on nearly 8,000 HIV patients who had taken part in an unrelated Swiss study between 1988 and 2004. They looked at the relationship between hepatitis C infection and how each person acquired HIV, their sexual practices, injection drug use, and condom use.

Furrer and his associates learned that, overall, the prevalence of HCV infection was 33% among these patients. However, 90 percent of them with the viral infection had reported previous injection drug use. The number of cases of HCV among HIV-infected injection drug users was nearly 30 times that of those who reported no such use, the study found. "We suppose that transmission among IDUs [injection drug users] in our cohort is through their handling of injecting instruments," Furrer told Priority Healthcare. "This may be needle-sharing, but could also be sharing other [drug paraphernalia] like filters [or] spoons."

By comparison, the incidence of hepatitis C infection was much lower among those without a history of injection drug use, even in cases involving unsafe sexual practices, such as intercourse without the use of a condom. Among those who reported they did not inject drugs and practiced safe sex, the incidence of hepatitis C infection was the lowest. "HCV infection incidence in the Swiss HIV Cohort Study was mainly associated with injection drug use," Furrer and his associates wrote. "In HIV infected MSM [men who had sex with men], HCV infection was associated with unsafe sex."

The findings strongly suggest that more education is necessary for men infected with the AIDS virus who practice unsafe sex or HIV-infected people who inject illicit drugs, Furrer stressed. "But we doubt that education alone is sufficient," he said. "And integral programs are difficult to build up." He explained the findings are "disappointing"

because they reflect the inability to educate people with HIV who inject illicit drugs about the risks of transmitting HCV. That's the case, he said, in a country that has high standards of needle exchange and substitution programs.

This study mostly focused on homosexual men who have been diagnosed with HIV. According to the Centers for Disease Control and Prevention, while there is a risk of contracting hepatitis C from heterosexual activity, it is very small. The National Institutes of Health puts it at around 0.6% for couples who are in long-term monogamous relationships when only one partner is infected. Those who have multiple sex partners, however, face a somewhat higher risk of contracting hepatitis C from their partner. As such, those infected with HCV who have multiple sex partners or are in short-term relationships are advised to use condoms to provide additional protection against transmitting the virus.

Hepatitis A Vaccine Urged for Hep C Patients

<http://www.foxnews.com/story/0,2933,166661,00.html>

Despite recommendations, few people with chronic hepatitis C are being vaccinated against the hepatitis A virus. In most people, the hepatitis A virus causes a relatively mild, short-lived infection. But in people with hepatitis C, a hepatitis A infection can be much more serious — even deadly.

Although the hepatitis A vaccine has been available since 1995, a surprisingly low number of people with hepatitis C were vaccinated, the researchers write. Their study appears in the new issue of *Hepatology*. Edward J. Bini, MD, MPH, and his colleagues identified 1,193 patients who were diagnosed with hepatitis C in the year 2000. Bini is a physician with the New York University School of Medicine.

Follow-up information was collected through June 30, 2002, to establish the number of patients who were tested for hepatitis A and the number who actually received the hepatitis A vaccine. A blood test looking for antibodies to the virus can determine if someone is immune to the hepatitis A virus. Patients were considered to be vaccinated if they received one or more doses of the vaccine. A second dose of hepatitis A vaccine is typically given 6 to 18 months after the first shot.

Less than 54 percent of patients were tested for hepatitis A antibody despite having been seen an average of 10 times by their doctor. Almost half of these were susceptible to hepatitis A infection. Yet only 94 patients received the hepatitis A vaccine and of these, 45 received only one dose. A total of three hepatitis C patients also developed hepatitis A infection, one of whom died of liver failure. All of them were known to be susceptible to hepatitis A - but none had received the vaccine.

"The low rates of hepatitis A testing and vaccination are striking given the presence of recommendations since 1996 to vaccinate these individuals against hepatitis A, the long duration of follow-up, and the high number of visits with their primary care provider," Bini writes.

Hepatitis C co-infection blunts response to antiretroviral therapy

<http://www.aidsmap.com/en/news/6B6EC4F2-C5C6-43AB-93C1-A9836498851F.asp>

Co-infection with the hepatitis C virus (HCV) reduces CD4 cell count gains by an average of 33 cells/mm³ after a year of antiretroviral therapy in HIV-positive patients, according to the results of a meta-analysis published in the 1st September edition of *Clinical Infectious Diseases*. This finding may support calls for the earlier initiation of antiretroviral or anti-HCV therapy in co-infected patients, in order to optimise immune restoration or to eradicate HCV from the body prior to starting HIV treatment.

Previous studies examining the influence of HCV infection on the response to anti-HIV treatment have produced mixed findings. Some investigators have found that co-infection blunts the rises in CD4 cell count, while others have seen no difference between HIV patients with and without HCV.

To understand the relationship between HCV and immune restoration more fully, investigators from the United States carried out a 'meta-analysis' of clinical trials. This is a method of combining the results from a set of similar studies to work out the average overall finding. Meta-analyses are regarded as providing more reliable results than individual studies as they contain more participants and data collected in different geographical areas and at different times.

After an extensive search of the medical literature, the researchers identified eight studies that were eligible for inclusion in their meta-analysis, including a total of 6216 patients. These studies all compared CD4 cell count rises after the initiation of antiretroviral therapy in HIV-positive patients with and without HCV co-infection. The studies took place in North America, Europe and Australia. After weighting each study according to the degree of variability in its results, the researchers calculated that the HCV co-infected patients had a CD4 cell count rise that

was a mean of 33.4 cells/mm³ (95% confidence interval: 23.5 – 43.4 cells/mm³) lower than the patients with HIV alone. They calculated this from the first reported CD4 cell count change measured after twelve months in each study.

“Our meta-analysis showed that the increase in the CD4 cell count in patients who started receiving highly active antiretroviral therapy (HAART) for HIV infection is significantly lower if they have HCV co-infection,” they conclude. “HIV-infected patients are likely to have a better immunological response to antiretroviral therapy if they are not co-infected with HCV.” However, the researchers note that their study does not indicate that the co-infected patients have a poorer outcome. “Future research should examine whether an impaired immunologic response corresponds with meaningful virologic and clinical outcomes,” they write. Studies including patients co-infected with hepatitis B were not excluded from their analysis, as this virus is not believed to affect the response to anti-HIV treatment.

The investigators speculate that the higher number of intravenous drug users in the HCV co-infected group may explain their findings, at least in part. “This population often has less access to health care and typically has worse adherence to HIV regimens, compared with the population of patients who contracted HIV infection by other means,” they explain. “Adherence to HAART in this population may be directly related to improvements in the CD4 cell count,” they write.

The researchers point out that their analysis may have been affected by a number of factors that were not reported in the original research papers. These include baseline CD4 cell counts, HIV viral loads and the possibility that some of the patients with HCV antibodies may have cleared the virus before starting anti-HIV therapy. However, they found that the year in which antiretroviral therapy was started, whether the studies followed patients prospectively or used previously-collected data and the length of follow-up had no significant effect on the outcome. Similarly, no one study had a disproportionate effect on the outcome of the meta-analysis.

Nurse Shares Story of Hepatitis C, the 'Silent Epidemic'

http://www.ksdk.com/news/health_article.aspx?storyid=83561

A former nurse is sharing the story of her battle with Hepatitis C in the hopes of lowering the stigma attached to the disease. Kathie Bryson is one of an estimated five million people in this country with the liver disease Hepatitis C, a viral illness five times more common than HIV-AIDS. It's called a silent epidemic because so many people have it and don't know it. Bryson hopes by breaking the silence, more people at high risk will get tested.

"It's like AIDS was in the 80's. People have the belief that if you got it, well somehow you deserved it," says Bryson. This former nurses' story isn't unusual. Hepatitis C is considered an occupational hazard in the health care field, and Bryson got the disease from a needle stick. What is unusual is that her first symptom of the disease was not a gradual scarring of the liver as is typical, but liver cancer. "Maybe that's the deal. Maybe that's what God intended to do. To give me this and try to get people to wake up and and look at it," she says.

"In my practice, 90 per cent of people don't have excess alcohol as a cause of their liver disease and a good large percentage of the people who have Hepatitis C have it unrelated to needle use," explains Dr. Bruce Bacon, a liver specialist at St. Louis University School of Medicine who helped cure country western star Naomi Judd of hepatitis C. The treatment protocol uses two antiviral drugs, medicines that can cure 60 percent of patients. He recommends the following people be screened for the disease: health care workers, anyone who received a blood transfusion or organ transplant before July of 1992, injected illegal drugs at any time in the past, used inhaled drugs like cocaine, has piercings or tattoos, or is overly promiscuous, although the risk of sexual transmission is low.

Bryson is undergoing treatment for her cancer. She says knowing you have Hepatitis C is key to surviving the disease. "If people don't stop the silence and don't start talking about it, more people are going to die and I don't think we should die of something doctors have a good cure rate for." To help raise awareness about Hepatitis C, St. Louis University, and St. Louis University Hospital are sponsoring a two-evening gala, dubbed "Denim & Diamonds." On September 12, Willie Nelson will perform in a sold-out concert at the Pageant. Country singer Naomi Judd will speak at a black-tie event on September 13. Proceeds from both events go to the St. Louis University Liver Center.

Senate Approves Needle-Exchange bill (California)

<http://www.ukiahdailyjournal.com/Stories/0,1413,91~3089~3024165,00.html>

The full state Senate approved Assemblywoman Patty Berg's needle-exchange bill Tuesday, moving the measure just one step away from Gov. Arnold Schwarzenegger's desk for consideration. Assembly Bill 547 awaits a

concurrence vote from the Assembly floor before heading to the governor, and the full Assembly has supported the bill, so passage is expected, according to Berg.

Supported by California's public health officers and law enforcement groups, the bill is designed to help fight the spread of HIV-AIDS and Hepatitis-C. The measure would eliminate a section of state law that requires cities and counties to declare a health emergency every two weeks to operate a needle-exchange program. "This bill is about saving lives and protecting communities from disease. It was in everyone's interest that we find common ground, and I am very happy that we did," Berg, D-Eureka, said.

Schwarzenegger vetoed a similar version of the measure last year, but Berg has since worked closely with administration officials to craft a bill the governor could support. She has also drawn support from the California Peace Officers' Association and the California Narcotic Officers' Association, both of which have opposed similar measures proposed by Berg. This is the third year Berg has authored a bill regarding needle-exchange programs, but this is the first time she has received support from law enforcement agencies.

The governor's office would not speculate on planned action for the measure after the Senate approved the bill with a 24-15 vote Tuesday. According to Berg, exchange programs have proven effective in controlling the spread of blood-borne diseases and not only protect intravenous drug users, but everyone who is knowing or unknowingly linked to them. The Mendocino County AIDS Volunteer Network operates the local needle-exchange program and distributed some 76,000 clean syringes in the county last year to help battle HIV, Hepatitis-C and other communicable diseases.

According to MCAVN Executive Director Cyril Colonius, Berg's bill would benefit existing programs and possibly open other needle-exchange efforts in counties without established programs. "We are doing needle exchanges and it would be hard to suddenly stop it for two weeks and start it again. The HIV and HCV (Hepatitis-C Virus) crisis does not stop every two weeks," Colonius said. "We are actually collecting 75,000 syringes out of the community because most exchanges are made on a one-to-one basis. Last year, we got back about 2,000 syringes less than the estimated 76,000 we gave out."

The local exchange program started in 2001 and there was actually an underground exchange for clean needles before that time, Colonius said. Distributing needles through in-house exchanges in Ukiah and Fort Bragg, MCAVN also operates a secondary exchange program where volunteers network with drug users in the area to distribute clean needles. MCAVN is one of only five such programs in the state and receives some \$76,000 annually from the California Office of AIDS to recruit needle users.

"We recruit needle users and people who have contact with needle users as peer educators. The goal is to recruit 15 people each year," Colonius said. "We have conversations with people about topics that we are concerned about to try and reduce their risks. We are currently engaging with 500 or so needle users and we probably have about 2,500 needle users in the county. Our goal is to make every injection a safe injection."

With local program participants exchanging anywhere from one to 200 needles, Colonius said they are constantly talking with people to become involved with the secondary exchange program. With some 5,000 cases of Hepatitis-C and about 150 individuals who have contracted HIV currently living in Mendocino County, he said needle exchange programs and other protective measures are the best way to confront the problem.

Distributing needles, alcohol swabs, antibiotic kits, condoms, drug cookers, cotton balls and other protective materials, Colonius said MCAVN wants to develop relationships with needle users so when they are ready to address their drug use problems or want treatment, they will come back for help. "Condoms are an attraction and needles are an attraction for users and that is a way to speak and discuss other safe practices," he said. "We are not only into the distribution of syringes, we want to create a healthy community."

Migenix to test hepatitis C drug

http://www.pharmaceutical-business-review.com/article_news.asp?guid=3595201E-8F70-4B24-A519-0C176EE1E679

Migenix has received authorization from Health Canada to begin a phase IIb combination study of MX-3253, a compound in development for the treatment of chronic hepatitis C virus infections. Enrollment in the study is expected to commence in the next few weeks with results expected around mid-year 2006. MX-3253 (celgosivir) is an alpha-glucosidase I inhibitor and is currently the only oral anti-hepatitis C virus (HCV) drug in development that acts through host-directed glycosylation. In preclinical studies, celgosivir has demonstrated strong synergy with

interferon-alpha plus ribavirin suggesting it has the potential to be included as part of a combination therapeutic approach to improve efficacy.

Celgosivir is currently being evaluated in a phase IIa monotherapy study in treatment-naive and interferon-intolerant genotype I HCV patients with results of the study expected before the end of the third quarter of calendar 2005. The phase IIb combination study of MX-3253 is a randomized, multi-center, active-controlled, 12 week evaluation of MX-3253 in three treatment arms of up to 20 chronic HCV patients each: celgosivir plus peginterferon alfa-2b plus ribavirin (three-way combination); celgosivir plus peginterferon alfa-2b (two-way combination); and placebo plus peginterferon alfa-2b plus ribavirin (control).

Patients for the phase IIb study will be selected based on having genotype 1 chronic HCV and having failed to respond to pegylated alpha interferon plus ribavirin therapy (non-responders). Patients who respond to therapy during the phase IIb trial will have the option to continue on treatment for up to 48 weeks. The study will measure viral load at various time points, as well as a number of safety parameters.

"This is an important step in the development of celgosivir", stated Dr Jim DeMesa, president and CEO of Migenix. "Our recent agreement with Schering- Plough, the strong preclinical synergy of celgosivir with interferon-alpha plus ribavirin, and the participation of many of the same investigators from our phase IIa trial - combined with this regulatory approval - give us great encouragement for success in this phase IIb trial."

HIV-positive patients coinfecting with HCV up to 80% more likely to die even with HIV treatment

<http://www.aidsmap.com/en/news/812944F5-6A70-4F45-A1C9-229FCEA3420C.asp>

Infection with hepatitis C virus increases the risk of death in HIV-positive individuals by between 30% - 80%, even after factors such as the use and success of anti-HIV treatment are controlled for, according to a US study published in the August 15th edition of the *Journal of Acquired Immune Deficiency Syndromes*. The investigators, from the US's largest provider of HIV care, the Department of Veterans' Affairs, question whether currently available treatment for hepatitis C, which has a lower response rate in HIV-positive individuals, would significantly reduce this level of excess mortality and suggest instead that efforts should be made to treat the high levels of mental illness and drug and alcohol abuse present in their coinfecting patients, factors which they believe "contribute directly and indirectly to poor outcome in HIV and HCV coinfection." It is estimated that as many as 300,000 HIV-positive individuals (15% - 30% of all HIV cases) are coinfecting with hepatitis C virus. Since effective anti-HIV therapy became available, liver disease caused by hepatitis C has emerged as a major cause of illness and death in HIV-positive patients.

Investigators wished to determine the impact of hepatitis C infection on mortality in HIV-positive patients receiving antiretroviral therapy. Their analysis controlled for potential confounding factors including virologic and immunologic response to anti-HIV treatment. The study included a total of 12,216 individuals who were treated with their first potent anti-HIV treatment regimen at the Department of Veterans' Affairs between early 1997 and 2003. To be included in the study individuals also had to have been tested for hepatitis C and to have CD4 and viral load tests conducted prior to starting HIV therapy.

A total of 4,668 patients (38%) were coinfecting with hepatitis C virus. Coinfecting individuals were older than patients who tested negative for hepatitis C and were also more likely to be black or Hispanic, have a history of psychiatric illness (71% versus 60%, $p < 0.001$), abuse drugs (62% versus 20%, $p < 0.001$), and have alcohol problems (63% versus 30%, $p < 0.001$). Prior to starting potent anti-HIV therapy, hepatitis C coinfecting patients had higher viral loads than patients who were only infected with HIV (median 26,000 copies/ml versus 19,000 copies/ml, $p < 0.001$), but baseline CD4 cell counts were comparable between the two groups of patients (median 257 cell/mm³ versus 248 cells/mm³).

Hepatitis C-infected and hepatitis C-negative individuals had a similar virologic response to HAART with approximately 80% of both groups of patients achieving an undetectable viral load at least once. Nor was there any difference in the proportion of patients who maintained good control of HIV replication (37% hepatitis C-infected, versus 39% hepatitis C-negative). CD4 cell gain was, however, lower amongst the patients infected with hepatitis C (median peak gain 199 cells/mm³ versus 239 cells/mm³ for hepatitis C-uninfected patients, $p < 0.001$).

A total of 2087 deaths occurred during follow-up. There were proportionately more deaths amongst hepatitis C virus-infected patients than individuals who were not infected with hepatitis C (22% versus 14%, $p < 0.001$). The unadjusted risk of death was 6.4 per 100 patient years for coinfecting patients and 4 per 100 patient years for patients who only had HIV. This difference was highly statistically significant ($p < 0.001$).

The investigators repeated their analysis, limiting their analysis to patients with controlled HIV replication on at least one occasion and still found that coinfecting patients had a significantly higher risk of death (hazard ratio, 1.77, $p < 0.001$). The result was similar when analysis was restricted to individuals with well-controlled viral load - coinfecting patients having a hazard ratio of death of 1.69, $p < 0.001$). The investigators then controlled for CD4 cell response to anti-HIV therapy and still found a significantly increased hazard ratio of death for coinfecting patients (1.34, $p < 0.001$).

“Hepatitis C virus infection increases the risk of death in HIV patients who received HAART, controlling for numerous demographic and clinical factors, including exposure to HAART and response to HAART”, write the investigators. They add, “depending on the factors for which we controlled, we found that the risk of death among HAART-treated HIV patients was between 30% and 80% higher for those who were also infected with HCV.”

The investigators suggest that their study “raises the pressing question of whether HCV treatment can ameliorate the observed increase in the risk of death.” They note that the study was largely completed before pegylated interferon and ribavirin became the standard of treatment for hepatitis C virus. However, they emphasize that the response to hepatitis C therapy is poorer in patients who are coinfecting with HIV. They therefore suggest that until better hepatitis C treatment becomes available efforts to treat the high rates of mental illness, and drug and alcohol abuse seen in their cohort may help lower mortality.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Everson GT, et al. *Hepatology*. 2005 Aug;42(2):255-62.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16025497&query_hl=7

Patients with advanced hepatitis C virus (HCV) are at risk of death and are candidates for liver transplantation. After transplantation, HCV recurs and may rapidly progress to cirrhosis and graft loss. Treatment is needed to prevent progression of disease and minimize recurrence after liver transplantation. We evaluated the effectiveness, tolerability, and outcome of a low accelerating dose regimen (LADR) of antiviral therapy in the treatment of patients with advanced HCV. One hundred twenty-four patients (male/female ratio 81:43; age range 37-71 years; 70% genotype 1) were treated with LADR. Sixty-three percent had clinical complications of cirrhosis (ascites, spontaneous bacterial peritonitis, varices, variceal hemorrhage, encephalopathy). The mean Child-Turcotte-Pugh (CTP) score was 7.4 +/- 2.3, and the mean MELD score was 11.0 +/- 3.7. Fifty-six patients were CTP class A, 45 were class B, and 23 were class C. Forty-six percent were HCV RNA-negative at end of treatment, and 24% were HCV RNA-negative at last follow-up. Sustained virological response (SVR) was 13% in patients infected with genotype 1 HCV and 50% in patients infected with non-1 genotypes ($P < .0001$). Non-1 genotype, CTP class A (genotype 1 only), and ability to tolerate full dose and duration of treatment ($P < .0001$) were predictors of SVR. Twelve of 15 patients who were HCV RNA-negative before transplantation remained HCV RNA-negative 6 months or more after transplantation. In conclusion, in a sizeable proportion of patients with advanced HCV, LADR may render blood free of HCV RNA, stabilize clinical course, and prevent posttransplantation recurrence.

Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. von Wagner M, et al. *Gastroenterology*. 2005 Aug;129(2):522-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16083709&query_hl=7

BACKGROUND & AIMS: Standard therapy of patients with chronic hepatitis C virus (HCV) infected with HCV genotype-2 or -3 is the combination of pegylated interferon-alpha and ribavirin for 24 weeks. Whether shorter treatment durations are possible for these patients without compromising sustained virologic response rates is unknown. **METHODS:** Patients chronically infected with HCV-2 ($n = 39$), HCV-2/3 ($n = 1$), or HCV-3 ($n = 113$) were treated with peginterferon-alpha-2a (180 microg/wk) plus ribavirin 800-1200 mg/day. HCV RNA was quantitatively assessed after 4 weeks. Patients with a rapid virologic response (HCV RNA below 600 IU/mL) were randomized for a total treatment duration of 16 (group A) or 24 weeks (group B). All patients with HCV RNA $>$ or $=$ 600 IU/mL at week 4 (group C) were treated for 24 weeks. End-of-treatment and sustained virologic response were assessed by qualitative RT-PCR (sensitivity 50 IU/mL). **RESULTS:** Only 11 of 153 patients (7%) were allocated to group C. End-of-treatment and sustained virologic response rates were 94% and 82%, (group A), 85% and 80% (group B), and 73% and 36% (group C), respectively. In patients infected with genotype HCV-3 and high

viral load (>800,000 IU/mL), a significant lower sustained virologic response rate was found than in patients infected with HCV-3 and a viral load lower or equal to 800,000 IU/mL (59% vs 85%, respectively; P = .003).

CONCLUSIONS: In HCV-2 and -3 (low viral load)-infected patients who have a rapid virologic response, treatment for 16 weeks with peginterferon-alpha-2a and ribavirin is sufficient. In patients infected by HCV-3 (high viral load), longer treatment may be necessary.

Hepatitis B virus DNA integration in hepatocellular carcinoma after interferon-induced disappearance of hepatitis C virus. Tamori A, et al. Am J Gastroenterol. 2005 Aug;100(8):1748-53.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16086711&query_hl=7

OBJECTIVES: Hepatocellular carcinoma (HCC) has been reported in patients in whom hepatitis C virus (HCV) was eliminated by interferon (IFN) therapy. We examined the pathogenesis of HCC in patients with sustained viral response. **METHODS:** Operable HCC developed in 7 of 342 patients cured of HCV infection by IFN monotherapy. No patient abused alcohol or had diabetes mellitus or obesity. Resected specimens of HCC were histologically evaluated. DNA extracted from HCC was examined by polymerase chain reaction (PCR) to locate hepatitis B virus (HBV) DNA. HBV integration sites in human genome were identified by cassette-ligation-mediated PCR. **RESULTS:** HBV DNA was not amplified in serum samples from any of the seven patients with HCC and was found in liver in four patients. In the latter four patients, HBV DNA was integrated into the human genome of HCC. In two of these patients, covalently closed circular HBV (cccHBV) was also detected. The patients with HBV DNA integration were free of HCV for more than 3 yr. In two of the three patients without HBV DNA integration, the surrounding liver showed cirrhosis. The liver of HCC with HBV DNA integration had not progressed to cirrhosis. Three of the four tumors with HBV integration had one integration site each, located at chromosomes 11q12, 11q22-23, and 22q11, respectively. The other tumor had two integration sites, situated at chromosomes 11q13 and 14q32. At chromosome 11q12, HBV DNA was integrated into protein-coding genome, the function of which remains unclear. **CONCLUSION:** Integrated HBV DNA may play a role in hepatocarcinogenesis after the clearance of HCV by IFN treatment.

Growth in the First 5 Years of Life is Unaffected in Children with Perinatally-acquired Hepatitis C Infection. European Paediatric Hcv Network. J Pediatr. 2005 Aug;147(2):227-32

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16126055&query_hl=7

OBJECTIVES: To identify the effect of vertical hepatitis C virus (HCV) infection or exposure on growth in childhood. **STUDY DESIGN:** Children (n=1203) born to HCV-infected mothers were followed up from birth prospectively in centers of the European Paediatric Hepatitis C virus Network. Z-scores compared height- and weight-for-age in HCV-infected and -uninfected children, adjusting for other factors using linear regression. We also quantified the effect of maternal chronic infection with HCV on childhood growth. **RESULTS:** There was no significant effect of vertical HCV infection on growth (height P=.223, weight P=.095) nor a significant effect of maternal chronic infection with HCV (height P=.733, weight P=.274). Prematurity and maternal injecting drug use were associated with a significant reduction in height (P < .001) and weight (P < .001) in all HCV-exposed children. **CONCLUSIONS:** This population of HCV exposed infants has higher rates of maternal injecting drug use and prematurity than standard populations and so there are implications for growth of these children, but this is not a direct result of HCV infection or exposure to chronic maternal HCV infection.

Diagnostic Discordance for Hepatitis C Virus Infection in Hemodialysis Patients. Kalantar-Zadeh K, Miller LG, Daar ES. Am J Kidney Dis. 2005 Aug;46(2):290-300.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16112048&query_hl=7

BACKGROUND: Hepatitis C virus (HCV) infection is associated with an increase in proinflammatory cytokine levels. Similar changes are seen in maintenance hemodialysis patients with malnutrition-inflammation-cachexia syndrome (MICS), which is associated with poor clinical outcomes in this population. We hypothesized that HCV transcription-mediated amplification (TMA), a sensitive qualitative molecular test for HCV RNA, may identify maintenance hemodialysis patients with HCV infection not detected by means of antibody enzyme immunoassay (EIA), particularly in those with MICS. **METHODS:** We evaluated HCV status in 314 maintenance hemodialysis patients by using HCV antibody EIA (version 2.0; Abbott Laboratories, Abbott Park, IL) and HCV TMA (Bayer Diagnostics Laboratories, Berkeley, CA). **RESULTS:** Twenty-five patients (8%) were EIA positive

(EIA+)/TMA+; 4 patients (1%), EIA+/TMA negative (TMA-), and 22 patients (7%), EIA-/TMA+. In the 47 TMA+ patients, the sensitivity of EIA for HCV infection was only 53%. TMA+ patients had lower albumin levels and higher tumor necrosis factor alpha and serum glutamic oxaloacetic transaminase levels than TMA- patients. EIA+/TMA+ patients were more likely than EIA-/TMA+ or EIA-/TMA- patients to have hypoalbuminemia and higher iron and transaminase levels. Of all TMA+ patients, EIA- patients were more likely to have diabetes, be on dialysis therapy longer, and have lower liver enzyme levels and higher proinflammatory cytokine levels, including tumor necrosis factor alpha and interleukin 6. **CONCLUSION:** Maintenance hemodialysis patients infected with HCV according to TMA have clinical features suggestive of MICS. In this population, HCV EIA appears to have a low sensitivity for the identification of HCV infection, which may be caused by the confounding effect of MICS or other demographic or clinical factors. These apparently false-negative HCV antibody test results are seen in persons with a longer time on hemodialysis therapy, mirroring observations in other populations with serious progressive conditions, such as human immunodeficiency virus infection.

Efficacy and tolerability of peginterferon alpha-2a with or without ribavirin in thalassaemia major patients with chronic hepatitis C virus infection. Inati A, et al. *Br J Haematol.* 2005 Aug;130(4):644-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16098081&query_hl=7

Thalassaemia patients with genotype 1 or 4 chronic hepatitis C virus (HCV) infection were randomised to receive peginterferon alpha-2a 180 mg/week ribavirin for 48 weeks. Primary efficacy variable was sustained viral response (SVR) at 72 weeks. Thirty-two patients were evaluated; 20 enrolled. Baseline characteristics were comparable. SVR occurred in four of 12 and five of eight patients in the monotherapy and combination groups (30% and 62.5%; $P=0.19$), respectively. Undetectable RNA at 12 weeks and age <18 years were associated with improved SVR ($P<0.05$). Transfusion requirements rose by 34% in the combination arm ($P=0.08$). Peginterferon/ribavirin was effective in thalassaemics with HCV and moderate iron overload.

Is interferon-alpha therapy safe and effective for patients with chronic hepatitis C and inflammatory bowel disease? A case-control study. Bargiggia S, et al. *Aliment Pharmacol Ther.* 2005 Aug 1;22(3):209-15.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16091058&query_hl=7

BACKGROUND: Hepatitis C virus infection is more common in patients with inflammatory bowel disease than in general population. Limited data are available as to the safety and efficacy of alpha-interferon therapy for chronic active hepatitis C in patients with concomitant inflammatory bowel disease. **AIM:** To evaluate the efficacy and safety of alpha-interferon monotherapy in patients with chronic active hepatitis C and inactive or mildly active inflammatory bowel disease. **METHODS:** A total of 513 consecutive inflammatory bowel disease patients at a single centre were tested for antibodies to hepatitis C virus (anti-hepatitis C virus) between 1995 and 2000. Twenty-one patients had detectable anti-hepatitis C virus Ab and were hepatitis C virus-RNA positive with histologically proved chronic active hepatitis. Each of these patients, whose inflammatory bowel disease was in clinical remission or mildly active, was sex- and age-matched to three controls with similar histological grade and stage of chronic hepatitis C virus but without inflammatory bowel disease; and all were treated with human leucocyte alpha-interferon 6 million units given thrice weekly for 12 months. Responses to treatment were classified as follows: complete response--persistently normal alanine aminotransferase and viral clearance (hepatitis C virus-RNA-ve) at the end-of-treatment, incomplete response--alanine aminotransferase normalization without viral clearance (hepatitis C virus-RNA+ve), and sustained response--alanine aminotransferase normalization and hepatitis C virus clearance 12 months after the end-of-treatment. **RESULTS:** Twenty-one patients with chronic active hepatitis C and inflammatory bowel disease (10 with Crohn's disease and 11 with ulcerative colitis) and 63 sex- and age-matched controls with chronic hepatitis C virus alone received alpha-interferon monotherapy. Response rates to interferon were similar for inflammatory bowel disease patients compared with controls [CR 42% vs. 35% and SR 24% vs. 18% (P , not significant), respectively]. None of the 21 inflammatory bowel disease patients had severe adverse effects and the mild ones observed were comparable with those seen in the control group. No patients developed an inflammatory bowel disease relapse during the interferon treatment period or in the 12 months thereafter. **CONCLUSIONS:** The biochemical and virological response to a 12-month human leucocyte alpha-interferon treatment in patients with chronic active hepatitis C are similar to that observed in matched controls with chronic hepatitis C virus without inflammatory bowel disease. Adverse effects are similar in both groups of patients and unrelated to the underlying inflammatory bowel condition. This provides hepatologists with evidence that

alpha-interferon can be safely administered to patients with chronic hepatitis C virus and inflammatory bowel disease provided that the inflammatory bowel condition is in clinical remission.

Mood Alterations During Interferon-Alfa Therapy in Patients With Chronic Hepatitis C: Evidence for an Overlap Between Manic/Hypomanic and Depressive Symptoms. Constant A, et al. J Clin Psychiatry. 2005 Aug;66(8):1050-1057.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16086622&query_hl=7

BACKGROUND: Psychiatric side effects are common during interferon-alfa (IFN-alfa) therapy and often responsible for early treatment discontinuation, thus limiting its therapeutic potential. Depression is considered the hallmark of these side effects. However, irritability, anger/hostility, and manic/hypomanic episodes have also been reported, suggesting that these symptoms are important features of IFN-alfa-induced neuropsychiatric side effects. **OBJECTIVE:** The aim of this prospective study was to use item-by-item analysis to thoroughly characterize neuropsychiatric symptoms occurring during early IFN-alfa therapy in a large cohort of patients with chronic hepatitis C. **METHOD:** Ninety-three previously IFN-alfa-naive patients treated with pegylated IFN-alfa plus ribavirin for chronic hepatitis C were studied. Neuropsychiatric assessments were conducted before initiation and after weeks 4 and 12 of antiviral therapy. They included the Mini-International Neuropsychiatric Interview, the 10-item Montgomery-Asberg Depression Rating Scale, the State-Trait Anxiety Inventory, and the Brief Fatigue Inventory. **RESULTS:** Psychiatric events occurred in 30 patients (32%). They consisted of mood disorders in all cases: mania in 3 cases (10%), irritable hypomania in 15 cases (50%), and depressive mixed states in 12 cases (40%). Neurovegetative symptoms appeared within 4 weeks in most patients. In patients who developed mood disorders, sadness and depressive thoughts were present but minimal in severity. In contrast, inner tension and anxiety symptoms increased significantly over time only in these patients. **CONCLUSIONS:** Our results suggest that IFN-alfa-induced mood disorders are common and consist of an overlap between depressive and manic symptoms rather than a mere depression. The impact of such findings on therapeutic management should be investigated.

International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C.

Zeuzem S, et al. J Hepatol. 2005 Aug;43(2):250-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16082736&query_hl=9

BACKGROUND/AIMS: The aim of this study was to increase virologic response rates by individualized treatment according to the early virologic response. **METHODS:** Serum HCV-RNA was frequently quantified in patients with chronic hepatitis C (n=270) treated with peginterferon alfa-2a (180 microg/week) and ribavirin (1000-1200 mg/day). After 6 weeks patients were classified as rapid (RVR), slow (SPR), flat (FPR), or null responders (NUR) and randomized within each viral kinetic class to continue therapy either with an individualized or standard regimen. Individualized therapy comprised peginterferon monotherapy (48 weeks) or shorter combination therapy (24 weeks) for RVR, triple therapy with histamine (1 mg/day) (48 weeks) or prolonged combination therapy (72 weeks) for SPR, triple therapy for FPR, and high-dose peginterferon (360 microg/week) plus ribavirin for NUR patients. **RESULTS:** Patients were categorized as RVR (n=171), SPR (n=65), FPR (n=10), or NUR (n=22). Overall end-of-treatment and sustained virologic response rates were 77 and 60% in the individualized and 77 and 66% in the standard treatment arm, respectively. Histamine in addition to peginterferon and ribavirin and high-dose peginterferon plus ribavirin did not improve virologic response rates in patients with FPR and NUR, respectively. **CONCLUSIONS:** An improvement in virologic efficacy was not achieved with the available individualized treatment options.

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://amedeo.com/p2.php?id=16128946&s=chep>

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&list_uids=16136646&dopt=Abstract

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.

Effect of ondansetron, a 5-HT3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. Piche T, et al. Gut. 2005 Aug;54(8):1169-73.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16009690&query_hl=7

BACKGROUND AND AIMS: There are no available effective therapies for fatigue associated with chronic hepatitis C (CHC). The serotonin antagonist ondansetron has been shown to be effective in the chronic fatigue syndrome. In this randomised, placebo controlled, double blind trial, we investigated the effect of orally administered ondansetron on fatigue in CHC. **METHODS:** Thirty six patients with CHC were included if fatigue was their predominant symptom and they scored more than 4 on a visual analogue scale (0-10). During the study, fatigue and depression were measured on days 0, 15, 30, and 60 using a validated self report questionnaire (fatigue impact scale and Beck depression inventory). Patients were randomised to receive ondansetron tablets 4 mg twice daily or placebo for one month followed by an additional four weeks of observation. **RESULTS:** Fatigue score was 85.4 (28.2) and 98.2 (26.9) in the ondansetron and placebo groups, respectively (NS). Ondansetron significantly reduced the fatigue score with more than 30% improvement on day 15 (57.1 (38.9); p<0.01), day 30 (54.5 (37.6); p<0.01), and day 60 (60.8 (37.3); p<0.01) whereas placebo did not. Overall, the reduction in fatigue was significantly higher with ondansetron compared with placebo (ANOVA for repeated measurements) for the whole follow up period (p = 0.03) or for the treatment period only (p = 0.04). Ondansetron also significantly reduced depression scores. **CONCLUSIONS:** The 5-hydroxytryptamine receptor type 3 antagonist ondansetron had a significant positive effect on fatigue in CHC. These observations support the concept that fatigue involves serotonergic pathways and may encourage further evaluations of the efficacy of ondansetron on fatigue in chronic liver diseases.

Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Lok AS, et al. *Hepatology*. 2005 Aug;42(2):282-92.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15986415&query_hl=7

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

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Relationship between early HCV kinetics and T-cell reactivity in chronic hepatitis C genotype 1 during peginterferon and ribavirin therapy. Tang KH, et al. *J Hepatol*. 2005 Aug 31; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16139918&query_hl=7

BACKGROUND/AIMS: To gain understanding of inter-individual differences of treatment response in hepatitis C virus genotype 1 (HCV-G1) patients, we investigated simultaneously the early HCV kinetics and virus-specific T-cell reactivity. **METHODS:** Thirty, treatment-naive HCV-G1 patients received peginterferon-alfa2a 180µg/week plus ribavirin 1000-1200mg/day, with blood samples collected prospectively at protocol time-points. HCV RNA was quantitated with a TaqMan((R)) assay with mathematical modelling of HCV decay. Virus-specific CD4+/CD8+ T-cells were enumerated by Elispot assays. **RESULTS:** HCV kinetic analysis identified two subgroups: fast (18/30) and slow (12/30) treatment-responders. Although these subgroups did not differ in any baseline characteristics, fast responders (FR) showed greater antiviral efficacy (epsilon) than slow responders (SR) (84.5+/-3.2 vs. 65.2+/-7.0%, P=0.002), and a higher rate of infected cell loss (delta) (0.56+/-0.2 vs. 0.04+/-0.02, P=0.038). The viral load drop (baseline to treatment week 4) was higher in FR vs. SR group (3.5+/-1.1 vs. 1.4+/-0.6 log(10)IU/mL, P<0.001). T-cell reactivity to HCV increased only in FR (after the loss of viraemia), but not in SR patients. **CONCLUSIONS:** Assessment of early viral and T-cell kinetics during treatment reveals marked differences amongst HCV-G1 patients and may provide a basis for treatment individualization. Enhancement of antiviral T-cell reactivity requires rapid viraemia clearance, rather than immunostimulation alone.

Hepatitis C virus proteins exhibit conflicting effects on the interferon system in human hepatocyte cells.

Dansako H, Naka K, Ikeda M, Kato N. *Biochem Biophys Res Commun*. 2005 Aug 30; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16139243&query_hl=7

We previously found that hepatitis C virus (HCV) core protein (Core) activated the interferon (IFN)-inducible 40/46kDa 2'-5'-oligoadenylate synthetase (2'-5'-OAS) gene through an IFN-stimulated response element (ISRE) in non-neoplastic human hepatocyte PH5CH8 cells. Here, we found that Core and NS5B synergistically enhanced the 2'-5'-OAS gene promoter activity through ISRE. Further analysis revealed that amino acid positions 12 and/or 13 of Core and RNA-dependent RNA polymerase activity of NS5B were essential for the activation of the 2'-5'-OAS gene promoter. Interestingly, we observed that the activation by Core or NS5B was still partially enhanced by even the NS5B or Core mutant lacking the activating ability, respectively, suggesting an indirect interaction between Core and NS5B. Furthermore, we showed that the activation by NS5B could be explained by NS5B's induction of IFN-beta, however, IFN-beta was not induced by Core. Moreover, we showed that the synergistic effect of Core

and NS5B was not invalidated by NS3-4A, although NS3-4A significantly inhibited the activation by combination of Core and NS5B. Taken together, **our findings reveal** that NS5B/Core and NS3-4A exhibit conflicting effects (activation and inhibition) on the IFN system in PH5CH8 cells, and suggest that such effects may promote the distraction of the host defense system to lead to persistent infection.

Anterior cingulate activation and error processing during interferon-alpha treatment. Capuron L, et. al. Biol Psychiatry. 2005 Aug 1;58(3):190-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16084839&query_hl=7

BACKGROUND: There has been increasing interest in the role of immunologic processes, notably cytokines, in the development of behavioral alterations, especially in medically ill patients. Interferon (IFN)-alpha is notorious for causing behavioral symptoms, including depression, fatigue, and cognitive dysfunction, and has been used to investigate the effects of cytokines on the brain. **METHODS:** In the present study we assessed the effects of low-dose IFN-alpha on brain activity, using functional magnetic resonance imaging during a task of visuospatial attention in patients infected with hepatitis C virus (HCV). **RESULTS:** Despite endorsing symptoms of impaired concentration and fatigue, IFN-alpha-treated patients (n = 10) exhibited task performance and activation of parietal and occipital brain regions similar to that seen in HCV-infected control subjects (n = 11). Interestingly, however, in contrast to control subjects, IFN-alpha-treated patients exhibited significant activation in the dorsal part of the anterior cingulate cortex (ACC), which highly correlated with the number of task-related errors. No such correlation was found in control subjects. **CONCLUSIONS:** Consistent with the role of the ACC in conflict monitoring, ACC activation during IFN-alpha administration suggests that cytokines might increase processing conflict or reduce the threshold for conflict detection, thereby signaling the need to exert greater mental effort to maintain performance. Such alterations in ACC activity might in turn contribute to cytokine-induced behavioral changes.

Role of interleukin-18 and its Receptor in Hepatocellular Carcinoma Associated with Hepatitis C Virus Infection. Asakawa M, et al. Int J Cancer. 2005 Aug 17; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16108033&query_hl=7

Interleukin (IL)-18 is a proinflammatory cytokine that is up-regulated in patients with hepatitis C virus (HCV) infection, which is the most common underlying disease in hepatocellular carcinoma (HCC). The purpose of our study was to investigate the role of IL-18 in HCC associated with HCV infection. Sixty-five patients with HCC and HCV infections who received curative surgical resections were examined in our study. The expression of the IL-18 receptor was investigated in HCC tissues obtained from these patients and in 2 HCC cell lines. Nuclear factor (NF)-kappaB activity and the expression of Bcl-xL and xIAP mRNA were tested in the cell lines using recombinant human (rh) IL-18. The IL-18 receptor was expressed in both the HCC tissues and the cell lines. NF-kappaB activation and the expression of Bcl-xL and xIAP mRNA were increased by rhIL-18. Moreover, rhIL-18 suppressed the apoptosis of HCC cells which was induced by etoposide in vitro. The overall survival rate (55.4%) was significantly worse in the IL-18 receptor-positive patients than in the IL-18 receptor-negative patients (p = 0.015). In a Cox multivariate analysis, the expression of the IL-18 receptor was found to be a significant predictor of a poor outcome in HCC patients. The expression of the IL-18 receptor and an antiapoptotic mechanism involving NF-kappaB activation in HCC cells may be implicated in a poor patient outcome.

Mutagenic effects of ribavirin and response to interferon/ribavirin combination therapy in chronic hepatitis C. Asahina Y, Izumi N, et al. J Hepatol. 2005 Oct;43(4):623-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16098627&query_hl=7

BACKGROUND/AIMS: To elucidate whether ribavirin acts as a mutagen in the clinical setting and to clarify the relationship between ribavirin-induced mutations and virological response to combined therapy. **METHODS:** Thirty-four patients with hepatitis C virus (HCV) genotype 1b received ribavirin monotherapy for 4 weeks, followed by a 24-week course of IFN/ribavirin therapy. HCV mutations during a non-treatment observation period and during subsequent ribavirin monotherapy were determined, and the relationship between mutations and response to subsequent IFN/ribavirin therapy was evaluated. **RESULTS:** Serum HCV significantly decreased from 6.90 to 6.56 log(10)copy/ml in response to ribavirin monotherapy (P<0.0001). Nucleotide mutations in the NS5A and NS5B regions occurred during ribavirin monotherapy at a rate of 2.9x10⁽⁻²⁾/site/year and 1.3x10⁽⁻²⁾/site/year,

respectively, a significantly higher rate than the mutation rates during the prior non-treatment observation period (0.60×10^{-2} /site/year and 0.24×10^{-2} /site/year, $P=0.02$, respectively). Mutation rates in the NS5A region were significantly higher in sustained viral responders (SVRs, $n=10$) than in non-responders (8.8×10^{-2} /site/year vs. 0.38×10^{-2} /site/year, $P=0.0005$, respectively). In the NS5A region, non-synonymous mutations only occurred in SVRs. **CONCLUSIONS:** Ribavirin may act as a mutagen, and mutations occurring during ribavirin therapy correlate with the virological response to subsequent IFN/ribavirin combination therapy.

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=7

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 ± 1.4 vs. 2.9 ± 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.

Hepatitis C virus stimulates the expression of cyclooxygenase-2 via oxidative stress: role of prostaglandin E2 in RNA replication.

Waris G, Siddiqui A. J Virol. 2005 Aug;79(15):9725-34.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16014934&query_hl=7

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, which can lead to the development of liver cirrhosis and hepatocellular carcinoma. Recently, the activation of cyclooxygenase-2 (Cox-2) has been implicated in the HCV-associated hepatocellular carcinoma. In this study, we focus on the signaling pathway leading to Cox-2 activation induced by HCV gene expression. Here, we demonstrate that the HCV-induced reactive oxygen species and subsequent activation of NF-kappaB mediate the activation of Cox-2. The HCV-induced Cox-2 was sensitive to antioxidant (pyrrolidine dithiocarbamate), Ca²⁺ chelator (BAPTA-AM), and calpain inhibitor (N-acetyl-Leu-Leu-Met-H). The levels of prostaglandin E₂ (PGE₂), the product of Cox-2 activity, are increased in HCV-expressing cells. Furthermore, HCV-expressing cells treated with the inhibitors of Cox-2 (celecoxib and NS-398) showed significant reduction in PGE₂ levels. We also observed the enhanced phosphorylation of Akt and its downstream substrates glycogen synthase kinase-3 β and proapoptotic Bad in the HCV replicon-expressing cells. These phosphorylation events were sensitive to inhibitors of Cox-2 (celecoxib and NS-398) and phosphatidylinositol 3-kinase (LY294002). Our results also suggest a potential role of Cox-2 and PGE₂ in HCV RNA replication. These studies provide insight into the mechanisms by which HCV induces intracellular events relevant to liver pathogenesis associated with viral infection.

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

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

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15977232&query_hl=7

Chronic hepatitis C virus (HCV) infection leads to increased oxidative stress in the liver. Hepatic antioxidant enzymes provide an important line of defense against oxidative injury. To understand the antioxidant responses of hepatocytes to different HCV proteins, we compared changes in antioxidative enzymes in HCV-core and HCV-nonstructural protein expressing hepatocyte cell lines. We found that expression of HCV-core protein in hepatocyte cell lines leads to increased oxidative stress as determined by increased in the oxidant-sensitive probe 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate (CM-DCFH₂) fluorescence, decreased reduced glutathione (GSH), and increased oxidation of thioredoxin (Trx). Although the expression of HCV-nonstructural (HCV-NS) proteins led to increased oxidative stress as well, the antioxidant enzymatic responses were different. Over-expression of HCV-NS proteins increased antioxidant enzymes (MnSOD and catalase), heme oxygenase-1

(HO-1), and GSH, indicating different mechanism(s) of prooxidative activity than HCV-core protein. Our findings show that different HCV proteins induce different antioxidant defense responses in hepatocytes. These findings may facilitate understanding the interaction of different HCV proteins with infected liver cells and help identify possible factors contributing to hepatocyte damage during HCV infection.

Differential contribution of hepatitis C virus NS5A and core proteins to the induction of oxidative and nitrosative stress in human hepatocyte-derived cells. Garcia-Mediavilla MV, et al. J Hepatol. 2005

Oct;43(4):606-13.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16112247&query_hl=7

BACKGROUND/AIMS: We aimed to explore the effects of hepatitis C virus (HCV) core and NS5A proteins on reactive oxygen (ROS) and nitrogen species (RNS) formation and on gene expression profile of iNOS in human hepatocyte-derived cells. **METHODS:** Production of ROS and RNS and nitrotyrosine residues accumulation were determined by flow cytometry and fluorescent microscopy as well as by Western blot, respectively, in NS5A- and core-transfected cells. Northern blot, Western blot, real-time PCR, and luciferase assays were used to assess iNOS gene expression in both transfectants. **RESULTS:** Cytokine-activated NS5A- and core-transfected cells induced ROS and RNS production but an earlier and more marked increase was observed in NS5A-expressing cells. Superoxide production was also augmented, showing a similar temporal pattern of appearance in both NS5A- and core-transfected cells. Although both NS5A and core HCV proteins were able to up-regulate iNOS gene expression, accompanied by a nitrotyrosine-containing proteins accumulation, an earlier iNOS overexpression was observed in NS5A-expressing cells, suggesting a different time course of iNOS activation pattern for core and NS5A HCV proteins. **CONCLUSIONS:** Our results indicate a differential contribution of both HCV proteins to oxidative and nitrosative stress generation.

The Expression of BCL-2 in Chronic Liver Diseases. Mutluay R, et al. Saudi Med J. 2005 Aug;26(8):1245-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16127523&query_hl=7

OBJECTIVE: Bcl-2 is an oncogene that prevents apoptosis (programmed cell death). Expression of bcl-2 protein has been reported in association with a variety of human tumors. **METHODS:** This study was conducted in the Department of Gastroenterology and Pathology, Faculty of Medicine Gazi University, Ankara, Turkey during the period 1996 to 2000 on formalin-fixed paraffin embedded tissue specimens of 69 liver biopsy with chronic liver disease. To evaluate the clinical importance of bcl-2 expression in chronic liver disease and its correlation with biochemical parameters, underlying liver disease types and histopathological parameters; we studied the bcl-2 expression in 69 biopsy proven patients. These were diagnosed with chronic liver disease, and had no other disease or had not received any treatment. Of these patients, 30 were diagnosed as having hepatitis C, 20 with hepatitis B, 19 with liver cirrhosis. **RESULTS:** The bcl-2 expression was significantly higher in the hepatitis C group when compared with the hepatitis B group ($p < 0.001$). No significant correlation was found among serum transaminase, bilirubin, albumin, hepatitis C virus - RNA, hepatitis B virus - DNA levels, prothrombin time and bcl-2 expression ($p > 0.05$). **CONCLUSION:** The reason for the increased expression of bcl-2 in hepatitis C is unclear and may be related to difference in the injury mechanism of the virus, differences in the infection period, and immunology.

Deficient Stat3 DNA-binding is associated with high Pias3 expression and a positive anti-apoptotic balance in human end-stage alcoholic and hepatitis C cirrhosis. Starkel P, De Saeger C, Leclercq I, Strain A, Horsmans Y. J Hepatol. 2005 Oct;43(4):687-95.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16098628&query_hl=7

BACKGROUND/AIMS: In vitro and animal data suggest that alcohol and hepatitis C virus (HCV) proteins might interfere with Stat3 signaling, a potential regulator of liver cell apoptosis and proliferation. **METHODS:** We assessed Stat3 expression, activity and the apoptotic-proliferation balance in end-stage HCV and alcoholic liver disease (ALD) in man. Explanted livers of HCV and ALD patients were compared to normal and primary biliary cirrhosis (PBC) livers. **RESULTS:** Although Stat3 expression and phosphorylation was not altered in HCV and ALD cirrhosis, Stat3 DNA-binding was not detected in all ALD and most HCV samples. Deficient Stat3 DNA-binding was associated with high Pias3 expression, but not with increased Socs3 levels. Bcl-2 was up-regulated in HCV and ALD together with decreased Caspase3 activity. Compared to base-line cell proliferation in normal donor livers, HCV cirrhosis showed a marked reduction in cyclin D1 and PCNA, whereas both markers were only slightly

reduced in ALD. **CONCLUSIONS:** End-stage HCV and ALD cirrhosis is characterized by impaired Stat3 DNA-binding possibly through up-regulation of Pias3. Therefore, impaired activation of Stat3 target genes might contribute to disturbed liver regeneration and repair. The attempt in cirrhotic livers to favor anti-apoptotic over pro-apoptotic pathways is not sufficient to compensate for the low cellular proliferation rates.

CD8+ T Cell Depletion Amplifies Hepatitis C Virus Replication in Peripheral Blood Mononuclear Cells. Li Y, et al. *J Infect Dis.* 2005 Sep 15;192(6):1093-101. Epub 2005 Aug 10.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16107965&query_hl=7

We investigated the ability of CD8(+) T cells to inhibit hepatitis C virus (HCV) replication in peripheral blood mononuclear cells (PBMCs). PBMCs isolated from 11 of 20 HCV-infected subjects had no detectable HCV RNA. Removal of CD8(+) T cells from these PBMCs resulted in detection of HCV RNA, and depletion of CD8(+) T cells from PBMCs that had detectable HCV RNA amplified HCV replication. Reconstitution of CD8(-) PBMCs with autologous CD8(+) T cells led to inhibition of HCV replication. Interferon- gamma produced by CD8(+) T cells was partially responsible for CD8(+) T cell-mediated noncytotoxic anti-HCV activity in PBMCs. This noncytotoxic anti-HCV activity was confirmed in HCV replicon cells. Supernatants from CD8(+) T cell cultures inhibited HCV RNA expression in the replicon cells. These findings may have important implications for the immunopathogenesis of HCV in both immune and hepatic cells and are relevant to the development of host innate immunity-based anti-HCV interventions.

Modulation of Vaccine-Induced Immune Responses to Hepatitis C Virus in Rhesus Macaques by Altering Priming before Adenovirus Boosting. Rollier C., et al. *J Infect Dis.* 2005 Sep 1;192(5):920-9. Epub 2005 Aug 1.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16088843&query_hl=7

BACKGROUND: Preventive and therapeutic vaccine strategies aimed at controlling hepatitis C virus (HCV) infection should mimic the immune responses observed in patients who control or clear HCV, specifically T helper (Th) type 1 and CD8(+) cell responses to multiple antigens, including nonstructural protein (NS) 3. Given the experience with human immunodeficiency virus, the best candidates for this are based on DNA prime, pox, or adenovirus boost regimens. **METHODS:** In rhesus macaques, we compared NS3-expressing DNA prime and adenovirus boost strategy with 2 alternative priming approaches aimed at modifying Th1 and CD8(+) responses: DNA adjuvanted with interleukin (IL)-2- and -12-encoding plasmids or Semliki Forest virus (SFV). **RESULTS:** All prime-boost regimens elicited NS3-specific B and T cell responses in rhesus macaques, including CD8(+) responses. SFV priming induced higher lymphoproliferation and longer Th1 memory responses. The use of IL-2- and IL-12-expressing vectors resulted in reduced Th2 and antibody responses, which led to increased Th1 skewing but not to an increase in the magnitude of the IFN- gamma and CD8(+) responses. **CONCLUSIONS:** All strategies induced Th1 cellular responses to HCV NS3, with fine modulations depending on the different priming approaches. When they are developed for more HCV antigens, these strategies could be beneficial in therapeutic vaccine approaches.

In vitro studies of cross-resistance mutations against two hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061. Lin C J., et al. *Biol Chem.* 2005 Aug 8; [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16087668&query_hl=7

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 Ala(156) 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.

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.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15955819&query_hl=10

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.

Reduction of serum ghrelin concentration during interferon-alpha therapy in patients with chronic hepatitis C. Watanabe H, et al. *Hepato Res.* 2005 Aug 18; [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16112898&query_hl=7

The efficacy of interferon (IFN) therapy for chronic hepatitis C is dependent on compliance. Anorexia is an important adverse effect in determining compliance. To clarify the mechanisms underlying anorexia, the level of ghrelin was determined during therapy. Fourteen patients with chronic hepatitis C received IFN-alpha2b with or without ribavirin (Rib+ or Rib- group; n=7 in each group) for 24 weeks. Serum ghrelin concentrations and body weight were determined before, 2 and 24 weeks after initiation of therapy. Serum ghrelin concentrations and body weight significantly decreased 2 weeks after initiation of therapy ($P=0.0008$ and 0.0062 , respectively), and then returned to the level before therapy. The Deltaghrelin concentration correlated with Deltabody weight after 2 weeks ($r=0.726$, $P=0.023$). Percentage reduction of serum ghrelin was significantly higher in the Rib+ group than in the Rib- group ($P=0.046$). Percentage reduction in body weight tended to be higher in the Rib+ group ($P=0.057$). IFN-alpha2b therapy causes short-term reduction of serum ghrelin and body weight, and this may occur to a greater extent with combination therapy. Reduction of serum ghrelin might contribute partly to anorexia, leading to weight loss.

HIV/HCV COINFECTION

Failure of Hepatitis C Therapy in HIV-Coinfected Drug Users Is Not Due to a Shift in Hepatitis C Virus Genotype. Soriano V, et al. *J Infect Dis.* 2005 Oct 1;192(7):1245-8. Epub 2005 Aug 24. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16136468&query_hl=7

Because most patients coinfecting with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are injection drug users (IDUs) who might have been exposed to multiple HCV genotypes while sharing needles, coinfection with distinct HCV genotypes could be frequent in them. Blood samples from 203 coinfecting IDUs who did not respond to at least 24 weeks of interferon (IFN)-based therapies were analyzed. At baseline, 131 patients had HCV genotype 1, 4 had HCV genotype 2, 52 had HCV genotype 3, and 16 had HCV genotype 4. Changes in HCV genotype were not found in any patient when samples obtained before and after HCV therapy were compared. HCV therapy did not appear to select for IFN-resistant HCV genotypes that might have been present at baseline. Coinfection with distinct HCV genotypes is unlikely in former IDUs coinfecting with HIV and does not explain the lower efficacy of HCV therapy in this population.

Prediction of liver fibrosis in HIV/HCV-coinfecting patients by simple noninvasive indexes. Macias J, et al. *Gut.* 2005 Aug 23; [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16118349&query_hl=7

[query_hl=7](#)

BACKGROUND: Liver biopsy is an invasive technique with associated major complications. There is no information on the validity of five noninvasive indexes based on routinely available parameters, estimated and validated in hepatitis C virus (HCV)-monoinfected patients, in human immunodeficiency virus (HIV)/HCVcoinfected patients. **AIM:** To validate these predictive models of liver fibrosis in HIV/HCV-coinfected patients. **PATIENTS:** Three hundred and fifty-seven (90%) of 398 patients from five hospitals, who underwent liver biopsy and who had complete data to validate all of the models considered. **METHODS:** The predictive accuracy of the indexes was tested by measuring the areas under the receiver operating characteristic curves. The diagnostic accuracy was calculated by estimating sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively). **RESULTS:** The models considered performed better when liver biopsies ≥ 15 mm were used as reference. In this setting, the Forns and the Wai indexes, models aimed at discriminating significant fibrosis, showed PPV of 94% and 87%, respectively. Using these models, from 27% to 34% of the patients could benefit from exclusion of liver biopsy. If both models are applied sequentially, 41% of the liver biopsies could be spared. The indexes aimed at predicting cirrhosis achieved NPV up to 100%. However, they showed very low PPV. **CONCLUSIONS:** The diagnostic accuracy of these models was lower in HIV/HCV-coinfected patients than in the validation studies performed in HCV-monoinfected patients. However, simple fibrosis tests may render liver biopsy unnecessary in deciding anti-HCV treatment in over one third of the patients with HIV infection

Hepatitis C virus infection in HIV type 1-infected individuals does not accelerate a decrease in the CD4+ cell count but does increase the likelihood of AIDS-defining events. Stebbing J, et al. Clin Infect Dis. 2005 Sep 15;41(6):906-11. Epub 2005 Aug 5.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16107994&query_hl=7

Human immunodeficiency virus type 1 (HIV-1) appears to adversely affect hepatitis C, but whether hepatitis C virus (HCV) has a reciprocal effect on HIV-1 infection remains a point of controversy. In a multivariate analysis of a cohort of 5832 individuals, we found that individuals coinfecting with HCV and HIV-1 (prevalence of coinfection, 5.8%) had a CD4+ cell count that decreased at a rate similar to that for individuals infected with HIV-1 alone. However, coinfection was associated with a statistically significant increased likelihood of onset of an acquired immunodeficiency syndrome-defining illness or developing a CD4+ cell count of < 200 cells/mm³, compared with infection with HIV-1 alone (hazard ratio, 1.52; 95% confidence interval, 1.072-1.7). Patients who were naive to highly active antiretroviral therapy were significantly less likely to progress to either end point, because of their higher CD4+ cell counts. **In conclusion**, there was an increased number of adverse events in coinfecting individuals, compared with individuals infected with HIV-1 alone.

Fibrosis progression in chronic hepatitis C patients with occult hepatitis B co-infection. Hui CK, et al. J Clin Virol. 2005 Aug 12; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16103008&query_hl=7

Occult hepatitis B virus (HBV) infection in individuals without hepatitis B surface antigen (HBsAg) can be identified in hepatitis C virus (HCV) infected patients. However, its role in fibrosis progression remains uncertain. This retrospective study compared the fibrosis progression (defined as fibrosis progression by at least one stage) and progression to severe fibrosis (fibrosis stage 3 or 4) in HCV patients with occult HBV infection. Occult HBV infection was diagnosed by the detection of HBV DNA in the serum of 74 consecutive anti-HCV positive patients by PCR. Thirty-one patients (41.9%) had occult HBV infection. All 74 patients had a median of 2 (range 2-3) liver biopsies. The median time between the first and last liver biopsy was 57.7 (range 15.0-132.8) months. Eleven of the 31 patients with occult HBV infection compared with 12 of the 43 patients without occult HBV infection had fibrosis progression (35.5% versus 27.9%, respectively, $p=0.608$). Six of the 31 patients with occult HBV infection compared with 8 of the 43 patients without occult HBV infection developed severe fibrosis (19.4% versus 18.6%, respectively, $p=0.946$). **In conclusion**, chronic HCV patients with occult HBV co-infection does not seem to progress more than patients without occult HBV infection. However, more large-scale studies are needed before a definite conclusion can be obtained.

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=7

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.

Hepatitis C infection is not associated with systemic HIV-associated non-Hodgkin's lymphoma: a cohort study. Waters L, et al. *Int J Cancer*. 2005 Aug 10;116(1):161-3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15756687&query_hl=10

Immunosuppression induced by the human immunodeficiency virus (HIV) increases the risk of developing non-Hodgkin's lymphoma (NHL). As the hepatitis C virus (HCV) has been implicated in the development of B cell lymphomas, we compared the incidence of systemic NHL during HIV infection compared to HIV and HCV co-infection. Of 5,832 individuals studied during the era of highly active anti-retroviral therapy (HAART), 102 patients were diagnosed with systemic NHL. The incidence of systemic NHL was 6.9 of 10(4) patient years during HIV infection compared to 7.1 of 10(4) patient years during HIV alone ($p = 0.9$). In this immunocompromised patient population, there was no association between HCV infection and an increased risk of lymphoma.

Effects of hepatitis C virus coinfection on survival in veterans with HIV treated with highly active antiretroviral therapy. Backus LI, et al. *J Acquir Immune Defic Syndr*. 2005 Aug 15;39(5):613-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16044016&query_hl=7

BACKGROUND: With highly active antiretroviral therapy (HAART) available for patients with HIV, hepatitis C virus (HCV) infection has emerged as a potentially important cause of mortality in coinfecting patients. Several studies have investigated the effect of coinfection on mortality, with conflicting results. **METHODS:** The study cohort consisted of HIV-infected veterans on HAART receiving care at US Department of Veterans Affairs facilities. Inclusion was based on first HAART prescription between January 1997 and February 2003, HCV antibody test result, and baseline CD4 and HIV viral load results within 1 year of starting HAART. We fitted Cox proportional hazards models to study the effect of HCV serostatus on survival time from HAART initiation, controlling for patient demographic and clinical characteristics, facility characteristics, HAART exposure, HAART response, and HCV treatment. **RESULTS:** Of 12,216 patients in the study cohort, 38% were HCV-seropositive. During an observation time averaging 3.5 years, 2087 patients died. The adjusted hazard ratio for HCV-seropositive patients was 1.56 (95% confidence interval [CI]: 1.42-1.70; $P < 0.0001$) without a HAART exposure measure and 1.38 (95% CI: 1.26-1.51; $P < 0.0001$) with the measure. We obtained similar results in analyses also controlling for HAART response. **CONCLUSIONS:** HCV seropositivity was independently associated with increased risk of death in a large cohort of HAART-treated HIV-infected veterans. Given the success of HAART in extending the lives of HIV patients, HCV has become an important predictor of their mortality.

Hepatic steatosis in HIV/hepatitis C coinfection: prevalence and significance compared with hepatitis C mono-infection. Monto A, et al. *Hepatology*. 2005 Aug;42(2):310-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16025515&query_hl=7

Liver disease in patients coinfecting with HIV and hepatitis C virus (HCV) has received increasing attention in recent years. Steatosis is accepted as an important contributor to liver disease in patients with HCV, but despite coinfecting patients having several reasons to have steatosis, the prevalence and significance of such changes has received scant attention. We examined steatosis in an unselected cohort of coinfecting patients and compared its prevalence and predictors with findings in mono-infected patients, where these relationships have been established. We studied 92 coinfecting and 372 mono-infected patients undergoing staging liver biopsy. Baseline characteristics of the two groups differed significantly, pointing at different contributors to steatosis in each. Histological inflammation and fibrosis were very similar in the two groups, but steatosis was less in coinfecting patients. Steatosis had a univariate association with fibrosis in both groups, but retained a multivariate association only in mono-infected patients. Other multivariate predictors of steatosis in mono-infected patients were the accepted variables of elevated body mass index, male sex, and genotype 3a infection, as well as age. In coinfecting patients, however, age was the only multivariate predictor. Undetectable HIV viral load was associated with steatosis in coinfecting patients in univariate analysis, but highly active antiretroviral therapy or its individual components could not be initially linked to steatosis. **In conclusion**, steatosis is less common in HIV/HCV coinfecting patients than similar HCV mono-infected patients, and predictors of steatosis differ between the two groups.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Non-interferon-based therapy: an option for amelioration of necro-inflammation in hepatitis C patients who cannot afford interferon therapy. El-Zayadi AR, et al. *Liver Int.* 2005 Aug;25(4):746-51. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16086711&query_hl=7

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

Blood micronutrient, oxidative stress, and viral load in patients with chronic hepatitis C. Ko WS, et al. *World J Gastroenterol.* 2005 Aug 14;11(30):4697-702. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16094713&query_hl=7

AIM: To assess the extent of micronutrient and oxidative stress in blood and to examine their linkages with viral loads in chronic hepatitis C patients. **METHODS:** Hepatitis C virus (HCV)-RNA levels were quantified in the serum from 37 previously untreated patients with chronic hepatitis C. The plasma and erythrocyte micronutrients (zinc, selenium, copper, and iron) were estimated, and malondialdehyde (MDA) contents were determined as a marker to detect oxidative stress. Antioxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione reductase (GR) activities in blood were also measured. The control group contained 31 healthy volunteers. **RESULTS:** The contents of zinc (Zn), and selenium (Se) in plasma and erythrocytes were significantly lower in hepatitis C patients than in the controls. On the contrary, copper (Cu) levels were significantly higher. Furthermore, plasma and erythrocyte MDA levels, and the SOD and GR activities in

erythrocytes significantly increased in hepatitis C patients compared to the controls. However, the plasma GPX activity in patients was markedly lower. Plasma Se ($r = -0.730$, $P < 0.05$), Cu ($r = 0.635$), and GPX ($r = -0.675$) demonstrated correlations with HCV-RNA loads. Significant correlation coefficients were also observed between HCV-RNA levels and erythrocyte Zn ($r = -0.403$), Se ($r = -0.544$), Cu ($r = 0.701$) and MDA ($r = 0.629$) and GR ($r = 0.441$). **CONCLUSION:** The levels of Zn, Se, and oxidative stress (MDA), as well as related anti-oxidative enzymes (GR and GPX) in blood have important impact on the viral factors in chronic hepatitis C. The distribution of these parameters might be significant biomarkers for HCV.

MISCELLANEOUS WORKS

Barriers to the treatment of hepatitis C. Patient, provider, and system factors. Morrill JA, Shrestha M, Grant RW. *J Gen Intern Med.* 2005 Aug;20(8):754-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16050887&query_hl=7

BACKGROUND: Hepatitis C virus (HCV) infection is both prevalent and undertreated. **OBJECTIVE:** To identify barriers to HCV treatment in primary care practice. **DESIGN:** Cross-sectional study. **SETTING AND PARTICIPANTS:** A cohort of 208 HCV-infected patients under the care of a primary care physician (PCP) between December 2001 and April 2004 at a single academically affiliated community health center. **MEASUREMENTS:** Data were collected from the electronic medical record (EMR), the hospital clinical data repository, and interviews with PCPs. **MAIN RESULTS:** Our cohort consisted of 208 viremic patients with HCV infection. The mean age was 47.6 (+/-9.7) years, 56% were male, and 79% were white. Fifty-seven patients (27.4% of the cohort) had undergone HCV treatment. Independent predictors of not being treated included: unmarried status (adjusted odds ratio [aOR] for treatment 0.36, $P = .02$), female gender (aOR 0.31, $P = .01$), current alcohol abuse (aOR 0.08, $P = .0008$), and a higher ratio of no-shows to total visits (aOR 0.005 per change of 1.0 in the ratio of no-shows to total visits, $P = .002$). The major PCP-identified reasons not to treat included: substance abuse (22.5%), patient preference (16%), psychiatric comorbidity (15%), and a delay in specialist input (12%). For 13% of the untreated patients, no reason was identified. **CONCLUSIONS:** HCV treatment was infrequent in our cohort of outpatients. Barriers to treatment included patient factors (patient preference, alcohol use, missed appointments), provider factors (reluctance to treat past substance abusers), and system factors (referral-associated delays). Multimodal interventions may be required to increase HCV treatment rates.

High prevalence of alcohol use among hepatitis C virus antibody positive injection drug users in three US cities. Campbell JV, et al. *Drug Alcohol Depend.* 2005 Aug 26; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16129567&query_hl=7

Injection drug users (IDUs) acquire the majority of new hepatitis C virus (HCV) infections and frequently use alcohol. Alcohol abuse accelerates liver disease among HCV-infected persons, can reduce the effectiveness of treatment for HCV infection and may be a contraindication for HCV treatment. HCV seropositive, HIV-negative IDUs aged 18-35 years in Baltimore, New York City and Seattle who were enrolled in a behavioral risk-reduction intervention trial underwent computerized self-interviews to assess baseline alcohol use and dependence and medical history. We measured problem alcohol use using the 10-item Alcohol Use Disorders Identification Test (AUDIT) scale. Of 598 participants, 84% responded "false" to: "it is safe for a person with HCV to drink alcohol". Problem drinking, defined as score ≥ 8 on AUDIT, was identified in 37%. Correlates of scoring ≥ 8 on AUDIT included homelessness, male gender, primarily injecting speedballs, having injected with used needles, prior alcohol treatment and depression. Although most HCV seropositive IDUs in our sample appear informed about their increased risk of liver disease from alcohol, two-fifths screened positive for problem alcohol use. These findings underscore the importance of referring HCV-positive persons to effective alcohol treatment programs to reduce future liver damage and improve eligibility for and effectiveness of treatment of HCV.

Molecular epidemiology of hepatitis C among drug users in Flanders, Belgium: association of genotype with clinical parameters and with sex- and drug-related risk behaviours. Mathei C, et al. *Eur J Clin Microbiol Infect Dis.* 2005 Aug 19; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16133411&query_hl=7

The aim of this study was to determine the genotypic variation of hepatitis C among drug users in Flanders and to relate the distribution of genotypes to the characteristics of the population. Hepatitis C virus RNA (HCV-RNA) quantification and genotyping was performed on stored samples from 161 anti-HCV-positive injecting and non-injecting drug users. Information on sociodemographic status, drug-related risk behaviour and sexual risk behaviour was available for each drug user. HCV-RNA was present in 152 of 161 samples (94.4%). Genotype 1 was predominant (48.7%), followed by genotype 3 (41.2%), genotype 4 (8.8%) and genotype 2 (1.4%). In the multivariate analysis, lack of a history of injecting drug use was confirmed as a statistically significant predictor for infection with genotype 1. Predictors for infection with genotype 3 were the presence of anti-HBc antibodies and a history of injecting drug use. Being tattooed emerged as a statistically significant predictor for infection with genotype 4. The 94.4% prevalence of HCV-RNA among anti-HCV-positive drug users was considerably higher than the 54-86% chronicity rate found globally among HCV-infected patients. **The results of this study suggest** the existence of separate transmission networks for injecting drug users and non-injecting drug users. Finally, the results suggest that tattooing practices play a role in the spread of HCV among drug users.

Correlation between detection of antibodies against hepatitis C virus in oral fluid and hepatitis C virus RNA in serum. De Cock L, Hutse V, Vranckx R. Eur J Clin Microbiol Infect Dis. 2005 Aug 19; [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16133413&query_hl=7

Reported here are the results of a study designed to determine the correlation between hepatitis C virus (HCV) RNA positivity in serum and the detection of antibodies against HCV in oral fluid by testing paired serum/oral fluid samples. For the 85 serum samples found positive for antibodies against HCV, using a screening assay and a confirmation assay, 70 of the corresponding oral fluid samples tested positive for HCV antibodies using a previously modified screening assay. For 52 of the 59 serum samples found positive for HCV RNA, the corresponding oral fluid samples also tested seropositive for HCV, while 18 of the 26 serum samples that were negative for HCV RNA had corresponding oral fluid samples that tested seropositive for HCV. For the control group of 54 serum samples that were negative for HCV antibodies, all of the corresponding oral fluid samples were also negative for HCV antibodies, while 53 of the serum samples tested negative for HCV RNA. **These results suggest** that HCV antibody detection in oral fluid has a slightly higher sensitivity when used to test patients whose serum samples are positive for HCV RNA (chi-square test, $p=0.035$; Mid-P exact, $p=0.049$).

Does prevalence of transfusion-transmissible viral infection reflect corresponding incidence in United States blood donors? Wang B, et al. Transfusion. 2005 Jul;45(7):1089-96. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15987352&query_hl=2

BACKGROUND: Calculation of viral residual risk is dependent on estimating incidence, which is not easily obtainable by most blood centers. Prevalence, however, is readily available. Understanding whether prevalence reflects corresponding incidence may help blood centers monitor disease risks. **STUDY DESIGN AND METHODS:** With data on 12 million allogeneic donations, prevalence and incidence of transfusion-transmitted viral infections (TTVIs) were calculated. Relationships between prevalence (in total, first-time, and repeat donations) and incidence were analyzed for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) relative to temporal and donor demographic stratifications, respectively. **RESULTS:** Overall prevalence of HIV, HBV, and HCV did not consistently reflect corresponding incidence. The relationship between prevalence and incidence varied with time and donors' age and was virus-specific. **CONCLUSION:** Incidence of TTVIs cannot be easily predicted from overall prevalence. Accurate assessment of TTVI risk necessitates knowledge about donation histories and person-years at risk. Establishing comprehensive frameworks for monitoring blood donations and infectious disease markers remains a key to monitoring blood safety.

Geospatial analysis of hepatitis C in Connecticut: a novel application of a public health tool.

Trooskin SB, Hadler J, St Louis T, Navarro et al. VJ. Public Health. 2005 Aug 4; [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16084545&query_hl=7

OBJECTIVES: This study aimed to use geographic information systems (GIS) that facilitate analysis of associations between location, environment and disease to document the non-random distribution of hepatitis C, identify infection cluster areas, and describe the demographic characteristics of those areas. **METHODS:** Spatial analysis was conducted of newly reported positive hepatitis C test results using the Connecticut Hepatitis C

Reporting Database. A complete database of unduplicated hepatitis C laboratory reports that were sent to the Connecticut Department of Public Health during 1999 was created. Spatial filtering was used to eliminate random noise generated by sparsely populated towns or small number of cases per town. Cluster analysis was used to determine whether cases of hepatitis C virus (HCV) infection tend to occur closer in space to other cases than would be expected by chance alone. The demographic attributes of identified clusters of HCV-positive reports were examined. **RESULTS:** Areas with the highest concentration of HCV reports roughly correspond to the major metropolitan areas of Connecticut. Six significant clusters of HCV reports were identified in Connecticut. Four of the six clusters identified were located in the most densely populated and most urban areas of the state. All but one identified cluster had been described previously as areas of substantial injection drug use, as indicated by their designation as five of the sites of syringe exchange programmes in Connecticut. This finding suggests that geospatial analysis may assist in the identification of clusters that would not otherwise be suspected based on local demographics or other characteristics. **CONCLUSIONS:** These findings contribute significantly to the understanding of the state-specific epidemiology of HCV infection. This methodology can be applied wherever a similar database exists to enable the implementation of targeted prevention and educational campaigns to raise awareness of HCV risk factors, the importance of being tested, and treatment options.

Patients' Experiences Related to Anti-viral Treatment for Hepatitis C. Fraenkel L, McGraw S, Wongcharatrawee S, Garcia-Tsao G. Patient Educ Couns. 2005 Aug 9; [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16098705&query_hl=7

OBJECTIVE: To conduct a qualitative study to elicit patients' descriptions of their own experiences with treatment for hepatitis C (HCV). **METHODS:** Focus groups were conducted until thematic saturation was reached. **RESULTS:** A total of 40 patients (80% male) participated in eight focus groups. The themes that emerged most frequently during the focus groups centered on adverse effects and quality of care. The discussions highlighted discrepancies between patients' anticipated effects of drug toxicity versus their actual experiences, gaps in communication between physicians, and the lack of social support as important shortcomings in the healthcare of HCV patients. **CONCLUSIONS:** The issues raised by the participants in this study highlight several important areas that may lead to improved care for patients with HCV. **PRACTICE IMPLICATIONS:** This study suggests that care for patients with HCV might be improved by using patient testimonials to improve accuracy of expectations, having both the primary care physician and liver specialist devise a plan to treat symptoms arising during the course of therapy, and ensuring that patients have the option of participating in a support group.

Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. Bini EJ, et al. Am J Gastroenterol. 2005 Aug;100(8):1772-9 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16086714&query_hl=7

BACKGROUND: Many veterans may not be candidates for hepatitis C virus (HCV) treatment due to contraindications to therapy. The aims of this study were to determine the proportion of HCV-infected veterans who were eligible for interferon alfa and ribavirin therapy and to evaluate barriers to HCV treatment. **METHODS:** We prospectively enrolled 4,084 veterans who were referred for HCV treatment over a 1-yr period at 24 Veterans Affairs (VA) Medical Centers. Treatment candidacy was assessed using standardized criteria and the opinion of the treating clinician. **RESULTS:** Overall, 32.2% (95% CI, 30.8-33.7%) were candidates for HCV treatment according to standardized criteria, whereas 40.7% (95% CI, 39.2-42.3%) were candidates in the opinion of the treating clinician. Multivariable analysis identified ongoing substance abuse (OR = 17.68; 95% CI, 12.24-25.53), comorbid medical disease (OR = 9.62; 95% CI, 6.85-13.50), psychiatric disease (OR = 9.45; 95% CI, 6.70-13.32), and advanced liver disease (OR = 8.43; 95% CI, 4.42-16.06) as the strongest predictors of not being a treatment candidate. Among patients who were considered treatment candidates, 76.2% (95% CI, 74.0-78.3%) agreed to be treated and multivariable analysis showed that persons ≥ 50 yr of age (OR = 1.37; 95% CI, 1.07-1.76) and those with >50 lifetime sexual partners (OR = 1.44; 95% CI, 1.08-1.93) were more likely to decline treatment. **CONCLUSIONS:** The majority of veteran patients are not suitable candidates for HCV treatment because of substance abuse, psychiatric disease, and comorbid medical disease, and many who are candidates decline therapy. Multidisciplinary collaboration is needed to overcome barriers to HCV therapy in this population.

An assessment of hepatitis C virus infection among health-care workers of the National Cancer Institute of Naples, Southern Italy. Montella M, et al. Eur J Public Health. 2005 Jul 21; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16037074&query_hl=3

BACKGROUND: As many people with chronic hepatitis C virus (HCV) infection are asymptomatic, HCV infection could spread easily among the health-care workers of the National Cancer Institute of Naples (especially before the identification of HCV and in the absence of good, effective preventative measures, e.g. sterile syringe use, gloves, protective glasses). **METHODS:** In order to determine whether there is a transmission risk for HCV infection from patient to health-care worker, we carried out a cross-sectional study of a cohort of National Cancer Institute health-care workers in Naples, Southern Italy. **RESULTS:** The chi(2)-test was not significant; we did not find any significant risk for HCV in the 'other untrained staff' group [odds ratio (OR) 2.2; 95% confidence interval (CI) 0.4-10.9] or in the health-care workers group (OR 1.6; 95% CI 0.4-7.0). In the health-care worker subgroups, doctors were the reference category because of the low prevalence of HCV in this subgroup (3.3%). A non-significant association was found in the professional nurses group (OR 2.7; 95% CI 0.8-8.8), as well as in the categories of technicians and biologists. **CONCLUSIONS:** No excessive risk was found among the health-care workers as a whole or among the different categories of personnel, confirming that health-care employees have benefited sufficiently from preventative measures.

Determining the Extent of Quality Health Care for Hospitalized Patients with Cirrhosis. Talwalkar JA. Hepatology. 2005 Aug;42(2):492-4.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15942950&query_hl=10

BACKGROUND/AIMS: Since few data are available concerning the clinical course of decompensated hepatitis C virus (HCV)-related cirrhosis, the aim of the present study was to define the natural long-term course after the first hepatic decompensation. **METHODS:** Cohort of 200 consecutive patients with HCV-related cirrhosis, and without known hepatocellular carcinoma (HCC), hospitalized for the first hepatic decompensation. **RESULTS:** Ascites was the most frequent first decompensation (48%), followed by portal hypertensive gastrointestinal bleeding (PHGB) (32.5%), severe bacterial infection (BI) (14.5%) and hepatic encephalopathy (HE) (5%). During follow-up (34+/-2 months) there were 519 readmissions, HCC developed in 33 (16.5%) patients, and death occurred in 85 patients (42.5%). The probability of survival after diagnosis of decompensated cirrhosis was 81.8 and 50.8% at 1 and 5 years, respectively. HE and/or ascites as the first hepatic decompensation, baseline Child-Pugh score, age, and presence of more than one decompensation during follow-up were independently correlated with survival. **CONCLUSIONS:** Once decompensated HCV-related cirrhosis was established, patients showed not only a very high frequency of readmissions, but also developed decompensations different from the initial one. These results contribute to defining the natural course and prognosis of decompensated HCV-related cirrhosis.

Cost comparison of two combination therapies with peginterferon alfa and ribavirin for the treatment of hepatitis C [Article in German] Telser H, Mulhaupt B, Helbling B, Zweifel P. Schweiz Rundsch Med Prax. 2005 Aug 10;94(32):1207-14.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16128208&query_hl=7

The two approved combination therapies for the treatment of hepatitis C in Switzerland (Pegasys/Copegus, PAC; PegIntron/Rebetol, PIR) are very similar in terms of efficacy and safety. This study aims at comparing the cost of the two therapies and determining the cost-efficient treatment algorithm. Average cost amounts to CHF 21700.- (PAC) and CHF 19700.- (PIR) for patients with genotype 1 and to CHF 15600.- (PAC) and CHF 15000.- (PIR) for patients with genotype 2/3, respectively. The consistent use of PIR is 9 to 12% cheaper than PAC. Further cost savings of 3% are possible if patients with a bodyweight below 85 kg (genotype 1) or below 75 kg (genotype 2/3) are treated with PIR while patients with a bodyweight over 85 kg (genotype 1) or over 75 kg (genotype 2/3) are treated with PAC.

Intrafamilial transmission of hepatitis C in Egypt. Mohamed MK, et al. Hepatology. 2005 Jul 19; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16032698&query_hl=2

The incidence of hepatitis C (HCV) infection and associated risk factors were prospectively assessed in a cohort of 6,734 Egyptians from 2 rural villages who were negative for antibodies to HCV (anti-HCV). Initial and follow-up sera were tested for anti-HCV by enzyme immunoassay (EIA), and possible incident cases were confirmed by using

the microparticle enzyme immunoassay (MEIA) and tested for HCV RNA. All follow-up serum samples converting from negative to positive without detectable HCV-RNA were further tested by recombinant immunoblot assay. Over an average of 1.6 years, asymptomatic anti-HCV seroconversion occurred in 33 people (3.1/1,000 person-years [PY]), including 28 (6.8/1,000 PY) in the Nile Delta village (AES), where prevalence was 24% and 5 (0.8/1,000 PY) in the Upper Egypt village (baseline prevalence of 9%). The strongest predictor of incident HCV was having an anti-HCV-positive family member. Among those that did, incidence was 5.8/1,000 PY, compared ($P < .001$) with 1.0/1,000 PY; 27 of 33 incident cases had an anti-HCV-positive family member. Parenteral exposures increased the risk of HCV but were not statistically significant; 67% of seroconverters were younger than 20 years of age, and the highest incidence rate (14.1/1,000 PY) was in children younger than 10 who were living in AES households with an anti-HCV-positive parent. In conclusion, young children would especially benefit from measures reducing exposures or preventing infection with HCV.

ICSI for treatment of human immunodeficiency virus and hepatitis C virus-serodiscordant couples with infected male partner. Mencaglia L, et al. Hum Reprod. 2005 Aug;20(8):2242-6. Epub 2005 Jun 9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15946998&query_hl=10

BACKGROUND: Assisted reproductive technology with semen washing can offer a significant reduction in risk of sexual and vertical transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in serodiscordant couples with infected male partner. **METHODS:** Among couples coming to our centre for reproductive problems from January 2001 to December 2003, we selected 43 couples with seropositive male and seronegative female: 25 couples with HIV-seropositive males, 10 couples with HIV/hepatitis C virus (HCV)-seropositive males and eight couples with HCV-seropositive males. Sperm samples were washed and used for ICSI. **RESULTS:** Seventy-eight cycles of ICSI were performed. The mean fertilization rate was 70.34 +/- 20.14% (mean +/- SD). A mean number of 3.55 +/- 1.11 (range: 1-5) embryos of good quality was transferred for each patient. We obtained 22 pregnancies (21 singletons and one twin), with a pregnancy rate per transfer of 28.2% and an implantation rate per transfer of 15.2%. The cumulative pregnancy rate was 51.2%. At follow-up, no seroconversion was detected in any patient. **CONCLUSIONS:** Our data suggest that sperm wash and ICSI could be useful for reducing the risk of HIV and/or HCV transmission in serodiscordant couples with infected male wishing to have a child, irrespective of their fertility status.

Community incidence of hepatitis B and C among reincarcerated women. Macalino GE, et al. Clin Infect Dis. 2005 Oct 1;41(7):998-1002. Epub 2005 Aug 30.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16142665&query_hl=7

BACKGROUND: The incarceration rate has increased 239% in the United States over the past 2 decades. This increase in incarceration has been fueled by the movement towards a criminal, rather than medical, response to the problem of drug dependence. For women in particular, incarceration and drug use are interdependent epidemics. Given that incarceration is common among drug-dependent persons, infectious diseases--including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection--are prevalent among incarcerated persons. We sought to determine the incidence of HBV and HCV infection among recidivist women prisoners. **METHODS:** From 1996 through 1997, excess from serum samples collected during HIV testing of female admittees to a state Department of Corrections facility were tested for HBV and HCV. Multiple samples obtained from women incarcerated multiple times during the study period were compared for incidence. **RESULTS:** Baseline prevalences of markers of HBV and HCV were 36% and 34%, respectively. Incidence rates for HBV and HCV infection among reincarcerated women were 12.2 and 18.2 per 100 person-years, respectively. The majority of the time spent between serial intakes was not spent in the correctional facility; thus, incident infections likely occurred in the community. **CONCLUSIONS:** Incidences of HBV and HCV infection among reincarcerated women were high. Prisons and jails can be efficient locations for the diagnosis, treatment, and prevention of hepatitis B and C through programs such as testing, counseling, education, vaccination, and linkage to medical and drug treatment services.

Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. Colletta C, et al. Hepatology. 2005 Aug 24; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16121354&query_hl=7

The course of hepatitis C virus (HCV) infection carriers with normal/near-normal aminotransferases (NALT) is usually mild; however, in a few, fibrosis progression occurs. We aimed to verify whether monitoring by liver biopsy might be replaced by noninvasive methods and to identify factors associated with fibrosis progression in patients with persistently normal alanine aminotransferases. We studied 40 untreated HCV-RNA-positive subjects (22 male; median age, 44 years), who underwent two liver biopsies, with a median interval of 78.5 months, during which alanine aminotransferase concentrations (median number of determinations: 12) never exceeded 1.2 times the upper normal limit. Within 9 months from the second biopsy, they were tested by the shear elasticity probe (Fibroscan) and the artificial intelligence algorithm FibroTest. METAVIR fibrosis scores were analyzed in relationship to demographic, clinical, and viral parameters. Weighted kappa analysis was used to verify whether the results of noninvasive methods agreed with histology. Significant fibrosis (\geq F2), present at the first biopsy in only one patient (2.5%), was observed at the second biopsy in 14 patients (35%). At multivariate analysis, excess alcohol consumption in the past (>20 g/d; $P = .017$) and viral load ($>8.0 \times 10^6$ copies/mL; $P = .021$) were independent predictors of progression. In identifying patients with significant fibrosis, inter-rater agreement was excellent for Fibroscan (weighted kappa = 1.0), and poor for FibroTest (weighted kappa = -0.041). **In conclusion**, among HCV carriers with NALT, Fibroscan is superior to the FibroTest in the noninvasive identification of fibrosis, for which excess alcohol consumption in the past and high viral load represent risk factors.

Simultaneous detection of hepatitis C virus (HCV) core antigen and anti-HCV antibodies improves the early detection of HCV infection. Laperche S, et al. J Clin Microbiol. 2005 Aug;43(8):3877-83.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16081925&query_hl=7

To evaluate whether a new enzyme immunoassay developed for the simultaneous detection of hepatitis C virus (HCV) core antigen (Ag) and anti-HCV antibodies (anti-HCV Ab) (Monolisa HCV Ag/Ab ULTRA; Bio-Rad) could improve the early detection of HCV infection, we compared its sensitivity to that of anti-HCV, HCV core Ag, and HCV RNA assays. The populations studied included 12 blood donor samples positive for HCV RNA and HCV core Ag but negative for anti-HCV antibodies and 23 hemodialysis patients who developed anti-HCV Ab (seroconversion) during the follow-up. From these 23 individuals, 83 samples sequentially collected prior to seroconversion and 108 samples collected after seroconversion were tested. Six of 12 blood donations were positive by the HCV Ag/Ab assay. In the hemodialysis cohort, the 24 HCV RNA-negative samples were negative by the HCV Ag/Ab assay and 23 of the 59 HCV RNA-positive samples (39%) were positive. The HCV Ag/Ab assay detected HCV infection on average 21.6 days before the most sensitive antibody assay. The HCV Ag/Ab assay did not detect HCV infection as early as the HCV RNA assay (mean delay, 30.3 days) or HCV Ag assay (mean delays, 27.9, and 16.3 days by the HCV core Ag quantification assay and the HCV Ag blood screening assay, respectively). This new assay provides a notable improvement for the early detection of HCV infection during the so-called window period compared with anti-HCV Ab assays and could be a useful alternative to HCV RNA detection or HCV core Ag assays for diagnosis or blood screening when nucleic acid technologies or HCV core Ag detection are not implemented.

Evolution over a 10 year period of the epidemiological profile of 1,726 newly diagnosed HCV patients in Belgium. Gerard C, et al. J Med Virol. 2005 Aug;76(4):503-10.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15977247&query_hl=7

In order to evaluate the future burden of hepatitis C, there is a need to quantify the evolution with time of some crucial parameters such as disease frequency and age, modes of infection and infecting genotypes of patients presenting for the first time at consultation. The yearly evolution of these parameters was analyzed retrospectively in a cohort of 1,726 patients living in Belgium, who were diagnosed as hepatitis C virus (HCV) carriers by polymerase chain reaction (PCR) between 1992 and 2002. The epidemiological profile of HCV patients showed significant changes during this period. The number of new patients increased with time. The proportion of patients under 50 increased linearly at a rate of 3% per year. The rate of newly presenting patients infected by transfusion before 1990 decreased, but only by 2.7% per year. The proportion of intravenous (IV) drug users increased by 2.5% per year. Patients presenting "undefined" risk factors increased by 2.1% per year. Nosocomial acquisition of HCV infection exhibited a disturbing relative stability in time whereas dialysis tended to disappear as a cause of infection. There was a significant linear annual decrease of 2.3% in the frequency of genotype 1b, which was counterbalanced by a significant increase of 0.7% for genotype 1a and 1.1% for genotype 4. Genotypes 2 and 3 did

not vary significantly with time. Such figures are useful for evaluating the epidemiological changes of C virus infection and for anticipating the future economical cost of hepatitis C treatment in the next few years.