

HEPATITIS C CARING AMBASSADORS PROGRAM NEWSLETTER
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IN THE NEWS

Hepatitis C Infection Associated With Type 2 Diabetes

<http://www.medscape.com/viewarticle/515409?src=hp20.news>

There appears to be a connection between non-cirrhotic hepatitis C virus (HCV) infection and type 2 diabetes, Italian researchers report in the October issue of Diabetes Care. Dr. Alessandro Antonelli of the University of Pisa and colleagues note that there have been some reports of an association between type 2 diabetes and HCV but at least one large study did not confirm this. To investigate further, the researchers studied 564 patients with non-cirrhotic HCV, 82 with non-cirrhotic hepatitis B virus (HBV) infection and 302 matched controls.

Significantly more of the HCV patients (12.6%) had diabetes compared with the HBV patients (4.9%) and the controls (7.0%). The data, say the researchers, suggest that HCV-related hepatitis is associated with diabetes at a stage when liver function is largely preserved. They also note that HCV patients with diabetes were significantly leaner, with a body mass index of 25.7 versus 29.7 for HCV-negative diabetics. Their LDL cholesterol concentration was also lower (3.2 versus 3.6 mmol/L). The team calls for investigation of the underlying mechanisms and "to test whether antiviral therapy for HCV infection may prevent the appearance of type 2 diabetes."

Public Health Groups to Hold L.A. Hepatitis C Summit

<http://www.drugpolicy.org/news/110205hepc.cfm>

The Alliance and other public health groups are teaming up to hold the third annual Hepatitis C Summit in Los Angeles on November 17. The summit will provide a forum for education and discussion among local elected and appointed officials, community-based organizations, medical experts and consumers on the emerging hepatitis C epidemic and the impact of the disease on infected individuals and at-risk populations in Los Angeles County.

"Our aim in this third year is to raise awareness about a potentially deadly disease that lacks community and media attention," said Alliance Southern California regional director Alberto Mendoza, who is also the Los Angeles County Hepatitis C Task Force co-chair. "We will educate the public, honor key leaders and share the latest information on this disease through this important summit."

The California Department of Corrections estimates that half of the female prison population and 40 percent of male prisoners are infected with the hepatitis C virus (HCV). Coinfection with HIV, especially among injection drug users, is a significant problem, with some estimates suggesting that as many as one-quarter of people with HIV are coinfecting with HCV. HCV infection is more serious in HIV-infected persons, leading to liver damage more quickly and possibly affecting the treatment of HIV infection. Los Angeles Mayor Antonio Villaraigosa and Supervisor Gloria Molina will co-chair the summit, which will also be attended by Assembly member Paul Koretz (D-West Hollywood), who will receive an award for his work to combat hepatitis C through sound public policy. The keynote address will be delivered by L.A. City AIDS Coordinator Stephen David Simon. The general public is welcome at the summit and attendance is free, but space is limited so advance registration is advised. For information on how to register please call (213) 381-0515.

Hepatitis C Leadership Summit, October 29-30, Seeks to Elevate the Current Response to the Hepatitis C Epidemic

http://www.genengnews.com/news/bnitem.aspx?name=1090901XSL_NEWSML_TO_NEWSML_WEB.xml

The Healthcare Advocacy and Research Collaboration Project (HARCP), a non-profit organization, and The Bruckner Group, are pleased to announce the Hepatitis C Leadership Summit (HCVLS), a private meeting taking place October 29-30 in Boston. With 4 million hepatitis C (HCV) infections in the U.S. and 3 million chronic infections, HCV is a serious public health crisis for which the current response is vastly inadequate. The HCVLS, a

new initiative, is bringing together stakeholder leaders in hepatitis C for a series of discussions aimed at elevating the response to the epidemic. The HCVLS will specifically explore opportunities to increase the number of patients tested and treated for hepatitis C using currently-available resources.

While there are many worthwhile areas for discussion, the HCVLS is focusing on these three specific areas:

1. Hepatitis C and the Insurance Industry: A discussion of the private and public insurance issues around the identification and treatment of hepatitis C patients.
2. Care options for HCV patients, with a focus on best practices that maximize patient outcomes.
3. Partnering with community faith organizations to expand HCV awareness and patient support.

Attendees at the HCVLS include the majority of the State Hepatitis C coordinators, leading managed care payers, state Medicaid organizations, the CDC, leading clinicians, advocates, and manufacturers. "The HARCP and The Bruckner Group are pleased to bring together this distinguished group of stakeholder participants to discuss how we can collectively do better in the fight against HCV," said Michael J. Russo, President of The Bruckner Group. "The need and the urgency for action could not be clearer. I'm heartened by the unusually strong buy-in to this process. We'd like to especially commend the State Hepatitis C coordinators, as well as public and private insurance industry stakeholders, for their enthusiastic participation. We expect actionable items to emerge from the HCVLS."

The HCVLS will commence with a video welcome from Senator Edward M. Kennedy (MA). Senator Kennedy has for years demonstrated tireless leadership in the congressional fight for greater visibility and resources in efforts to combat HCV. His unstinting efforts deserve the widest possible recognition, and the HCVLS is honored by his participation. The HCVLS, initiated and organized by the HARCP and The Bruckner Group, is sponsored by Roche Pharmaceuticals and The Bruckner Group, with additional support from Schering-Plough Corporation, Valeant Pharmaceuticals International, and Vertex Pharmaceuticals.

The Healthcare Advocacy and Research Collaboration Project is a non-profit organization dedicated to improving access to, quality of, and delivery of healthcare services, particularly in under-served disease areas and patient populations. The HARCP conducts research studies and projects, develops and disseminates information, and demonstrates leadership in activities and efforts to fight disease. Current HARCP initiatives include activities in hepatitis C, hemophilia, and autoimmune disorders.

The Bruckner Group are strategy and research consultants in the pharmaceutical and biotechnology industries. BGI are the leading experts in value strategy, helping clients define, prove, and leverage the healthcare value of their therapeutics to build successful product launch strategies and post-launch brand strategies. BGI's strategies emerge from an understanding of the intersection of therapeutic outcomes, healthcare value at the standard of care, and a determination of unmet market needs of payers, physicians, and patients. BGI's unique and systematic approach creates market success by maximally addressing the healthcare value needs in therapeutic markets.

Hepatitis C complicated by morphine withdrawal

http://www.xagenia.it/news/medicineneeds_net_news/35e2dcdbea1950a7a290dd0c282da0a0.html

Researchers at the University of Pennsylvania have demonstrated that Morphine withdrawal complicates hepatitis C by suppressing IFN-alpha-mediated immunity and enhancing virus replication. The paper by Wang et al., "Morphine withdrawal enhances hepatitis C virus (HCV) replicon expression," appears in The American Journal of Pathology.

Hepatitis C virus (HCV) is common among intravenous drug users, with 70 to 80% of abusers infected in the United States. This high association has peaked interest in determining the effects of drug abuse, specifically opiates, on progression of the disease. The discovery of such an association would impact treatment of both HCV infection and drug abuse. Wen-Zhe Ho has been interested in such interplay for some time. His laboratory has previously shown using cell culture that Morphine enhances virus replication and inhibits IFN-alpha, a natural anti-viral factor. To further these results, his lab has used a cell model system to determine the consequences of Morphine withdrawal, which is a common recurring event in opioid users.

Chuan-Qing Wang and colleagues examined the effects of Morphine withdrawal (MW) on HCV-infected cultured liver cells by exposing cells to the drug for four days followed by its removal. They also assessed the effects of using Naloxone, to block the opioid receptors, in conjunction with drug removal, i.e. precipitated Morphine withdrawal (PW). To measure HCV replication, they used a virus-like "replicon" that mimics the events that occur in liver cells and expression of viral RNA and proteins that HCV uses. Although the replicon does not produce the infectious virus, the HCV replicon system represents the best available system for examining the impact of opiates on HCV at the time of their research study.

Similar to their previous results, the authors found that MW and PW increased levels of HCV replicon RNA and protein expression. In addition, both withdrawal scenarios inhibited IFN-alpha expression in liver cells in the presence or absence of HCV replicon. Since IFN-alpha is a critical self-defense mechanism utilized by liver cells to fight off viral infection, including HIV, this study suggests that Morphine withdrawal weakens host cell immunity and provides a favorable environment for HCV growth in the liver.

The authors extended their study by examining the mechanism behind these observations. MW and PW inactivated the IFN-alpha promoter by directly inhibiting its activator, interferon regulatory factor-7 (IRF-7), and this effect was more pronounced in HCV replicon-containing cells. Finally, the ability of IFN-alpha treatment to block HCV replicon expression (85%) fell following MW (60%) and PW (50%). This finding, in conjunction with the earlier report by the same group, provides an explanation to the question of why so many HCV-infected patients fail to respond to IFN-alpha treatment.

Although the clinical relevance of this study remains to be determined, these data showing that withdrawal promotes HCV expression by suppressing anti-HCV factor (IFN-alpha) production by liver cells suggests that “opioid abuse may contribute to the chronicity of HCV infection and promote HCV disease progression.” The study also underscores the necessity of future clinical and epidemiological studies to define the role of opiate abuse in promoting HCV disease.

These results suggest that opioid abusers experiencing periods of drug abuse, followed by periods of withdrawal (due to lack of supplies) may lead to immunocompromised liver. These findings further support the need for methadone maintenance treatment as an additional benefit for opioid abusers.

Punk Rock Unites For Hepatitis C Awareness

<http://www.emediawire.com/releases/2005/10/emw294857.htm>

(PRWEB) October 12, 2005 -- In 2004, a national coalition of musicians was formed by singer Kelly Zirbes to help raise awareness about Hepatitis C. After many years of educating others about Hep C, Kelly and her band, Kelly's Lot, decided to invite other bands to join them in their cause. This coalition of musicians distributes postcards with facts about Hep C at shows and events all over the USA. Danny Commerford and his band Boobie Trap, were one of the first to get involved by organizing a yearly concert, "Punk Rock Unites For Hepatitis C" to raise awareness in Orange County but especially in the Punk Rock Community.

This year, the 2nd annual event will take place at The Brigg located at 17208 PCH in Huntington Beach. The bands playing for the cause this year are The Hudson Drags, The Misfortunes, Shutdown, Boobie Trap and FLOCK OF GOO GOO. The event will start at 7pm on Saturday October 22 and will run until after midnight. Lots of information will be provided at the show for those wanting more info about Hepatitis C. Sponsors include Black Fly's, 714 Clothing, Mo's Fullerton, HoCool.com, Superheroes H.B. and The Brigg. The proceeds from the concert will go to Hepatitis C Awareness, Inc to help fund the postcard campaign.

Genital tract a 'sanctuary site' for hepatitis C virus in coinfecting HIV-positive women

<http://www.aidsmap.com/en/news/1D230787-92CE-4CBA-900D-E9610838268A.asp>

Hepatitis C virus (HCV) appears to be compartmentalised in the genital tract of women coinfecting with HIV, and may replicate independently, according to a study from the United States and Poland published in the November 1st issue of *The Journal of Infectious Diseases*, now available online. The study, which also found that HIV interacts with HCV in the genital tract, may help to explain why mother-to-child transmission of HCV occurs at a comparatively higher rate in coinfecting women than in women who are monoinfected with HCV, and suggests that the risk of female-to-male sexually transmitted HCV infection may be increased in coinfecting women.

Despite growing evidence suggesting that female-to-male and mother-to-child transmission of HCV is on the increase, little is known about vaginal and cervical shedding of HCV in HIV-positive women. Consequently, researchers from the University of California Los Angeles, the Mayo Clinic in Scottsdale, Arizona and the Medical Academy in Warsaw, Poland, sought to examine factors that correlated with HCV genital shedding as well as examine HCV quasispecies composition in a group of HCV/HIV-coinfecting women. They undertook a cross-sectional study of 71 women that was nested within the Women's Interagency HIV Study (WIHS); a prospective, multicentre study that has been examining the impact of HIV infection on women since 1993.

This study included 58 of the 113 HCV/HIV-coinfecting women enrolled at the Los Angeles WIHS site, as well as thirteen of the 23 women monoinfected with HCV. HCV was measured in the genital tract by cervicovaginal lavage

(CVL). This is a method of "washing" the vaginal cavity to test the resulting fluid in order to determine HCV viral load in a woman's genital tract secretions. Most (65.5%) of the coinfecting women were aged 35 or older, 40% were black, 31% Hispanic, and 15% white, and 79% reported a history of injection drug use. Seventy percent had received highly active antiretroviral therapy (HAART) within the previous six months, but the researchers provide no further information on HAART or on the anti-HCV therapy, if any, undertaken by the women.

HCV RNA (viral load, with limit of detection of 600 copies/mL in plasma) was detected in plasma from 67% (39/58) of the coinfecting women, compared with 46% (6/13) of the mono-infected women. The coinfecting women also had higher HCV plasma viral loads than the mono-infected women (data not shown). HCV RNA (viral load, with limit of detection of 60 copies/mL in CVL) was detected in CVL fluid from 31% (18/58) of the coinfecting women, although the researchers note that the viral loads were relatively low (median 1500 copies/mL; range, undetectable to 4000 copies/mL); 16 of the 58 women had CVL HCV viral loads below 800 copies/mL. The only significant difference between the coinfecting women with and without detectable HCV shedding was that the women with HCV shedding had higher plasma HCV viral loads ($p=0.04$). None of the mono-infected women had detectable HCV viral load in CVL ($p=0.03$).

Univariate analysis showed that there was no correlation between HCV viral load in CVL fluid and HIV viral load in plasma, the number of white blood cells in CVL fluid, or anti-HIV therapy. There were, however, possible associations between the presence of HCV viral load in CVL fluid and CD4 cell count, the presence of HCV viral load in plasma, the presence of HIV viral load in CVL fluid, and blood contamination. However, in multivariate analysis that adjusted for plasma HCV viral load, CVL HIV viral load, plasma HIV viral load and CD4 cell count, the only statistically significant predictors of HCV shedding in CVL fluid were the presence of HCV viral load in plasma (OR, 16.81; 95% CI, 1.53-185.31) and the presence of HIV viral load in CVL fluid (OR 19.87; 95% CI, 1.70-231.65).

Nine women (six coinfecting women and three mono-infected women) were randomly selected for intense molecular evaluations in order to assess whether compartmentalisation of HCV led to genetic diversity between blood and genital HCV. HCV viral load was detected by a highly sensitive RT-PCR method in both plasma and CVL fluid from five women (three coinfecting and two mono-infected women). In the three coinfecting women, HCV from CVL contained unique sequences that were not seen in HCV derived from their plasma or PBMCs. This suggests, say the study's authors, "that a local HCV genital tract reservoir may exist and that this may be the source of infection for those suspected to have been infected sexually, a possibility further supported by the analysis of HCV quasispecies isolated from plasma, PBMCs, and CVL fluid."

This is the first study to demonstrate that HCV is compartmentalised in the genital tract of HCV/HIV coinfecting women. In addition, it is also the first to suggest the possibility that HCV replicates in the genital tract independently of plasma. "These findings have important implications for both sexual and perinatal transmission of HCV," comment the study's authors, adding that "increased mother-to-infant and sexual HCV transmission in HCV/HIV-1-coinfecting women makes it especially urgent to study and understand the dynamics of HCV in this subset of patients."

The authors add that "our study also suggests that, among HIV-1-infected women who are HCV viremic, there is an association between shedding of both viruses and that local control of both viruses may be impaired in those found to be shedding. This may explain the increased rate of perinatal HCV transmission to HIV-1-infected newborns and the observation that sexual transmission may be increased in coinfecting patients." Currently it is unclear exactly how HIV and HCV may interact in the genital tract resulting in increased shedding. The authors suggest two plausible explanations: HIV and HCV may be infecting the same cells, resulting in increased HCV turnover; or local immune dysfunction allows both viruses to replicate.

The authors conclude: "we have found that HCV RNA can be detected in almost 30% of HCV/HIV-1-coinfecting women and that viral diversity does exist between local HCV and plasma HCV extracted from HCV/HIV-1-coinfecting women. Our findings may explain a comparatively higher rate of HCV vertical transmission by HIV-1-coinfecting women reported in several studies. The relationship between HIV-1 and HCV shedding is intriguing and suggests a unique local interaction between these two viruses in the genital tract."

Hepatitis-C virus stopped from multiplying

<http://www.sciencedaily.com/upi/index.php?feed=Science&article=UPI-1-20051017-13334300-bc-japan-hepatitisc.xml>

A Japanese research team says it has found a method that prevents the hepatitis-C virus from multiplying.

The method deals with cells infected with the virus, not the virus itself, meaning drugs could be developed to stop the multiplication process while preventing the virus from becoming resistant, the researchers said. It is still unknown how hepatitis-C virus multiplies once inside infected cells. But researchers know once the virus enters the cell, it develops a platform for multiplication by combining itself with a certain lipid, an organic compound.

Masayuki Sudo and colleagues at the Chugai Pharmaceutical Co. in Tokyo used the lipid to pinpoint the platform inside cells where the HCV had combined itself with the lipid. Without the platform, the HCV is unable to duplicate itself, the researchers said. Using human liver cells, the team added a substance to the lipid that prevented it from combining with the HCV. Thus, the platform for multiplication could not synthesize, the researchers said. "If we can target the mechanism of virus-infected cells, it could prompt the development of more effective drugs," Sudo said. The team's report appears on the Web site of the journal Nature Chemical Biology.

Alliance Emerges as Leader in Hepatitis C Prevention and Treatment Policy

<http://www.drugpolicy.org/news/101305hepc.cfm>

Although the words *hepatitis* or *liver* do not appear in the organization's name, the Drug Policy Alliance has emerged as one of the leading hepatitis C virus prevention and treatment advocates in the United States. Syringe sharing is the leading cause of hepatitis C in the U.S. today, and most medical experts agree that access to clean syringes is the best deterrent against spreading debilitating liver diseases such as hepatitis C.

To this end the Drug Policy Alliance has made substantial headway in promoting liver health through litigation and legislative efforts. This summer the Alliance, in conjunction with the ACLU, prepared and filed an amicus brief in the U.S. Court of Appeals for the Second Circuit on behalf of medical and public health experts (*Morgan v. Wright*). They argued that the policy of the New York State Department of Corrections, which delayed or denied hepatitis C treatment to inmates with a history of drug use, flouted both the law and accepted medical practice. The Attorney General of New York, tasked with defending the Corrections Department policy, recently decided to drop the state's appeal and is no longer trying to defend the policy. Meanwhile, at the Drug Policy Alliance's state capitol offices in California and New Jersey, the organization has both crafted and supported legislation designed to combat hepatitis C.

In Sacramento this legislative session, the Drug Policy Alliance actively supported a bill recently signed into law by the governor to require prisons, where a large number of hepatitis C cases originate, to give information and voluntary screening to prisoners upon intake. In Trenton, two syringe access bills have passed the New Jersey Assembly this year, and will likely be considered further this fall.

The Alliance has also worked with and been integral in forming other groups that directly deal with hepatitis C issues. Alberto Mendoza, director of the Alliance's Southern California office, has been the co-chairman of the Los Angeles County Hepatitis C Task Force since last year, and helped make HIV-hepatitis co-infection a central issue for the Southern California HIV Advocacy Coalition, which he co-chaired in 2004.

Reena Szczepanski, who heads the Drug Policy Alliance's New Mexico office, formerly worked for the New Mexico Department of Health, where she founded the nonprofit Hepatitis C Alliance last year. This is the first organized advocacy group for those infected with the disease, and the Alliance New Mexico is now actively working with the group to craft legislation related to hepatitis C prevention and care.

With the Centers for Disease Control and Prevention estimating that 80% of injection drug users across the country are infected, there is a clear need for improved syringe access and hepatitis C treatment on a national scale. The Alliance will continue to advocate for prevention and treatment using its range of strategies, from litigation to coalition-building, to meet this need.

Past Illegal Blood Donation In China Linked To Hepatitis C Virus Infection

<http://www.sciencedaily.com/releases/2005/10/051021021407.htm>

Research in a rural province of central China has documented that illegal blood donation practices led to high hepatitis C virus (HCV) infection rates in blood and plasma donors during the 1980s and early 1990s, and that failure to screen for HCV in transfusion recipients increased their risk of infection as well, according to an article in the November 15 issue of *The Journal of Infectious Diseases*, now available online.

Some blood donation facilities in rural China illegally pooled blood and reinfused compatible red blood cells to permit more frequent donations. Although government action has markedly curtailed such practices since the late

1990s, blood collection and banking methods in such settings still need to be monitored and improved, the article noted.

Researchers from the United States and China, including Han-zhu Qian, MD, PhD, of the University of Alabama at Birmingham, conducted a survey in 2003 among a random sample of 538 adult residents from 12 former commercial plasma-donating villages in Shanxi Province. Structured questionnaires were administered and blood samples tested for HCV antibodies. HCV rates were 8% in all participants, 28% in former plasma/blood donors, and about 3% in non-donors. Selling blood or plasma was the strongest independent predictor for HCV-positive findings. Receiving a blood transfusion was also independently associated with HCV; villagers who received blood transfusion had about 8 times the risk of HCV infection than those who had no history of blood transfusion.

Among the 538 villagers, 22 percent had a history of selling blood or plasma; from village to village, the rates ranged from 9 percent to 49 percent. The most common reasons for the practice were a need for money and being talked into it by other people. Villagers began to sell blood as early as in 1973 and as late as 1998; the main reasons for stopping were improved economic status, concern about health effects of blood drawing, abnormal liver function tests or hepatitis, and shut-down of the illegal blood center.

The investigators concluded that unhygienic plasma donation and receipt of blood transfusion are strong risk factors for HCV infection in rural central China, and that improved blood collection and blood banking practices remain an urgent health priority. "Technical support and drugs are needed to assist these central Chinese provinces cope with the care and treatment needs of HCV patients," the investigators added.

In an accompanying editorial, Roger Y. Dodd, PhD, of the American Red Cross noted that the study is "a snapshot of past events and should not be taken to define the present circumstances." Nevertheless, it illustrates that "short cuts, shoddy practice, pursuit of the bottom line, and lack of oversight can have devastating outcomes, not only for patients but also for donors."

MultiCell and Thomas Jefferson University to study potential Hepatitis C treatment

http://www.masshightech.com/displayarticledetail.asp?Art_ID=70041

MultiCell Technologies Inc. has entered into a research collaboration with Thomas Jefferson University, a medical and health sciences university in Philadelphia, to evaluate the company's immortalized human liver cells as model systems to identify new drugs to treat hepatitis C viral (HCV) infection. No financial details of the collaboration deal were announced.

There are an estimated 170 million people chronically infected with HCV (hepatitis C virus) worldwide who are at high risk for the development of chronic hepatitis, cirrhosis, and liver cancer, according to officials from Lincoln, R.I.-based MultiCell. The lack of cell-based models capable of supporting infection and replication of HCV has hampered the identification of new drugs to treat HCV related diseases. According to MultiCell's chief science officer, Ron Faris, the studies will lead to the development of new high speed drug testing kits to screen for antiviral drugs using the company's proprietary immortalized human liver cells.

Artist Takes on New Role as Hepatitis C Spokesperson

http://www.downtownexpress.com/de_127/artisttakeson.html

Penny Arcade is accustomed to being noticed. The 55-year-old performance artist has been a poster child for the East Village avant-garde art scene since Andy Warhol roamed the city. In recent years she's become a vocal proponent for artists living in this increasingly gentrified neighborhood. So when she was diagnosed with hepatitis C two-and-a-half years ago, it was only natural that she would slip into the role of unofficial spokesperson for sufferers of a disease that often strikes people living on the margins.

Arcade was diagnosed with hepatitis C virus, a blood-borne disease that attacks the liver, in the spring of 2003. Less than a year later, her 57-year-old brother-in-law, Guy Gouin, died of H.C.V. While Gouin lay dying, Arcade scoured literature about the disease they both shared as part of a quest to conquer her own illness.

"When you're confronted with having an illness, you enter into a maze and it's up to you to make a decision," she told The Villager in a telephone interview. "We have to take responsibility for our own treatment. I had to really become an expert on hepatitis C to find out what was the most appropriate thing for me."

A chronic disease, H.C.V. has wildly different effects on different people. According to the New York City Department of Health, 10 percent of people clear the virus from their system after contracting it, but 80 to 90

percent become chronic carriers. Anywhere between 5 and 20 percent of carriers will develop cirrhosis of the liver. Of those with cirrhosis, between 1 and 3 percent will develop liver cancer.

A small virus that lives in blood, H.C.V. is quite easy to contract and far more prevalent than H.I.V., the virus that causes AIDS, although H.C.V. rates are much higher among H.I.V. patients than the general population. In New York City alone, between 200,000 and 300,000 people are infected with H.C.V., compared with about 90,000 New Yorkers infected with H.I.V. in 2003, according to the Health Department.

People who have injected drugs and those who had blood transfusions before 1992, when blood-screening tests improved, are most at risk. Although anyone in contact with infected blood, including healthcare workers and infants born to infected mothers, is at risk.

Since most people don't develop symptoms or serious liver damage for decades — and some never do at all — few know they carry a contagious disease that might ravage their liver. "Even though it's set to be a pandemic in this country, very few people know about it," said Arcade.

In August, from the stage at Joe's Pub on Lafayette St. where she performed "The Essential Penny Arcade" as part of the East Village HOWL! Festival, Arcade told her audience she had H.C.V. "I want to make people aware," she told *The Villager*. "There's a lot of stigma to illness in this country... I spent a lot of time with people with AIDS and I know how people treat people with contagious diseases."

Ironically, Allen Ginsberg, author of the poem "Howl" for which the festival was founded, died of complications from H.C.V. He is not the only 60s icon struck by the disease. Phil Lesh of the Grateful Dead, who received a liver transplant several years ago, as did David Crosby of Crosby Stills and Nash, both suffer from H.C.V. Ken Kesey, author of "One Flew Over the Cuckoo's Nest" and famous for his drug experimentation with the Merry Pranksters, died of liver cancer in 2001 and suffered from H.C.V.

Arcade is not entirely sure how she contracted the illness. During her youth in the East Village she was part of Andy Warhol's Factory scene, appearing in the 1971 film "Andy Warhol's Women in Revolt. She also participated in the "the Lower East Side drug culture of the late '60s" when she was 17, she said. But she also wonders if she might have contracted it during the four years she lived in Spain in the 1970s or while traveling in Thailand, India and Indonesia in the 1990s. She believes her brother-in-law contracted H.C.V. while serving in Vietnam. A 2002 survey of 597 homeless veterans found that 42 percent were infected with the virus, according to the Health Department.

Stigma might be part of the reason why H.C.V. is so rarely discussed in the public arena. "Once there's a certain level of stigma, it becomes harder to give people accurate information about a disease and that can be really problematic," said Tracy Swan, co-infection project director for H.I.V. and H.C.V. at the Treatment Action Group, an AIDS advocacy group at Houston St. and Broadway. "There's something about human nature where people really wonder: how'd you get that?" Miles Keaton Andrew, a 52-year-old author who contracted H.C.V. when he experimented with intravenous drugs as a teenager, has kept a blog, www.mkandrew.com, since 2001 about his experiences battling H.C.V. His blog has received a million hits in the past year. "I understand the whole stigma thing," he told *The Villager*. "There are a lot of people like me who might have experimented with drugs. Some of us got sick from it and it isn't anything to be ashamed about."

This week, Arcade began a 24-week-long treatment program in the hopes of curing herself. Already, she is sharing her experience with the East Village and Lower East Side community. In an Oct. 2 e-mail to the Federation of East Village Artists listserv, an organization founded to support the arts community here, Arcade penned, "I start [treatment] tomorrow and I have no idea how I will feel, as each person is different. Although my understanding is that you feel worse when the drugs build up in your system." A few days later, she wrote the group, "Tonight's [FEVA] meeting is supposed to be about health insurance. I am not attending as I have started serious medicine for hepatitis C and do not feel well enough to go out."

She plans to keep a diary of her treatment, which causes extreme flulike symptoms that Arcade compared to chemotherapy. "I want to write about it," she told *The Villager*. Arcade suffers from a strain of H.C.V. that is less common in the United States and more easily treatable, she said. People with her strain have an 88 percent cure rate after treatment, she said. The typical treatment for most American strains ranges from a three-month to a two-year drug therapy program. Treatment does not eradicate the virus in all cases. Some people, however, do not need drug therapy at all.

“Before you go on Interferon” — a drug commonly used to treat H.C.V. — “you try to imagine the sickest you’ve ever been and you figure you’ll be that sick, but the truth is you can’t imagine how sick you’ll be,” said Andrew. “For a year it completely consumes your life.” Arcade lived in the East Village during the AIDS crisis — she moved there when she was 17 — and remembers a time when there was little information about the disease that ravaged her community. “A lot of us thought we were going to get it [AIDS] and we didn’t get it,” she said. “Ten years later to find out that you have a potentially fatal disease is a huge shock.”

Arcade’s self-anointed role as East Village H.C.V. spokesperson coincides with the July launch of an H.C.V. ad campaign by Hoffman La Roche, a pharmaceutical company. The campaign — plastered throughout the city’s subways, in magazines and newspapers — depicts a man’s face, severely beaten and bruised. The text reads: “If Hep. C was attacking your face instead of your liver, you’d do something about it. Ready to fight back?”

The startling image of a brutalized face has not received a warm welcome from the H.C.V. healthcare community. “It’s rude and cruel and horrible and stupid,” said Dr. David Ores, a general practitioner on Clinton St. Several of his patients suffer from H.C.V. “What if you don’t have insurance? What if you have no access to care? You can’t even get tested. Whoever put up those posters, are they offering free healthcare?” “It’s extremely alarming, from a purely feminist perspective; could you imagine that ad with a woman who’d been beaten black and blue?” said Swan, adding that not all H.C.V. patients need treatment or develop serious liver damage. “If you had hep C and you saw that, wouldn’t you think ‘Oh my God?’ ”

The ad was intended to alarm, said Bob Madison, a spokesperson for Hoffman La Roche. “We really wanted to break through the clutter and do something to separate us from the noise; that’s why it’s such a distinctive campaign,” he said, adding that some response has been negative. “This is a very dramatic call to action.” Arcade has a publicity campaign of her own in the works. She is currently working with the Lower East Side Biography Project, a media-training program, on a series of public service announcements she hopes will run on cable TV in the spring.

For those working in the health industry, Arcade’s decision to go public comes as a welcome voice in a silent arena. There is currently no federal funding for H.C.V. “It’s extremely useful and it’s great that she’s doing this,” said Swan. “Like with the H.I.V. activist model, it’s important to have people in the community sharing information about their experience.”

Hepatitis C Found More Frequently in Semen of Men Coinfected with HIV/HCV

<http://www.aidsmap.com/en/news/66CC79E7-7D38-4DE3-B27F-05FB368E5690.asp>

Hepatitis C virus is found significantly more frequently in the semen of men who are coinfecting with HIV than in the semen of men who are only infected with hepatitis C (HCV), according to research published in the November 4th edition of AIDS. Sexual transmission of hepatitis C virus has recently been observed in HIV-positive gay men and the investigators write, “our results partly illustrate how the recent increase in sexually transmitted hepatitis C virus in homosexual men could arise.” The investigators also found that hepatitis C virus in semen originated in the blood with no evidence of hepatitis C replication in the genitals.

Sexual transmission of hepatitis C is a controversial subject. There is little evidence of transmission of the virus between heterosexual couples and large studies involving HIV-negative gay men have failed to find any evidence of sexual transmission of hepatitis C. In recent years there have been a number of studies reporting sexual transmission of hepatitis C amongst HIV-positive gay men, with evidence from the UK, Switzerland and France suggesting that unprotected anal sex, concurrent sexually transmitted infections, and “hard” sex which may involve trauma are risk factors.

To further understand the sexual transmission of hepatitis C, French investigators compared the prevalence of hepatitis C virus in the semen of men who were coinfecting with HIV and hepatitis C virus and men who were infected only with hepatitis C. They also wished to see if hepatitis C was reproducing in the genital tract of men.

A total of 120 men with hepatitis C were included in the investigators’ analysis. In addition to being infected with hepatitis C, 82 of the men were also HIV-positive. Paired blood and semen samples were obtained from each of the men. Repeat semen samples were obtained from 45 men (35 of whom were coinfecting). The blood and semen samples were tested for hepatitis C viral load.

None of the men were receiving anti-hepatitis C treatment. The HIV-positive individuals had a median CD4 cell count of 524 cells and a median viral load of below 50 copies/ml. All but seven HIV-positive patients were taking

antiretroviral therapy. A total of 191 semen samples were tested for hepatitis C and overall 27% were positive. In all, 32% of men provided at least one semen sample which was positive for hepatitis C.

Hepatitis C was detected with significantly greater frequency in the semen of HIV-positive men (38%) than HIV-negative men (18%, $p = 0.033$). Amongst the HIV-positive men, neither CD4 cell count nor viral load were significantly associated with having detectable hepatitis C in semen. Blood samples tested positive for hepatitis C in all 120 men. The investigators found that men who had detectable hepatitis C in their semen had hepatitis C viral loads in their blood. This difference was statistically significant for coinfecting men (median 6.22 \log_{10} IU/ml versus 5.95 \log_{10} IU/ml, $p = 0.038$).

Samples of blood and semen were further studied in two men (one HIV-positive and one HIV-negative) to see if there was any evidence of hepatitis C reproduction in the genitals. No evidence was found of hepatitis C replication in the genitals with hepatitis C in semen being genetically similar to hepatitis C in the blood. "In this study, hepatitis C virus RNA was more frequently found in the semen of HIV/hepatitis C virus coinfecting men than in the semen of non-coinfecting men", write the investigators. They note that even in men who had hepatitis C in their semen, detection of the virus was intermittent and "close to the detection threshold."

The investigators also observe that hepatitis C viral load was higher in the blood of coinfecting men than in HIV-negative men ($p = 0.017$) and they believe that "this may partly explain why the coinfecting men had a higher prevalence of hepatitis C in their semen." Rather than reproducing in the genitals, the investigators believe that hepatitis C was "transferring" between blood and semen.

Liver transplantation due to Hepatitis C: alpha-SMA, a biomarker, predicts recurrence of disease

http://www.xagen.it/news/medicineneu_net_news/8caa4453ee0a54b9cc35641a1044b3ca.html

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

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

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

In another study, led by Mark W. Russo of the University of North Carolina in Chapel Hill, 46 patients who underwent HCV-related liver transplants at the University of Florida between 1997 and 2001 were included. Patients were divided into two groups: those who developed advanced fibrosis within 2 years of liver transplant and those who developed mild or no fibrosis in the same period. Biopsies from 4 months, 1 year and 2 years post-transplant were scored for alpha-SMA. The results showed that HSC activation was significantly higher in the 4 month biopsies for those who developed advanced fibrosis within 2 years.

The authors note that alpha-SMA "is an attractive biomarker because it is determined from the organ of interest and there is biological plausibility for why increased stellate cell activity would lead to advanced fibrosis." In an accompanying editorial by A.J Demetris and J.G. Lunz III of the Thomas E. Starzl Transplantation Institute at the

University of Pittsburgh Medical Center in Pittsburgh, the authors note that the ability of alpha-SMA to predict disease at 4 months after transplant suggests that something triggers a chain of events that begins with mesenchymal and/or HSC activation and leads to the development of fibrosis. They speculate as to what the trigger might be and how it might explain the mechanism of liver disease, examining risk factors for recurrent HCV that might offer clues, as well as substances such as viral proteins and proteins secreted by liver cells.

In particular, they cite their research on p21, a protein made in the liver, which showed that progression of fibrosis was related to the effect of p21 on liver cell proliferation. "This model better fits observations about disease pathogenesis," they conclude. "It explains why any hepatocyte stressors, such as steatosis, iron, inflammation, HCV replication or spontaneously increased 21 expression, such as occurs with aging, can accelerate liver disease progression."

Survey indicates lack of public awareness Hepatitis C

<http://www.clickpress.com/releases/Detailed/4555005cp.shtml>

The survey, conducted by SYNOVATE research, studied the behavior of a varied group of UAE nationals and citizens. A well balanced mix of 330 Emiratis, Arab and Asian ex-pats coming from Abu Dhabi, Dubai and Al Ain were involved. The conclusions of the survey highlight the lack of awareness on how Hepatitis C is transmitted, the consequences of the disease and possible treatment of it.

The survey revealed that only 13% of the people surveyed had been tested for Hepatitis C. UAE nationals turned out having the lowest rates, only 10% of them ever had themselves tested for the disease. Comparatively, Asians scored 17% here. In addition, only 37% of the total people surveyed believed that Hepatitis C is a serious disease.

"The results of the survey are alarming, but not unexpected as we know that there has not been a lot of awareness creation done on the Hepatitis C disease. Public awareness and knowledge are the first steps to ensuring that people are protected against the disease. Visiting your doctor on a regular basis and being tested for the disease is an important way to protect yourself. Getting tested can be done with a very simple blood test." said Rima Khadra, communications manager at Roche. The survey also indicates the lack of information available to people about the causes and effects of the disease and the available treatment.

Only 24% of the people questioned had earlier learned about the disease, through their doctor. However, only 10% of them visited their doctor on a regular basis. The survey revealed that most people heard of the disease via word of mouth. 55% claimed word of mouth as the most common source of information. "This makes it even more important to spread awareness on Hepatitis C and provide the public with the correct information regarding, the transmission, effects and available treatment for the disease." added Rima.

The survey revealed that there are a lot of misconceptions around the modes of transmission of hepatitis C. Unlike most other serious and highly infectious diseases, people are not sure how Hepatitis C is contracted. Although people understood that the disease can be passed via blood, a very low percentage knew that contaminated personal items, like scissors or tweezers, can also cause infection.

"Protecting your self from Hepatitis C is extremely important. However people can only do this when they are correctly informed on how they can be infected. Unfortunately this lack of knowledge also transcends to people who maybe have the disease but are unaware of the available treatment. Most importantly, although treatment is available for people infected with Hepatitis C, a third of the number of people interviewed, were not aware that the virus is curable." said Rima.

"I did not know I had the disease, up till the moment I went to the doctor for a regular check up. The blood tests revealed that I had been contaminated with Hepatitis C. When I heard this I was shocked and felt shamed. I have always considered myself to be a very neat and clean person. My doctor explained to me however, that I might have caught it unknowingly. I felt relieved when he told me that there are good treatments available for the disease now a days" Myrvat a Hepatitis C patient states.

CLINICAL TRIALS, COHORT STUDIES, AND PILOT STUDIES

Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, Alter MJ. J Infect Dis. 2005 Dec 1;192(11):1880-9. Epub 2005 Oct 28.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16267758&query_hl=2

Background. The goal of the present study was to assess risk factors for perinatal hepatitis C virus (HCV) transmission and the natural history of infection among HCV-infected infants. **Methods.** In a cohort study, 244 infants born to HCV-positive mothers were followed from birth until age ≥ 12 months. Maternal serum was collected at enrollment and delivery; infant serum was collected at birth and at 8 well-child visits. Testing included detection of antibody to HCV, detection of HCV RNA (qualitative and quantitative), and genotyping. HCV-infected infants were followed annually until age 5 years. **Results.** Overall, 9 of 190 (4.7% [95% confidence interval {CI}, 2.3%-9.1%]) infants born to mothers who were HCV RNA positive at delivery became infected, compared with 0 of 54 infants born to HCV RNA-negative mothers ($P=.10$). Among HCV RNA-positive mothers, the rate of transmission was 3.8% (95% CI, 1.7%-8.1%) from the 182 who were human immunodeficiency virus (HIV) negative, compared with 25.0% (95% CI, 4.5%-64.4%) from the 8 who were HIV positive ($P<.05$). Three infected infants resolved their infection (i.e., became HCV RNA negative). In multivariate analysis restricted to HCV RNA-positive mothers, membrane rupture ≥ 6 h (odds ratio [OR], 9.3 [95% CI, 1.5-179.7]) and internal fetal monitoring (OR, 6.7 [95% CI, 1.1-35.9]) were associated with transmission of HCV to infants. **Conclusion.** If duration of membrane rupture and internal fetal monitoring are confirmed to be associated with transmission, interventions may be possible to decrease the risk of transmission.

A Significant Sex--but Not Elective Cesarean Section--Effect on Mother-to-Child Transmission of Hepatitis C Virus Infection. European Paediatric Hepatitis C Virus Network. *J Infect Dis.* 2005 Dec 1;192(11):1872-1879. Epub 2005 Oct 28.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16267757&query_hl=2

Background. Risk factors for mother-to-child transmission of hepatitis C virus (HCV) are poorly quantified. **Methods.** We conducted a European multicenter prospective study of HCV-infected pregnant women and their infants. Children with ≥ 2 positive HCV RNA polymerase chain reaction test results and/or anti-HCV antibodies after 18 months of age were considered to be infected. **Results.** The overall HCV vertical transmission rate was 6.2% (95% confidence interval [CI], 5.0%-7.5%; 91/1479). Girls were twice as likely to be infected as boys (adjusted odds ratio [OR], 2.07 [95% CI, 1.23-3.48]; $P=.006$). There was no protective effect of elective cesarean section (CS) delivery on HCV vertical transmission (adjusted OR, 1.46 [95% CI, 0.86-2.48]; $P=.16$). HCV/human immunodeficiency virus-coinfected women more frequently transmitted HCV than did women with HCV infection only, although the difference was not statistically significant (adjusted OR, 1.82 [95% CI, 0.94-3.52]; $P=.08$). Maternal history of injection drug use, prematurity, and breast-feeding were not significantly associated with transmission. Transmission occurred more frequently from viremic women, but it also occurred from a few nonviremic women. **Conclusions.** Our results strongly suggest that women should neither be offered an elective CS nor be discouraged from breast-feeding on the basis of HCV infection alone. The sex association is an intriguing finding that probably reflects biological differences in susceptibility or response to infection.

Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. Reichenberg A, Gorman JM, Dieterich DT. *AIDS.* 2005 Oct;19 Suppl 3:S174-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16251815&query_hl=2

OBJECTIVES: This study assessed the rates and course of depressive symptomatology and neurocognitive deficits in hepatitis C virus (HCV) patients undergoing interferon treatment, and explored possible predictors of depression and neurocognitive deficits. **DESIGN:** In order to obtain objective assessments of depression, and to evaluate cognitive impairment, a 72-week prospective study, comprising 48 weeks of treatment and 24 weeks of post-treatment follow-up was utilized. **METHODS:** A total of 50 HCV patients were assessed at baseline, and 14 times during pegylated interferon plus ribavirin treatment. Patients were also assessed on four timepoints after the termination of treatment. All patients have previously been treated for hepatitis C infection with interferon and were judged to be treatment resistant in these treatments. Depression was assessed using the Center for Epidemiological Studies Depression (CES-D) questionnaire, and patients were interviewed regarding problems with memory, attention and concentration. **RESULTS:** Eighty-two per cent of interferon-treated patients developed severe enough depressive symptoms to meet the CES-D criteria for possible major depressive disorder (MDD). Possible MDD onset was most frequent by the first week of treatment, and almost all possible MDD cases were observed by week 8. More severe depressive symptoms at baseline were associated with higher depressive symptoms during

interferon treatment. Thirty per cent of patients complained about cognitive problems. In half of these patients cognitive impairments were still reported after the termination of treatment. There was no association between depression during interferon treatment and subjective cognitive complaints. **CONCLUSIONS:** The findings suggest that depression and cognitive impairments are frequent and persistent side-effects of interferon treatment in treatment-resistant patients.

Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial.

Fontana RJ, et al. J Hepatol. 2005 Oct;43(4):614-22.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16237784&query_hl=2

BACKGROUND/AIMS: Prior studies have demonstrated neuropsychological abnormalities in chronic hepatitis C (CHC) patients even with mild fibrosis. The aim of this study was to determine the frequency, type, and severity of cognitive impairment in a large group of CHC patients with advanced fibrosis. **METHODS:** Ten validated neuropsychological tests were administered to 201 CHC patients. Standard scores for individual tests were calculated using normative population data that controlled for age, gender, and/or education. Lifetime psychiatric history, alcohol consumption, and mood status were also determined. **RESULTS:** 33% of patients met criteria for cognitive impairment (i.e. standard score <40 on at least 4 tests). Mild impairment in verbal recall and working memory were noted with other domains remaining intact. Liver disease severity and lifetime psychiatric/substance abuse history did not correlate with group mean cognitive test results or the presence of cognitive impairment. In contrast, IQ and depression scores were significant and independent predictors of cognitive impairment (ROC = 0.84). **CONCLUSIONS:** 33% of patients entering the HALT-C trial have evidence of a mild, non-focal subcortical processing deficit which was highly correlated with IQ, education, and occupation. Future studies of cognitive function in CHC patients should control for general cognitive ability.

Ribavirin monotherapy for chronic hepatitis C. Brok J, Gluud L, Gluud C. Cochrane Database Syst Rev. 2005 Oct 19;4:CD005527.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16235408&query_hl=2

BACKGROUND: Hepatitis C is a major cause of liver-related morbidity and mortality. The disease progresses without symptoms for several decades. Ribavirin monotherapy may represent a treatment for some patients. **OBJECTIVES:** To assess the beneficial and harmful effect of ribavirin monotherapy for patients with chronic hepatitis C. **SEARCH STRATEGY:** We identified trials through electronic databases, manual searches of bibliographies and journals, authors of trials, and pharmaceutical companies until May 2005. **SELECTION CRITERIA:** We included all randomised trials irrespective of blinding, language, or publication status comparing ribavirin versus no intervention, placebo, or interferon for chronic hepatitis C. **DATA COLLECTION AND ANALYSIS:** The primary outcome measures were the six months sustained loss of hepatitis C virus RNA in blood after end of treatment and liver-related morbidity plus all-cause mortality. Secondary outcome measures were end of treatment virological response, biochemical response, histological response, and adverse events. Random- and fixed-effects meta-analyses with 95% confidence intervals (CI) were performed for all outcomes. We used Peto odds ratios (OR) for analysis of morbidity plus mortality and relative risks (RR) for the remaining outcomes. **MAIN RESULTS:** We identified 13 randomised trials including 594 patients with chronic hepatitis C. Most trials had low methodological quality. Compared with placebo/no intervention, ribavirin had no significant effect on sustained (RR 1.01, 95% CI 0.96 to 1.07, five trials) or end of treatment virological response (RR 1.00, 95% CI 0.94 to 1.07, ten trials). Ribavirin had no significant effect on liver-related morbidity plus mortality (Peto OR 1.96, 95% CI 0.20 to 19.0, eleven trials). Ribavirin significantly improved end of treatment biochemical and histological response but not sustained biochemical response. Further, ribavirin significantly increased the risk of anaemia. Ribavirin was significantly inferior to interferon regarding virological and biochemical response (four trials). **AUTHORS' CONCLUSIONS:** We found that ribavirin versus placebo/no intervention had no significant beneficial effect on virological response and liver morbidity, but may improve biochemical and histological response transiently. Ribavirin increased the risk of anaemia. Therefore, we cannot recommend ribavirin monotherapy for patients with chronic hepatitis C outside randomised trials.

FAS promoter polymorphisms correlate with activity grade in hepatitis C patients. McIlroy D, et al.

Eur J Gastroenterol Hepatol. 2005 Oct;17(10):1081-8

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16148554

[query_hl=3](#)

OBJECTIVE: Hepatocytes are susceptible to FAS-mediated apoptosis. The impact of polymorphisms in the FAS gene on histopathological features of HCV infection was therefore investigated. **DESIGN/METHODS:** Three single-nucleotide polymorphisms in the FAS promoter were assessed in 190 patients with chronic hepatitis C. Associations between FAS haplotypes and fibrosis stage and activity grade were tested by univariate and multivariate analyses. **RESULTS:** While there was no correlation between FAS promoter genotype and fibrosis stage, patients carrying the GCA haplotype ($P=0.03$, Fisher's exact test) and those homozygous for the GTG haplotype ($P = 0.06$) tended to have lower activity scores. Logistic regression showed that these associations were independent of patient age, sex and alcohol consumption. In a logistic regression model incorporating only male gender (odds ratio 2.1, 95% confidence interval 1.1-4.1 $P = 0.04$), the presence of the GCA haplotype (OR 0.31 95% CI 0.13-0.78 $P = 0.01$), and GTG homozygosity (OR 0.26 95% CI 0.08-0.83 $P = 0.02$), all three factors were independently correlated with activity grade. Furthermore, the GTG haplotype appeared to have lower promoter activity than the wild type GTA haplotype in a hepatocellular carcinoma cell line. **CONCLUSIONS:** Genetic polymorphism in the FAS gene may account for some of the histopathological variability in chronic hepatitis C.

The spectrum of thyroid dysfunction in an Australian hepatitis C population treated with combination Interferon-alpha2beta and Ribavirin. Tran HA, Jones TL, Batey RG. BMC Endocr Disord. 2005 Oct 12;5:8. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16219106&query_hl=3

BACKGROUND: The study aims to assess the pattern of thyroid response to combination Interferon-alpha2beta (IFN-alpha) and Ribavirin (RBV) anti-viral therapy in an Australian hepatitis C cohort. These include the prevalence of thyroid dysfunction (TD) including hyperthyroidism and hypothyroidism and their possible predictors, the common overall pattern of thyroid function tests whilst receiving therapy and TD outcomes, and the correlation with HCV status outcome. **METHODS:** A retrospective analysis of all medical records was performed to assess thyroid function in Hepatitis C Virus (HCV) patients who were treated at the Hunter Area hepatitis C treatment center between 1995 and March 2004. The centre is part of the John Hunter hospital, a major tertiary referral centre in New South Wales, Australia. **RESULTS:** There were 272 cases available for review. The prevalence of TD is 6.7 percent and is made up predominantly of females (80 percent). There were 3 (1.1 percent) cases of hyperthyroidism with 2 (67 percent) females. Thirteen out of fifteen (80 percent) cases of hypothyroidism were females with the overall prevalence of 5.5 percent. The majority of hypothyroid patients still required Thyroxine supplement at the end of follow up. **CONCLUSION:** Ninety three percent of HCV treated patients have intact thyroid function at the end of treatment. The predominant TD is hypothyroidism. The predominant pattern of thyrotoxicosis (TTX) is that of thyroiditis although the number is small. Graves' like disease was not observed. People with pre-existing thyroid auto-antibodies should be closely monitored for thyroid dysfunction, particularly hypothyroidism.

Correlates of spontaneous clearance of hepatitis C virus among people with hemophilia. Zhang M, et al. Blood. 2005 Oct 4; [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16204310&query_hl=3

People with hemophilia were formerly at very high risk of infection with hepatitis C virus (HCV). Approximately 20% of HCV-infected patients spontaneously clear the virus. To identify correlates of spontaneous clearance of HCV, we studied a cohort of HCV-infected hemophilic subjects without human immunodeficiency virus infection who had never been treated with interferon. Plasma HCV RNA was persistently undetectable in 192 (27.0%) of 712 HCV-seropositive subjects. In multivariate analyses, HCV clearance was more likely in subjects infected with HCV at younger age, especially with infection before age 2 (40.1%) compared to after age 15 years (14.9%, $P_{trend} < 0.0001$), and with relatively recent infection, especially after 1983 (42.8%) compared to before 1969 (18.2%, $P_{trend} < 0.0001$). HCV clearance was marginally reduced with African ancestry (19%) and greatly increased with chronic hepatitis B virus (HBV) infection (59.1%, $P=0.0006$). Resolved HBV infection, coagulopathy types and severity, types of clotting factor treatment, and gender were not associated with HCV clearance. **In conclusion,** hemophilic subjects co-infected with chronic HBV and those infected with HCV before age 2 or after 1983 were significantly more likely to spontaneously clear HCV viremia. These data highlight and clarify the importance of non-genetic determinants in spontaneous recovery from HCV infection.

The impact of past alcohol use on treatment response rates in patients with chronic hepatitis C.

Chang A, Aliment Pharmacol Ther. 2005 Oct 15;22(8):701-6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16197490&query_hl=3

BACKGROUND: Studies have shown that past alcohol consumption reduces response rates in patients with chronic hepatitis C treated with interferon monotherapy. **AIM:** To clarify the importance of alcohol consumption on response rates in patients undergoing treatment with pegylated interferon and ribavirin. **METHODS:** In a single centre, prospective study, median daily alcohol consumption (determined by previously validated method) and quartiles of alcohol consumption were calculated. Univariate and binary logistic regression analyses were performed using treatment response status as the dependent variable. **RESULTS:** Overall, in an intention-to-treat analysis, 34 of 115 patients (30%) responded to treatment. In univariate analysis, black patients, especially those with hepatitis C virus genotype 1, high viral load and low alanine aminotransferase were significantly less likely to respond. Predictors of response by regression analysis included alcohol <30 g/day (OR=3.02, 95% CI: 1.02-8.93; P=0.04), non-genotype 1 status (OR=1.98, 95% CI: 1.03-3.80; P=0.04) and non-black race (OR=2.79, 95% CI: 1.33-5.85; P=0.006). **CONCLUSIONS:** Median daily alcohol use >30 g/day is associated with failure to respond to pegylated interferon and ribavirin for treatment of hepatitis C. Past alcohol use should be evaluated when considering treatment for hepatitis C.

Chronic hepatitis C in Latinos: natural history, treatment eligibility, acceptance, and outcomes.

Cheung RC, et al. Am J Gastroenterol. 2005 Oct;100(10):2186-93..

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16181367&query_hl=3

OBJECTIVES: The natural history of chronic hepatitis C and treatment response are different between blacks and Caucasians, but little comparable data is available about Latinos. **METHODS:** A cross-sectional secondary analysis to investigate differences between 421 anti-HCV-positive, treatment-naïve, HCV-viremic Latinos and 2,510 Caucasians in 24 VA medical centers enrolled in a prospective study. **RESULTS:** Latinos were infected at a younger age and were less likely to have blood contact during combat, surgery, and needle stick injury, but were more frequently HIV coinfecting (20.4%vs 3.9%, $p < 0.0001$) and prior HAV infection (39.9%vs 26.4%, $p = 0.0001$). Latinos were more likely to be treatment candidates, but less likely to actually initiate treatment. Liver histology (123 Latinos, 743 Caucasians) showed no difference in fibrosis or fibrosis rate, but steatosis (54.7%vs 43.2%, $p = 0.038$) was more common in Latinos. Eighty-eight Latinos and 481 Caucasians were subsequently treated with interferon-ribavirin: body mass index (BMI), duration of infection, baseline tests, liver histology and genotype distribution were similar. Compared with Caucasians, Latinos discontinued treatment prematurely more often (39.8%vs 28.9%, $p = 0.043$) and tended to have lower sustained virological response (SVR) rates (14.8%vs 22.5%, $p = 0.10$). Multivariate analysis found Latino race and history of recent alcohol use to be associated with early treatment discontinuation, whereas genotype and viral load but not ethnicity to be associated with SVR. **CONCLUSIONS:** Latinos were infected younger, more frequently HIV coinfecting, more likely to meet criteria for antiviral therapy yet less likely to initiate treatment and had a trend toward lower SVR rates than Caucasians, but not in severity of liver disease. Latino ethnicity was associated with early discontinuation but not as an independent predictor of SVR.

Risk factors for hepatitis C on the Texas-Mexico border. Hand WL, Vasquez Y. Am J Gastroenterol. 2005 Oct;100(10):2180-5.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16181366&query_hl=3

OBJECTIVES: Our clinical experience suggested that hepatitis C virus (HCV) infection in this Texas-Mexico border area might have features, especially risk factors, that differ from some other areas of the United States. Therefore, we conducted a prospective analysis to investigate the epidemiology, risk factors, and certain other characteristics of HCV infection in the El Paso region. **METHODS:** During a 2-yr period, individuals with a positive HCV serology were considered as "patients" and those with a negative hepatitis serology panel were "controls." A questionnaire survey was conducted in person or by telephone with individuals (patients and controls) who agreed to participate in the interview process. **RESULTS:** We identified and interviewed 320 patients and 307 controls. All of the contacted patients and controls agreed to be interviewed. Many established and potential risk factors for HCV transmission were documented in the patients. Furthermore, multiple potential risk factors were often present in individual patients. However, on multivariate analysis only injection drug use, blood transfusion,

and tattooing were found to be significant independent risk factors for HCV infection. In the great majority of patients, tattoos were applied by friends (including gang members), inmates in jail/prison, or self, rather than commercial parlors. **CONCLUSIONS:** Tattooing is an independent risk factor for HCV infection in this United States-Mexico border area. The role of nonsterile tattooing practices in HCV transmission merits additional examination in regard to precise risk settings, frequency, and mechanisms of infection.

Antiviral therapy after non-surgical tumor ablation in patients with hepatocellular carcinoma associated with hepatitis C virus. Hung CH, et al. J Gastroenterol Hepatol. 2005 Oct;20(10):1553-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16174073&query_hl=3

BACKGROUND: Antiviral therapy for chronic hepatitis C virus (HCV) infection has led to a reduction in the incidence of hepatocellular carcinoma (HCC). The purpose of the present paper was to assess whether antiviral therapy might suppress tumor recurrence and influence overall survival in patients with HCV-related HCC who had complete ablation of nodules by non-surgical treatments. **METHODS:** Twenty patients with three or fewer nodules of HCV-related HCC who were treated with percutaneous tumor ablation and/or transcatheter arterial embolization received combined interferon (IFN; 3 or 5 million units of IFN alpha-2b thrice weekly) plus ribavirin (1000-1200 mg per day) therapy for 24-48 weeks after complete ablation of lesions. During the same period, an additional 40 age- and sex-matched control patients with similar characteristics of tumors (sizes, numbers and treatment modalities) and severity of liver disease were recruited from the HCC database. Both recurrence-free survival and actuarial survival were evaluated. **RESULTS:** Of the 20 patients, 16 completed therapy and 10 showed a sustained response with normalization of alanine aminotransferase and negative HCV-RNA at 6 months after therapy completion. Due to severe side-effects experienced by Child B patients, who mostly discontinued antiviral therapy, clinical outcome was analyzed in the Child A treated (n = 16) and control (n = 33) patients. There was no significant difference in the incidence of local recurrence in sustained responders compared with non-responders or control patients (P = 0.174, 0.1284, respectively); but the second recurrence-free interval in the sustained responders was significantly longer than that of non-responders and the control group (P = 0.0141, 0.0243, respectively). Survival in sustained responders was better than in non-responders and control patients (P = 0.0691, 0.0554, respectively). **CONCLUSIONS:** These results indicate that successful antiviral therapy after non-surgical tumor ablation for HCV-related HCC may lower tumor recurrence rate and prolong survival.

Alcohol has no effect on hepatitis C virus replication: a meta-analysis. Anand BS, Thornby J. Gut. 2005 Oct;54(10):1468-72.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16162952&query_hl=3

BACKGROUND: Patients with chronic hepatitis C virus (HCV) infection who consume large quantities of alcohol have more severe liver disease compared with HCV patients without a history of alcohol consumption. The mechanism by which alcohol worsens HCV related liver disease is not properly understood. One possibility is that alcohol stimulates HCV replication, and the present meta-analysis was performed to examine this issue.

METHODS: The effect of alcohol on viral titres was assessed in three ways: comparison of the heaviest drinkers with non-drinkers; effect of graded doses of alcohol; and effect of abstinence in the same individual. **RESULTS:** A total of 14 studies were identified. Comparison of patients with the highest alcohol use with the abstinent group showed a significant association with viral load in three studies, five studies had a positive direction, while the remaining four studies found a negative relationship. Analysis of the combined results showed no association between alcohol consumption and virus levels (p = 0.29). Assessment of graded doses of alcohol also showed no significant difference between non-drinkers and moderate drinkers (p = 0.50), between non-drinkers and heavy drinkers (p = 0.35), or between moderate drinkers and heavy drinkers (p = 0.32). Five studies examined the influence of abstinence on viral titres but none provided sufficient data for statistical analysis. **CONCLUSIONS:** The present study has failed to show an association between alcohol use and HCV viral titres. These observations raise the possibility that the hepatic damage caused by alcohol and HCV may be purely additive, involving different mechanisms and pathways.

Mutagenic effects of ribavirin and response to interferon/ribavirin combination therapy in chronic hepatitis C. Asahina Y, 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=4

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 log₁₀copy/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 2.9 x 10⁽⁻²⁾/site/year and 1.3 x 10⁽⁻²⁾/site/year, respectively, a significantly higher rate than the mutation rates during the prior non-treatment observation period (0.60 x 10⁽⁻²⁾/site/year and 0.24 x 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 x 10⁽⁻²⁾/site/year vs. 0.38 x 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.

Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Adams LA, et al. Clin Chem. 2005 Oct;51(10):1867-73. Epub 2005 Jul 28.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16055434&query_hl=4

BACKGROUND: Staging hepatic fibrosis by liver biopsy guides prognosis and treatment of hepatitis C, but is invasive and expensive. We sought to create an algorithm of serum markers that accurately and reliably predict liver fibrosis stage among hepatitis C patients. **METHODS:** Ten biochemical markers were measured at time of liver biopsy in 117 untreated hepatitis C patients (training set). Multivariate logistic regression and ROC curve analyses were used to create a predictive model for significant fibrosis (METAVIR F2, F3, and F4), advanced fibrosis (F3 and F4), and cirrhosis (F4). The model was validated in 104 patients from other institutions. **RESULTS:** A model (Hepascore) of bilirubin, gamma-glutamyltransferase, hyaluronic acid, alpha(2)-macroglobulin, age, and sex produced areas under the ROC curves (AUCs) of 0.85, 0.96, and 0.94 for significant fibrosis, advanced fibrosis, and cirrhosis, respectively. In the training set, a score ≥ 0.5 (range, 0.0-1.0) was 92% specific and 67% sensitive for significant fibrosis, a score < 0.5 was 81% specific and 95% sensitive for advanced fibrosis, and a score < 0.84 was 84% specific and 71% sensitive for cirrhosis. Among the validation set, the AUC for significant fibrosis, advanced fibrosis, and cirrhosis were 0.82, 0.90, and 0.89, respectively. A score ≥ 0.5 provided a specificity and sensitivity of 89% and 63% for significant fibrosis, whereas scores < 0.5 had 74% specificity and 88% sensitivity for advanced fibrosis. **CONCLUSIONS:** A model of 4 serum markers plus age and sex provides clinically useful information regarding different fibrosis stages among hepatitis C patients.

Relative impact of fatigue and subclinical cognitive brain dysfunction on health-related quality of life in chronic hepatitis C infection. Kramer L, et al. AIDS. 2005 Oct;19 Suppl 3:S85-92.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16251834&query_hl=2

OBJECTIVES: To assess the relative impact of fatigue and subclinical cognitive brain dysfunction on the impairment of health-related quality of life (HRQL) in hepatitis C virus (HCV) infection. **DESIGN AND METHODS:** We performed a cross-sectional study in 120 patients with untreated chronic HCV infection to test the hypothesis that the severity of fatigue had an independent effect on HCV-associated impairment of HRQL. Patients were investigated using the short-form-36 questionnaire, the fatigue impact scale, the brief fatigue inventory, and P300 event-related potentials, as an objective correlate of neurocognitive function. Patients with decompensated cirrhosis or clinical depression were excluded. **RESULTS:** Relative to healthy controls, HCV-infected patients showed significant levels of fatigue (Fatigue Impact Scale, 49 versus 26 points, brief fatigue inventory, 3.0 versus 1.6 points, P < 0.001). Fatigue impact scale and brief fatigue inventory scores were highly correlated (r = 0.77, P < 0.001), demonstrating concurrent validity. Severity of fatigue and age were the only factors independently associated with the impairment of HRQL (P < 0.001). Fatigue was not related to the severity of hepatitis or the degree of subclinical brain dysfunction. **CONCLUSION:** In untreated patients with chronic HCV infection, fatigue severity and age but not neurocognitive dysfunction or hepatic function are independently associated with impaired HRQL. Both the fatigue impact scale and the brief fatigue inventory are suitable tools to assess the subjective burden of fatigue. Our findings stress the need for effective therapeutic interventions to reduce the burden of fatigue in patients with HCV infection.

Relationship between iron replacement and hepatic functions in hepatitis C virus-positive chronic haemodialysis patients. Ozdemir A, et al. *Nephrology (Carlton)*. 2005 Oct;10(5):433-437.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16221090&query_hl=3

AIM: To investigate the effects of intravenous (i.v.) iron replacement on hepatic functions of hepatitis C virus (HCV)-positive haemodialysis patients. **METHODS:** The present retrospective study included 89 HCV-positive and 57 HCV-negative haemodialysis patients. Alanine aminotransferase (ALT) levels were accepted as sustained high if the last three values were ≥ 20 U/L. All patients and the HCV-positive group were dichotomised into subgroups by the median for dialysis duration, the amounts of i.v. iron administered per year and totally.

RESULTS: Sustained high levels of ALT were significantly more frequent in the HCV-positive group ($P < 0.001$). In HCV-positive patients, the subgroup with ALT levels ≥ 20 U/L had significantly higher serum iron levels and mean amounts of i.v. iron administered per year and totally ($P < 0.001$) and the subgroup with the high mean total amount of i.v. iron had significantly higher serum ALT and iron levels ($P < 0.001$). Significant positive correlations were found in HCV-positive patients between ALT and serum iron levels ($P < 0.001$), as well as between ALT both with the mean amounts of i.v. iron administered per year ($P = 0.006$) and totally ($P = 0.015$). Regression analysis showed that the main parameters effecting ALT were the serum iron level ($P < 0.0001$) and the mean amount of parenteral iron administered per year ($P = 0.032$). **CONCLUSION:** We conclude that parenteral iron replacement might contribute to hepatocellular injury in HCV-positive haemodialysis patients.

Percentage of hepatitis C virus-infected hepatocytes is a better predictor of response than serum viremia levels. Rodriguez-Inigo E, et al. *J Mol Diagn*. 2005 Oct;7(4):535-43.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16237224&query_hl=2

Pegylated alpha-interferon plus ribavirin is the current therapy for chronic hepatitis C virus (HCV) infection. Serum HCV-RNA concentration before treatment has been identified as an independent predictive factor of response. We have compared the percentage of HCV-infected hepatocytes with the concentration of serum HCV-RNA in baseline samples as predictors of response. We included 97 patients with chronic HCV infection (genotype 1), treated with pegylated-interferon-alpha2b plus ribavirin. Of these 97, 38 (39%) were sustained responders and 59 (61%) were not. Statistical differences between responders and nonresponders were found regarding the percentage of infected hepatocytes (6.83 \pm 4.50% versus 13.44 \pm 10.05%; $P=0.00003$) but not in serum HCV-RNA concentration [1.71 \pm 2.70 ($\times 10^6$) IU/L versus 1.32 \pm 1.86 ($\times 10^6$) IU/L]; $P=0.40694$]. Other factors associated with response were age, gamma-glutamyl transpeptidase level, and absence of previous therapy. Logistic regression demonstrated that percentage of infected hepatocytes (odds ratio, 1.160; 95% confidence interval, 1.065-1.264) and previous therapy (odds ratio, 0.294; 95% confidence interval, 0.109-0.795) were significant predictive factors for response.

Therefore, the percentage of infected hepatocytes in liver biopsy before treatment is a better predictive factor of sustained response to 48 weeks of therapy with pegylated alpha-interferon plus ribavirin than serum HCV-RNA concentration in baseline serum sample.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

The modeled structure of the RNA dependent RNA polymerase of GBV-C Virus suggests a role for motif E in Flaviviridae RNA polymerases. Ferron F, *BMC Bioinformatics*. 2005 Oct 14;6(1):255 [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16225688&query_hl=3

BACKGROUND: The Flaviviridae virus family includes major human and animal pathogens. The RNA dependent RNA polymerase (RdRp) plays a central role in the replication process, and is thus a validated target for antiviral drugs. Despite the increasing structural and enzymatic characterization of viral RdRps, detailed replication mechanisms remain unclear at the molecular level. The hepatitis C virus (HCV) is a major human pathogen difficult to study in cultured cells. The bovine viral diarrhoea virus (BVDV) is often used as a surrogate model to screen antiviral drugs against HCV. The structure of BVDV RdRp was recently published. It presents several differences relative to HCV RdRp. These differences raise questions about the relevance of BVDV as a surrogate model, and cast novel interest on GBV-C. Indeed, GBV-C is genetically closer to HCV than BVDV, and can lead to productive infection of cultured cells. There is no structural data for the GBV-C RdRp. **RESULTS:** We show in

this study that the GBV-C RdRp is closest to the HCV RdRp. We report a 3D model of the GBV-C RdRp, developed using sequence-to-structure threading and comparative modeling based on the atomic coordinates of the HCV RdRp structure. Analysis of the predicted structural features in the phylogenetic context of the RNA polymerase family allows rationalizing most of the experimental data available. Both available structures and our model are explored to examine the catalytic cleft, allosteric and substrate binding sites. **CONCLUSIONS:** Computational methods were used to infer evolutionary relationships and to predict the structure of a viral RNA polymerase. Docking a GTP molecule into the structure allows the definition of a GTP binding pocket in the GBV-C RdRp, such as that of BVDV. The resulting model suggests a specific role for GTP and motif E in the mechanism of initiation of RNA synthesis, and may prove useful to design new experiments to implement our knowledge on the mechanism of RNA polymerases.

Undetectable phospho-STAT1 in peripheral blood mononuclear cells from patients with chronic hepatitis C who do not respond to interferon-alpha therapy. Aceti A, et al. *Liver Int.* 2005 Oct;25(5):987-93. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16162158&query_hl=3

BACKGROUND: Recent studies have suggested that phosphorylated signal transducers and activators of transcription 1 (STAT1) plays an important role in interferon (IFN)-mediated biological functions, including antiviral activity. Moreover, it has been demonstrated that suppressors of the cytokine signal 1 (SOCS1) negatively regulates IFN activities. **AIMS:** To investigate the involvement of phospho-STAT1 in the response to IFN-alpha therapy in patients with chronic hepatitis C and to evaluate the negative regulatory effect of SOCS1 on STAT1 activation. **METHODS:** Sixty-five patients with chronic hepatitis C and 25 healthy subjects were enrolled. Twenty-five of the patients had never been treated with IFN-alpha therapy (naive), while the remaining 40 patients had. The IFN-treated patients were divided into sustained responders (SRs) or non-responders (NRs) on the basis of their response to the antiviral therapy. Peripheral blood mononuclear cells (PBMCs) were obtained from each patient and control, and were either stimulated with IFN-alpha or left unstimulated. Total STAT1, phospho-STAT1 and SOCS1 were revealed by means of Western blot. **RESULTS:** Total STAT1 was equally expressed in unstimulated and stimulated PBMCs from all patients and controls. One hundred percent of the stimulated PBMCs from healthy controls and SRs, 96% from naive subjects, and 30% from NRs showed detectable phospho-STAT1. By contrast, 70% of the stimulated PBMCs from NRs showed undetectable phospho-STAT1. **CONCLUSIONS:** We have demonstrated that phospho-STAT1 proteins in 70% of patients with chronic hepatitis C who do not respond to IFN treatment are undetectable, which suggests that this protein may be involved in the mediation of IFN sensitivity. The down-regulation of the Jak-STAT pathway because of SOCS1 expression may be one of the possible underlying mechanisms involved in resistance to IFN.

Minimal T-cell-stimulatory sequences and spectrum of HLA restriction of immunodominant CD4+ T-cell epitopes within hepatitis C virus NS3 and NS4 proteins. Gerlach JT, et al. *J Virol.* 2005 Oct;79(19):12425-33. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16160170&query_hl=3

The hepatitis C virus (HCV)-specific CD4+ T-cell response against nonstructural proteins is strongly associated with successful viral clearance during acute hepatitis C. To further develop these observations into peptide-based vaccines and clinical immunomonitoring tools like HLA class II tetramers, a detailed characterization of immunodominant CD4+ T-cell epitopes is required. We studied peripheral blood mononuclear cells from 20 patients with acute hepatitis C using 83 overlapping 20-mer peptides covering the NS3 helicase and NS4. Eight peptides were recognized by > or = 40% of patients, and specific CD4+ T-cell clones were obtained for seven of these and three additional, subdominant epitopes. Mapping of minimal stimulatory sequences defined epitopes of 8 to 13 amino acids in length, but optimal T-cell stimulation was observed with 10- to 15-mers. While some epitopes were presented by different HLA molecules, others were presented by only a single HLA class II molecule, which has implications for patient selection in clinical trials of peptide-based immunotherapies. In conclusion, using two different approaches we identified and characterized a set of CD4+ T-cell epitopes in the HCV NS3-NS4 region which are immunodominant in patients achieving transient or persistent viral control. This information allows the construction of a valuable panel of HCV-specific HLA class II tetramers for further study of CD4+ T-cell responses in chronic hepatitis C. The finding of immunodominant epitopes with very constrained HLA restriction has implications for patient selection in clinical trials of peptide-based immunotherapies.

The role of the tumor necrosis factor (TNF)--Fas L and HCV in the development of hepatocellular carcinoma. Nada O, et al. J Clin Virol. 2005 Oct;34(2):140-6. Department of Pathology, Ain Shams University, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16157266&query_hl=3

Hepatocellular carcinoma (HCC) is a major public health problem in Egypt due to the high prevalence of hepatitis C viral (HCV) infection. The mechanism by which HCV exerts its carcinogenic effect on the liver is not yet understood. Previous research has suggested that perturbations of the Fas-Fas L tumor necrosis system could result in uncontrolled cancerous cell growth in the liver. This study aims to assess the relationship of Fas ligand (Fas L) to HCC. A total of 28 cases (HCC) and 56 controls (28 cirrhosis and 28 chronic hepatitis) were included in the study. Sera and tissue biopsies were tested for HCV antibody and HCV-RNA. Fas ligand expression in tissue was examined immunohistochemically using a rabbit purified polyclonal antibody. Levels of soluble Fas L were determined in serum by ELISA. The HCC cases were graded as: 17.9% Grade I, 32.1% Grade II, 35.7% Grade III and 14.3% were Grade IV. Among the cases, 81% had evidence of cirrhosis. All the cases and controls were positive for HCV-RNA. Tissue and serum PCR results were identical within the same subjects. Fas ligand cytoplasmic expression was more pronounced in HCC than in cirrhosis, and in cirrhosis more than in chronic hepatitis. This expression was higher with increasing grades of malignancy and in tissues adjacent to the tumor, than in those without nearby tumor. Soluble Fas L levels were higher in cases than in controls, with similar results as that of immunohistochemical expression. These results suggest that HCV and Fas ligand play a key role in hepatocarcinogenesis, consistent with the hypothesis that HCV induces overexpression of Fas ligand in the liver cells, resulting in escape from killing by the immune system cells, with subsequent uncontrolled growth of tissue and the development of malignancy.

Analysis of the Mononuclear Inflammatory Cell Infiltrate in the Cirrhotic, Dysplastic Nodules and Hepatocellular Carcinomas in Patients with Chronic Hepatitis C Infection. Hussein MR, Ahmed RA. Cancer Biol Ther. 2005 Oct 3;4(10) [Epub ahead of print] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16123584&query_hl=4

BACKGROUND: Hepatocarcinogenesis is a multistep process entailing the transitions from normal liver--> chronic hepatitis and cirrhotic nodules (CH/CNs) --> dysplastic nodules (DNs) --> hepatocellular carcinomas (HCCs). We hypothesized that hepatocarcinogenesis on top of chronic hepatitis C (CH-C) is associated with alterations in the mononuclear inflammatory cell infiltrate (MICs) in response to altered antigenicity of the damaged hepatocytes. **MATERIALS AND METHODS:** A total of 19 hepatic resection specimens entailing the entire continuum of the lesional steps of the hepatocarcinogenesis (on top of CH-C) were evaluated for MICs using immunohistological methods and mouse monoclonal antibodies (CD3, CD20, CD68 and T-cell intracellular associated antigen, TIA-1). **RESULTS:** HCCs were: 1) overrepresented in elderly males (56.1 +/- 2.0 years, with male to female ratio of 1.8:1), and 2) more common in the right than in left lobe (1.1:1) The transitions from normal liver to the subsequent lesional steps (CH-C/CNs, DNs and HCCs) was associated with statistically significantly ($p < 0.000$) increased density of: tumor infiltrating lymphocytes (9.5 +/- 0.2 vs. 87.1 +/- 1.3 vs. 73.6 +/- 1.6 vs. 72.1 +/- 3.5), CD20(+) B cells (4.4 +/- 0.2 vs. 35.0 +/- 2.9 vs. 11.3 +/- 1.8 vs. 11.3 +/- 1.6), CD68(+) macrophages (1.4 +/- 0.1 vs. 9.5 +/- 1.8 vs. 22.3 +/- 1.6 vs. 18.8 +/- 2.0), CD3(+) cells (5.4 +/- 0.1 vs. 87.0 +/- 1.3 vs. 62.2 +/- 1.3 vs. 61.0 +/- 3.4) and TIA-1(+) cytotoxic T cells (0.4 +/- 0.1 vs. 11.6 +/- 2.0 vs. 24.9 +/- 1.2 vs. 30.5 +/- 1.6). **CONCLUSIONS:** Increased MICs during hepatocarcinogenesis (on top of CH-C) may reflect change in the antigenicity of the damaged hepatocytes. Although both B (humoral response) and T (cell mediated immunity) lymphocytes were involved, the later were the most numerous immunocytes. A considerable fraction of these T cells was TIA-1(+) cells suggesting their cytotoxic potential.

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, et al. J 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=4

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.

Intrahepatic CD8+ T-cell failure during chronic hepatitis C virus infection. Spangenberg HC, et al. Hepatology. 2005 Oct;42(4):828-37.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16175596&query_hl=3

The precise mechanisms responsible for the failure of intrahepatic hepatitis C virus (HCV)-specific CD8+ T cells to control the virus during persistent infection have not been fully defined. We therefore studied the CD8+ T-cell response in 27 HLA-A2-positive patients using four previously well-defined HLA-A2-restricted HCV epitopes. The corresponding HCV sequences were determined in several patients and compared with the intrahepatic HCV-specific CD8+ T-cell response. The results of the study indicate: (1) intrahepatic HCV-specific CD8+ T cells are present in the majority of patients with chronic HCV infection and overlap significantly with the response present in the peripheral blood. (2) A large fraction of intrahepatic HCV-specific CD8+ T cells are impaired in their ability to secrete interferon gamma (IFN-gamma). This dysfunction is specific for HCV-specific CD8+ T cells, since intrahepatic Flu-specific CD8+ T cells readily secrete this cytokine. (3) T-cell selection of epitope variants may have occurred in some patients. However, it is not an inevitable consequence of a functional virus-specific CD8+ T-cell response, since several patients with IFN-gamma-producing CD8+ T-cell responses harbored HCV sequences identical or cross-reactive with the prototype sequence. (4) The failure of intrahepatic virus-specific CD8+ T cells to sufficiently control the virus occurs despite the presence of virus-specific CD4+ T cells at the site of disease. **In conclusion,** different mechanisms contribute to the failure of intrahepatic CD8+ T cells to eliminate HCV infection, despite their persistence and accumulation in the liver.

Host immune responses in hepatitis C virus clearance. Barrett S, Sweeney M, Crowe J. Eur J Gastroenterol Hepatol. 2005 Oct;17(10):1089-97.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16148555&query_hl=3

BACKGROUND AND AIM: The factors that determine the outcome of hepatitis C virus (HCV) infection are not fully understood. An increased and broadly targeted/multispecific T-cell response is thought to be paramount to a favourable outcome. Human leucocyte antigen (HLA) genes, in particular DRB1 and DQB1, are also reported to influence outcome of infection. We have previously demonstrated strong associations between DRB10101 and spontaneous viral clearance. The aim of the current study was to investigate HCV-specific T-cell response and the influence of DRB10101 in patients with long-term history of HCV clearance as compared to patients that developed persistent HCV infection. **METHODS:** The proliferation of peripheral blood mononuclear cells stimulated with five non-structural and core HCV antigens and 20 synthesized HCV peptides, designed using T-cell epitope-predictive software, was determined by the incorporation of H-thymidine. **RESULTS:** Although HCV-specific T-cell responses were more frequently detected and a broader range of peptides were targeted in the viral clearance group, the magnitude and breadth of the responses were not significantly different to that in the viral persistence group. The magnitude and breadth of the T-cell response was significantly associated, however, with possession of DRB10101. Furthermore DRB10101 positive individuals with viral clearance had broader HCV-specific T-cell responses. **CONCLUSION:** These findings lend further credence to the importance of the host immune system to the outcome of HCV infection and provide a rationale for the role of DRB10101 in the resolution of HCV infection.

Involvement of tumor necrosis factor-related apoptosis-inducing ligand and tumor necrosis factor-related apoptosis-inducing ligand receptors in viral hepatic diseases. Saitou Y, et al. Hum Pathol. 2005

Oct;36(10):1066-73.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16226105&query_hl=3

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis in tumor cells, but not in most normal cells. The role of TRAIL in hepatic cell death and hepatic diseases is not well understood. The present study investigated the expression of TRAIL and TRAIL receptors (TRAIL-Rs) in patients with hepatitis C virus infection using immunohistochemistry and examined physiological roles under viral infection in the HepG2 cell line. Staining of TRAIL or TRAIL-Rs was prominent in the cytoplasm and membrane of hepatocytes in the periportal area. Some liver-infiltrating lymphocytes also displayed positive staining for TRAIL. Staining intensity was significantly increased with disease progression, particularly in the periportal area. AdCMVLacZ (Q-BIOgene, Carisbad, Calif) infection was also found to induce apoptosis in HepG2 cells and significantly augment TRAIL-induced apoptosis. Anti-TRAIL antibody significantly inhibited apoptosis induced by AdCMVLacZ infection. Flow cytometry analysis revealed that both TRAIL-R2 and TRAIL were up-regulated on the cell surface of HepG2 cells with AdCMVLacZ infection. Transforming growth factor-beta1 also enhanced TRAIL expression in HepG2 cells. These results indicate that TRAIL/TRAIL-R apoptotic pathways play important roles in the hepatic cell death during viral infection.

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, et al. *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=4

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 proapoptotic pathways is not sufficient to compensate for the low cellular proliferation rates.

Hepatitis C Virus Nonstructural Protein 5A (NS5A) Is an RNA-binding Protein. Huang L, et al. *J Biol Chem.* 2005 Oct 28;280(43):36417-28. Epub 2005 Aug 25.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16126720&query_hl=4

Hepatitis C virus (HCV) nonstructural protein 5A (NS5A) has been shown to antagonize numerous cellular pathways, including the antiviral interferon-alpha response. However, the capacity of this protein to interact with the viral polymerase suggests a more direct role for NS5A in genome replication. In this study, we employed two bacterially expressed, soluble derivatives of NS5A to probe for novel functions of this protein. We find that NS5A has the capacity to bind to the 3'-ends of HCV plus and minus strand RNAs. The high affinity binding site for NS5A in the 3'-end of plus strand RNA maps to the polypyrimidine tract, an element known to be essential for genome replication and infectivity. NS5A has a preference for single-stranded RNA containing stretches of uridine or guanosine. Values for the equilibrium dissociation constants for high affinity binding sites were in the 10 nm range. Two-dimensional gel electrophoresis followed by Western blotting revealed the presence of unphosphorylated NS5A in Huh-7 cells stably expressing the subgenomic replicon. Moreover, RNA immunoprecipitation and NS5A pull-down experiments showed the capacity of replicon-derived NS5A to bind to synthetic RNA and the HCV genome, respectively. Deletion of all of the casein kinase II phosphorylation sites in NS5A supported stable replication of a subgenomic replicon in Huh-7. However, this derivative could not be labeled with inorganic phosphate, suggesting that extensive phosphorylation of NS5A is not required for the replication functions of NS5A. The discovery that NS5A is an RNA-binding protein defines a new functional target for development of agents to treat HCV infection and a new structural class of RNA-binding proteins.

Interferon resistance of hepatitis C virus replicon-harboring cells is caused by functional disruption of type I interferon receptors. Naka K, et al. *J Gen Virol.* 2005 Oct;86(Pt 10):2787-92. Department of Molecular

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16186233&query_hl=3

Hepatitis C virus (HCV) replicon-harboring cell lines possessing interferon (IFN)-resistant phenotypes have recently been established. These were divided into two classes: partially IFN resistant and highly IFN resistant. Here, the viral and cellular factors contributing to the IFN resistance of HCV replicon-harboring cells were evaluated. The results revealed that cellular factors rather than viral factors contributed to a highly IFN-resistant phenotype. The possibility of genetic abnormality of the factors involved in IFN signalling was investigated. As a result, nonsense mutations and deletions in type I IFN receptor genes (IFNAR1 and IFNAR2c) were found in replicon-harboring cells showing a highly IFN-resistant phenotype, but rarely appeared in cells showing a partially IFN-resistant phenotype. Furthermore, similar genetic alterations were also found in IFN-resistant phenotype, replicon-harboring cell lines obtained additionally by IFN-beta treatment. Moreover, it was shown that ectopic expression of wild-type IFNAR1 in IFN-resistant phenotype, replicon-harboring cells possessing the IFNAR1 mutant restored type I IFN signalling.

HIV/HCV COINFECTION

Pegylated interferon alpha-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-coinfected patients. Voigt E, et al. *J Infect.* 2005 Oct 31; [Epub ahead of print]

OBJECTIVES: HIV-coinfection accelerates the course of HCV-related liver disease. Since, highly active anti-retroviral therapy significantly improved survival of HIV-patients more coinfecting patients develop end stage liver disease. Therefore, treatment options for chronic hepatitis C in HIV-coinfected patients need to be evaluated.

METHODS: Efficacy and safety of pegylated interferon alpha-2b (peg IFN) plus ribavirin (RBV) was examined within this prospective, uncontrolled, multicentre trial. Patients received peg IFN (1.5µg/kg) once weekly plus RBV 800mg daily for 48 weeks for HCV genotypes (GT) 1/4 and 24 weeks for GT 2/3. **RESULTS:** One hundred and twenty-two patients were enrolled. Patients were predominantly male (68%) and former i.v. drug users (61%). Baseline characteristics (median) were as follows: age 39 years (range 23-58), CD4 count 494cells/µl (range 150-1578/µl), HIV-RNA 2.3log copies/ml (range <1.7-5.4log copies/ml). 61% currently received anti-retroviral treatment. Fifty-six percent had HCV GT 1. EOT response was achieved by 52%. However, only 25% achieved sustained response (SR) due to a high relapse rate. SR rates were significantly higher among patients with GT 2/3 compared to those with GT 1/4 (44 vs. 18%). SR was observed in only one patient without early response (ER). Discontinuation rate was 30%, 21% discontinued due to adverse events. **CONCLUSION:** Peg IFN/RBV appears safe and effective in HIV/HCV-coinfected patients. GT 2/3 is associated with better SR. Lack of ER strongly predicts non-response. High relapse rates substantially reduce treatment success. In terms of toxicity neuro-psychiatric side effects frequently required treatment discontinuation.

Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. Goulet JL, Fultz SL, McGinnis KA, Justice AC. *AIDS.* 2005 Oct;19 Suppl 3:S99-S105.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16251836&query_hl=2

OBJECTIVES: To determine the prevalence of hepatitis C virus (HCV) co-infection among HIV-infected veterans, assess the prevalence of comorbid conditions that may complicate or limit treatment options, and ascertain whether comorbid conditions were more common in co-infected veterans. **DESIGN AND METHODS:** We used the Veterans Administration electronic medical records system to identify all veterans receiving care for HIV during fiscal years 1997-2002. Demographic data and diagnostic codes for HIV, HCV, and comorbid conditions were extracted. The validity of using diagnostic codes was assessed by calculating the agreement between chart extraction and electronic data on a separate sample of veterans. Factor analysis was used to identify the structure underlying the intercorrelation between comorbid conditions. Logistic regression was used to compare the prevalence of comorbid conditions and factors between HIV/HCV-co-infected and HIV-mono-infected veterans, adjusting for age and race. **RESULTS:** We identified 25 116 HIV-infected veterans in care, of whom 4489 (18%) were HCV co-infected. A validity assessment revealed moderate agreement between chart extraction and electronic data for each of the comorbid conditions assessed. HIV/HCV-co-infected veterans were significantly more likely to have each of the comorbid conditions, and to have significantly more comorbid conditions. Factor analysis revealed three dimensions of comorbidity: mental disorders, medical disorders, and alcohol-related complications. Veterans with co-infection were significantly more likely to have mental disorders and alcohol-related complications. **CONCLUSIONS:** HIV/HCV-co-infected veterans had a higher prevalence of comorbid conditions that may

complicate and limit treatment options for HIV and for HCV co-infection. Strategies to improve treatment options for co-infected patients with comorbidities must be developed.

HIV, hepatitis C and HIV/hepatitis C virus co-infection in vulnerable populations.

Backus LI, Boothroyd D, Deyton LR. AIDS. 2005 Oct;19 Suppl 3:S13-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16251809&query_hl=2

OBJECTIVE: To describe basic patient demographic and clinical characteristics of HIV-infected and HIV/hepatitis C virus (HCV)-co-infected patients receiving care in the Department of Veterans Affairs (VA) with a focus on some patient factors that place such patients at an increased risk of poor health outcomes. **DESIGN:** An observational retrospective cohort study. **METHODS:** The study cohort consisted of veterans in the VA Immunology Case Registry who received care in the VA in 2002. **RESULTS:** Of 18 349 HIV-infected patients, 6782 (37.0%) were HCV seropositive. Compared with HIV-alone-infected patients, HIV/HCV-co-infected patients were older, more likely to be men, more likely to be black or Hispanic, and more likely to report intravenous drug use as a risk factor for HIV acquisition. HIV/HCV-co-infected patients were more likely to have diagnoses of mental health illness, depression, alcohol abuse, substance abuse and hard drug abuse compared with HIV-alone-infected patients. Co-infected patients were less likely to have a history of an AIDS opportunistic infection ever and were less likely to have received HIV antiretroviral drugs in 2002. **CONCLUSION:** The VA's HIV and HIV/HCV-co-infected patient populations have very high rates of additional comorbid conditions that complicate both the pharmacological therapy and clinical course of both HIV and HCV infections. Given the overlap in viral illness and comorbidities, optimal models of integrated care need to be developed for populations with HIV, HCV, and HIV/HCV co-infection and who need substance abuse treatment or mental healthcare.

Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. Richardson JL, AIDS. 2005 Oct 14;19(15):1659-1667.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16184036&query_hl=3

OBJECTIVE: To evaluate the neurocognitive function in 220 women enrolled in the Women's Interagency HIV Study (WIHS), a study of disease progression in women living with HIV/AIDS and in HIV-negative controls. **METHODS:** We evaluated the prevalence of abnormal neuropsychological (NP) results in hepatitis C virus (HCV)-positive compared with HCV-negative women in combination with HIV serostatus. **RESULTS:** NP impairment was significantly higher for HCV-positive women in comparison with HCV-negative women [odds ratio (OR), 2.03; 95% confidence interval (CI), 1.17-3.51]. Women co-infected with HCV and HIV demonstrated greater abnormal NP performance than those not infected with either, particularly if there was evidence of CD4 T-lymphocyte immunosuppression [$> 200 \times 10^6$ CD4 cells/l (OR, 3.48; 95% CI, 1.49-8.15) and $\leq 200 \times 10^6$ CD4 cells/l (OR, 5.38; 95% CI, 1.46-19.84)]. Women who were HCV-positive/HIV-positive and not taking antiretroviral therapy (ART) were more likely (OR, 7.03; 95% CI, 2.63-18.82) to demonstrate NP impairment than those who were HCV-negative/HIV-negative. In analyses controlling separately for education, intelligence quotient, depression, sedating drug use, head injury, ethnicity, and history of substance use, HCV continued to significantly predict NP impairment. The HCV effect did not reach significance when controlling for age in bivariate or multivariate analyses although the odds ratio for NP abnormalities in HCV-infected patients was only slightly reduced (ORs above 1.9). After testing for an interaction between age and infection status, we conducted age-stratified analysis and showed a significant effect of infection status for those aged under 40 years. **CONCLUSIONS:** The effect of aging on co-infected populations will require further study. This study has demonstrated the association of HCV with the risk of neurocognitive impairment in women living with HIV/AIDS and suggests that co-infection has an additive effect.

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=4

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.

Shared alterations in NK cell frequency, phenotype, and function in chronic human immunodeficiency virus and hepatitis C virus infections. Meier UC, et al. *J Virol.* 2005 Oct;79(19):12365-74.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16160163&query_hl=3

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) cause clinically important persistent infections. The effects of virus persistence on innate immunity, including NK cell responses, and the underlying mechanisms are not fully understood. We examined the frequency, phenotype, and function of peripheral blood CD3- CD56+ NK subsets in HIV+ and HCV+ patients and identified significantly reduced numbers of total NK cells and a striking shift in NK subsets, with a marked decrease in the CD56(dim) cell fraction compared to CD56(bright) cells, in both infections. This shift influenced the phenotype and functional capacity (gamma interferon production, killing) of the total NK pool. In addition, abnormalities in the functional capacity of the CD56(dim) NK subset were observed in HIV+ patients. The shared NK alterations were found to be associated with a significant reduction in serum levels of the innate cytokine interleukin 15 (IL-15). In vitro stimulation with IL-15 rescued NK cells of HIV+ and HCV+ patients from apoptosis and enhanced proliferation and functional activity. We hypothesize that the reduced levels of IL-15 present in the serum during HIV and HCV infections might impact NK cell homeostasis, contributing to the common alterations of the NK pool observed in these unrelated infections.

Detection of HCV and HIV-1 antibody negative infections in Scottish and Northern Ireland blood donations by nucleic acid amplification testing. Jarvis LM, et al. *Vox Sang.* 2005 Oct;89(3):128-34.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16146504&query_hl=3

BACKGROUND AND OBJECTIVES: To reduce the risk of transfusion-transmissible viruses entering the blood supply, the nucleic acid amplification testing (NAT) was implemented to screen Scottish and Northern Irish blood donations in minipools. After 5 years of NAT for hepatitis C virus (HCV) and 2 years for human immunodeficiency virus-1 (HIV-1), the yield of serologically negative, nucleic acid positive 'window donations' and cost-benefit of NAT is under review. **MATERIALS AND METHODS:** When the Scottish National Blood Transfusion Service (SNBTS) implemented NAT in 1999, a fully automated 'black box' system was not available. Therefore, an 'in-house' assimilated NAT assay was developed, validated and implemented. The system is flexible and allows testing for additional viral markers to be introduced with relative ease. **RESULTS:** The HCV and HIV NAT assays have 95% detection levels of 7.25 IU/ml and 39.8 IU/ml, respectively, as determined by probit analysis. One HCV (1 in 1.9 million) and one HIV (1 in 0.77 million) window donation have been detected in 5 and 2 years, respectively, of NAT. **CONCLUSION:** The SNBTS NAT assays are robust and have performed consistently over the last 5 years. The design of the in-house system allowed HIV NAT to be added in 2003 at a relatively small additional cost per sample, although for both assays, the royalty fee far exceeds the cost of the test itself. Clearly NAT has a benefit in improving the safety of the blood supply although the risks of transfusion-transmitted viral infections, as reported in the Serious Hazards of Transfusion (SHOT) report, are extremely low. Also, in UK the yield of HCV antibody negative, NAT positive donations is far lower than predicted although the early detection of an HIV window period donation and the increase of HIV in the blood donor and general populations may provide a stronger case for HIV NAT. **SUMMARY SENTENCE:** The yield of HCV and HIV NAT in UK is significantly less than that anticipated from statistical models.

Liver injury and changes in hepatitis C Virus (HCV) RNA load associated with protease inhibitor-based antiretroviral therapy for treatment-naïve HCV-HIV-coinfecting patients: lopinavir-ritonavir versus nelfinavir. Sherman KE, et al. *Clin Infect Dis.* 2005 Oct 15;41(8):1186-95. Epub 2005 Sep 13.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16163639&query_hl=3

BACKGROUND: Highly active antiretroviral therapy (HAART) initiation in patients coinfecting with human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) has been associated with transaminase and HCV viral load flares. Previous studies have included highly variable antiretroviral regimens. We compared effects

of 2 protease inhibitor-based regimens on alanine aminotransferase (ALT) levels and HCV loads in HCV-HIV-coinfected patients initiating HAART. **METHODS:** Seventy HIV-infected patients with positive baseline results of HCV enzyme-linked immunosorbant assay from a treatment trial comparing lopinavir-ritonavir with nelfinavir were evaluated during a 48-week period. HCV and HIV titers were analyzed at baseline, at weeks 24 and 48 of treatment, and during flares in the ALT level of >5 times the upper limit of normal. **RESULTS:** A total of 57 of 70 patients tested positive for HCV RNA at baseline. HCV titers for patients in lopinavir-ritonavir and nelfinavir groups, respectively, were as follows: baseline, 6.07 and 6.22 log IU/mL; week 24 of treatment, 6.68 and 6.48 log IU/mL; and week 48 of treatment, 6.32 and 6.44 log IU/mL. Of patients with a CD4+ cell count of <100 cells/mm³ at baseline, 5 of 11 in the nelfinavir group and 0 of 10 in the lopinavir-ritonavir group had an increase in the HCV load of >0.5 log IU/mL from baseline to week 48. The mean ALT level increased by 45 U/L at 24 weeks and 18 U/L at 48 weeks in the nelfinavir group but decreased by 18 U/L at 24 weeks and 7 U/L at 48 weeks in the lopinavir-ritonavir group. Eight patients in the nelfinavir group and 2 patients in the lopinavir-ritonavir group had grade 3 or 4 flares in the ALT level. **CONCLUSIONS:** HAART initiation is associated with increased HCV loads and ALT levels. A low baseline CD4+ cell count is associated with persistent increases in the HCV RNA load in nelfinavir-treated patients. These results warrant careful interpretation of abnormalities in the ALT load after HAART initiation in HCV-HIV-coinfected patients to prevent premature discontinuation of treatment.

Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. Tien PC. Am J Gastroenterol. 2005 Oct;100(10):2338-54.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16181388&query_hl=3

Nearly 40% of human immunodeficiency virus- (HIV-) infected veterans on highly active antiretroviral therapy (HAART) in the United States are coinfecting with hepatitis C virus (HCV). With the increased survival due to declining opportunistic infections as a result of HAART, HCV-associated liver disease has become a leading cause of death in HIV-infected individuals. HCV infection has been shown to lead to rapid progression of HCV-related liver disease in HIV infection. Results from recent clinical trials in HIV/HCV-coinfected patients show improved response rates using pegylated formulations of interferon plus ribavirin when compared to standard interferon plus ribavirin. However, the treatment of HCV in HIV/HCV-coinfected patients can be complicated by the hepatotoxic and myelosuppressive effects of HIV therapy and HIV infection itself. Prior to initiating HCV therapy, HIV therapy should be optimized by improving immune suppression and avoiding specific antiretroviral drugs that may cause hepatotoxicity and myelosuppression. In the event of treatment-related neutropenia or anemia during HCV therapy, the use of growth factors should be considered to maximize sustained virologic response to HCV therapy. In HIV/HCV-coinfected patients with end-stage liver disease, liver transplantation is being investigated and shows promise as a potential therapeutic option. With the recent advances in the treatment of HCV in HIV/HCV-coinfected individuals, all HIV/HCV-coinfected patients eligible for HCV treatment should be evaluated for HCV combination therapy with careful consideration of their HIV disease.

The influence of hepatitis C virus-human immunodeficiency virus co-infection on the appearance of liver enzyme elevation in people on high activity antiretroviral treatment. Olalla J, et al. Eur J Intern Med. 2005 Oct;16(6):405-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16198898&query_hl=3

BACKGROUND: Liver enzyme elevation (LEE) as a consequence of HAART is a problem among patients with HIV-HCV co-infection. **METHODS:** In this retrospective study, 145 patients with HIV who were on HAART and who developed LEE grades 3 and 4 of the World Health Organization (WHO) were followed up. Basal ALT, alcohol consumption, and HCV and HBV co-infection were recorded. Comparisons were made between patients with and without HCV co-infection. **RESULTS:** Three patients without co-infection presented LEE grade 3 versus 38 with co-infection (104 episodes). An increase in basal ALT (RR: 1.01) and HCV co-infection (RR: 6.6) were the variables associated with LEE grade 3. The number of days that HAART had to be withdrawn due to LEE was 58.15 and 4.85 in subjects with and without co-infection, respectively (p=0.024). **CONCLUSION:** Patients with HCV-HIV co-infection have more episodes of LEE and must go longer without HAART than people without co-infection.

Herbal medicines for liver diseases. Dhiman RK, Chawla YK. Dig Dis Sci. 2005 Oct;50(10):1807-12.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16187178&query_hl=3

Herbal medicines have been used in the treatment of liver diseases for a long time. A number of herbal preparations are available in the market. This article reviews four commonly used herbal preparations: (1) Phyllanthus, (2) Silybum marianum (milk thistle), (3) glycyrrhizin (licorice root extract), and (4) Liv 52 (mixture of herbs). Phyllanthus has a positive effect on clearance of HBV markers and there are no major adverse effects; there are no data from randomized controlled trials on clinically relevant outcomes, such as progression of chronic hepatitis to cirrhosis and/or liver cancer, and on survival. Silymarin does not reduce mortality and does not improve biochemistry and histology among patients with chronic liver disease; however, it appears to be safe and well tolerated. Stronger neominophagen C (SNMC) is a Japanese preparation that contains 0.2% glycyrrhizin, 0.1% cysteine, and 2% glycine. SNMC does not have antiviral properties; it primarily acts as an anti-inflammatory or cytoprotective drug. It improves mortality in patients with subacute liver failure and improves liver functions in patients with subacute hepatic failure, chronic hepatitis, and cirrhosis with activity. SNMC does not reduce mortality among patients with cirrhosis with activity. SNMC may prevent the development of hepatocellular carcinoma in patients with chronic hepatitis C, however, prospective data are lacking. Liv 52, an Ayurvedic hepatoprotective agent, is not useful in the management of alcohol-induced liver disease. Standardization of herbal medicines has been a problem and prospective, randomized, placebo-controlled clinical trials are lacking to support their efficacy. The methodological qualities of clinical trials of treatment with herbal preparations are poor. The efficacy of these herbal preparations need to be evaluated in rigorously designed, larger randomized, double-blind, placebo-controlled multicenter trials.

MISCELLANEOUS WORKS

Differential display analysis of gene expression in brains from hepatitis C-infected patients. Adair DM, et al. AIDS. 2005 Oct;19 Suppl 3:S145-50.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16251812&query_hl=2

OBJECTIVES: Hepatitis C virus (HCV) infection is often associated with cognitive dysfunction, fatigue and depression. The current study was undertaken to determine whether HCV infection affects gene expression in brain tissue. **DESIGN:** We analysed the gene expression pattern in brain tissue in a group of HCV-infected patients compared with HCV-negative controls. **METHODS:** Brain tissue samples were obtained at autopsy from three HCV-positive patients and three HCV-negative control patients. The analysis of gene expression was conducted using differential display and reverse Northern hybridization. Only those genes that were up or downregulated more than 1.8 times were considered to be differentially expressed. **RESULTS:** Altogether, 29 differentially expressed genes were identified by differential display and subsequently confirmed by reverse Northern hybridization. A prominent finding was the downregulation of mitochondrial oxidative phosphorylation genes in HCV-infected patients. The impairment of brain oxidative/energy metabolism has previously been suggested to be the proximate cause of many disorders that impair mentation. Another finding was the downregulation of some ribosomal protein genes and several genes involved in transcription regulation, perhaps reflecting reduced metabolic activities. **CONCLUSION:** Our findings suggest for the first time that there may be a biological basis for the neuropsychiatric symptoms and cognitive impairment associated with HCV infection.

Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: a European case-control study. Yazdanpanah Y, et al. Clin Infect Dis. 2005 Nov 15;41(10):1423-30. Epub 2005 Oct 6.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16231252&query_hl=2

BACKGROUND: Additional studies are required to identify risk factors for hepatitis C virus (HCV) transmission to health care workers after occupational exposure to HCV. **METHODS:** We conducted a matched case-control study in 5 European countries from 1 January 1991 through 31 December 2002. Case patients were health care workers who experienced seroconversion after percutaneous or mucocutaneous exposure to HCV. Control subjects were HCV-exposed health care workers who did not experience seroconversion and were matched with case

patients for center and period of exposure. **RESULTS:** Sixty case patients and 204 control subjects were included in the study. All case patients were exposed to HCV-infected fluids through percutaneous injuries. The 37 case patients for whom information was available were exposed to viremic source patients. As risk factors for HCV infection, multivariate analysis identified needle placement in a source patient's vein or artery (odds ratio [OR], 100.1; 95% confidence interval [CI], 7.3-1365.7), deep injury (OR, 155.2; 95% CI, 7.1-3417.2), and sex of the health care worker (OR for male vs. female, 3.1; 95% CI, 1.0-10.0). Source patient HCV load was not introduced in the multivariate model. In unmatched univariate analysis, the risk of HCV transmission increased 11-fold for health care workers exposed to source patients with a viral load $>6 \log_{10}$ copies/mL (95% CI, 1.1-114.1), compared with exposures to source patients with a viral load $\leq 4 \log_{10}$ copies/mL. **CONCLUSION:** In this study, HCV occupational transmission was found to occur after percutaneous exposures. The risk of HCV transmission after percutaneous exposure increased with deep injuries and procedures involving hollow-bore needle placement in the source patient's vein or artery. These results highlight the need for widespread adoption of needlestick-prevention devices in health care settings, together with other preventive measures.

Rapid genotyping of hepatitis C virus by primer-specific extension analysis. Antonishyn NA, et al.

J Clin Microbiol. 2005 Oct;43(10):5158-63.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16207978&query_hl=3

Quick and accurate genotyping of hepatitis C virus (HCV) is becoming increasingly important for clinical management of chronic infection and as an epidemiological marker. Furthermore, the incidence of HCV infection with mixed genotypes has clinical significance that is not addressed by most genotyping methods. We have developed a fluorescence-based genotyping assay called primer-specific extension analysis (PSEA) for the most prevalent HCV genotypes and have demonstrated the capacity of PSEA-HCV for detecting mixed-genotype HCV infections. PSEA-HCV detects genotype-specific sequence differences in the 5' untranslated region of HCV in products amplified by the COBAS AMPLICOR HCV Test, v2.0. Simulated mixed HCV infection of plasma with RNase-resistant RNA controls demonstrates that PSEA-HCV can detect as many as five genotypes in one specimen. Furthermore, in dual-genotype simulations, PSEA-HCV can unequivocally detect both genotypes, with one genotype representing only 3.1% of the mixture (313/10,000 IU in starting plasma). Compared to INNO-LiPA HCV II, both assays determined the same genotype for 191/199 (96%) patient specimens (175 subtype and 16 genotype-only identifications). Following the initial evaluation, PSEA-HCV was used routinely to genotype HCV from patient specimens submitted to our laboratory (n=312). Seventeen (5.4%) mixed infections were identified. The distribution of single-infection HCV genotypes in our population was 60.9% type 1 (n=190), 12.8% type 2 (n=40), 20.2% type 3 (n=63), 0.3% type 4 (n=1), and 0.3% other (n=1). In conclusion, PSEA-HCV provides an inexpensive, high-throughput screening tool for rapid genotyping of HCV while reliably identifying mixed HCV infections.

Prevalence of selected viral infections among temporarily deferred donors who returned to donate blood:

American Red Cross blood donor study. Zou S, et al. Transfusion. 2005 Oct;45(10):1593-600.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16181210&query_hl=3

BACKGROUND: Health history questions are introduced into the predonation interview to identify blood donors believed to pose a higher risk of infectious diseases to recipients. This study assesses the current impact of some of those questions. **STUDY DESIGN AND METHODS:** Donor deferral and donation data were extracted from a research database of the American Red Cross. The prevalence of hepatitis B surface antigen or antibodies to human immunodeficiency virus, hepatitis C virus, or human T-lymphotropic virus was obtained for different groups of donors who were temporarily deferred in 2000 through 2001 and later returned to donate blood in 2000 through 2003. The results were compared with either first-time or repeat donors in 2000 through 2003, while controlling for differences in sex, age, and year of donation. **RESULTS:** Of donors temporarily deferred in 2000 through 2001 who had had no donation or deferral during the previous 2 years, only 22.08 percent subsequently returned to donate blood in 2000 through 2003. Donations from returning donors who had been deferred for potential infectious disease risk did not show a higher prevalence for any of the viral markers when those with no donation or deferral during the previous two years were compared with first-time donations, and those with prior donation were compared with repeat donations. **CONCLUSION:** Blood donors temporarily deferred in 2000 through 2001 for potential risk of viral infection who later returned to donate blood did not appear to pose a higher risk compared to

first-time or repeat donors. The effectiveness of some of the currently used deferral questions in reducing viral risks warrants further study.

Hepatitis C identification and management by family physicians. Clark EC, et al. *Fam Med.* 2005 Oct;37(9):644-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16193428&query_hl=3

BACKGROUND AND OBJECTIVES: Many people with hepatitis C receive all or most of their care from primary care physicians, yet little information exists about the practice patterns, knowledge, and beliefs and attitudes of family physicians related to hepatitis C. **METHODS:** We mailed a written survey to a random sample of active members of the American Academy of Family Physicians. **RESULTS:** Nearly all respondents (94%) reported at least one patient with hepatitis C in their practice, and 66% had diagnosed at least one new case of hepatitis C in the past year. While most respondents (85%) correctly identified common hepatitis C risk factors, only 63% reported routinely asking patients about those risk factors. Respondents (74%) preferred to involve specialists in the care of hepatitis C patients, but half (50%) reported barriers to referral. A small number (5%) of respondents have prescribed antiviral medication within the past year. Most respondents think family physicians should screen (94%), diagnose (98%), and provide general care (69%) for hepatitis C patients. **CONCLUSIONS:** Family physicians know how to identify high-risk people and test for hepatitis C. Most prefer to refer patients with hepatitis C to specialists for workup and treatment but report frequent barriers to those referrals.

Health indicators among low income women who report a history of sex work: the population based Northern California Young Women's Survey. Cohan DL, et al. *Sex Transm Infect.* 2005 Oct;81(5):428-33..

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16199746&query_hl=3

OBJECTIVES: We examined differences in demographic characteristics, HIV related risk behaviour, prevalence of sexually transmitted infections (STI), and HIV and other health concerns among women with and without a history of sex work. **METHODS:** A secondary analysis of a population based, cross sectional survey of young, low income women in northern California. **RESULTS:** Of the 2543 women interviewed, 8.9% reported a history of sex work. These women reported more lifetime male sexual partners, were more likely to use drugs before sex, and were more likely to have a history of having sex with partners at high risk for HIV (that is, men who have sex with men, inject drugs, or were known to be HIV positive). They were significantly more likely to have positive serology for syphilis, herpes simplex virus type 2 (HSV-2), and hepatitis C regardless of their personal injecting drug use history; however, they were no more likely to have HIV, chlamydia, gonorrhoea, hepatitis A or hepatitis B infection compared to women without a history of sex work. Women with a history of sex work were significantly more likely to have a history of sexual coercion and tobacco use. **CONCLUSIONS:** These data measure the population prevalence of sex work among low income women and associated STI. Women with a history of sex work have health concerns beyond STI and HIV treatment and prevention.

Prevalence and correlates of hepatitis C infection among users of North America's first medically supervised safer injection facility. Wood E, et al. *Public Health.* 2005 Oct 6; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16214189&query_hl=3

BACKGROUND: North America's first medically supervised safer injection facility (SIF) for illicit drug users was opened in Vancouver, Canada on 22 September 2003. We examined the prevalence and correlates of hepatitis C (HCV) infection among a representative cohort of SIF users. **METHODS:** Users of the Vancouver SIF were selected at random and asked to enrol in the Scientific Evaluation of Supervised Injecting (SEOSI) cohort. At baseline, venous blood samples were collected and an interviewer-administered questionnaire was performed. Participants who were HCV-positive were compared with HCV-negative subjects using bivariate and logistic regression analyses. **RESULTS:** Between 1 December 2003 and 30 July 2004, 691 participants were enrolled into the SEOSI cohort, among whom 605 (87.6%) were HCV-positive at baseline. Factors independently associated with HCV infection in logistic regression analyses included: involvement with the sex trade [adjusted odds ratio (AOR) 3.7, 95% confidence interval (CI) 2.1-6.1], history of borrowing syringes (AOR 1.8, 95%CI 1.1-2.9), and history of incarceration (AOR 2.6, 95%CI 1.5-4.4). Daily heroin use was protective against HCV infection (AOR 0.6, 95%CI 0.3-0.9). **CONCLUSION:** The SIF has attracted injection drug users with a high burden of HCV infection and a substantial proportion of uninfected individuals. Although cross-sectional, this study provides some

insight into historical risks for HCV infection among this population, and prospective follow-up of this cohort will be useful to determine if use of the SIF is associated with reduced risk behaviour and HCV incidence.

High rates of uninsured among HCV-positive individuals. Ong JP, J Clin Gastroenterol. 2005 Oct;39(9):826-30.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16145347&query_hl=3

BACKGROUND AND GOALS: There are no published data on the health insurance status of Hepatitis C virus (HCV)-positive individuals. To address this issue, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III). **STUDY:** Individuals 18 years of age and older who participated in NHANES III were included in the study. We determined the rates of health insurance coverage according to HCV status. We also determined healthcare status and health service utilization according to health insurance status among HCV-positive persons. **RESULTS:** HCV-positive individuals were more likely to be uninsured compared with those who were HCV-negative (29.6% vs. 12.2%, $P = 0.0002$). Among those with health insurance, HCV-positive individuals were more likely to have government insurance compared with those who were HCV-negative (42.9% vs. 27.6%, $P < 0.005$). Among HCV-positive individuals, being uninsured was associated with younger age, being unmarried, living in the South, Mexican-American race/ethnicity, and not graduating from high school. Additionally, the uninsured were less likely than their insured counterparts to identify a healthcare facility for sick or routine care, and less likely to have regular contact with a healthcare professional. **CONCLUSIONS:** A high proportion of HCV-positive individuals are uninsured, and many HCV-positive individuals with health insurance have publicly funded insurance. This finding may have implications for access to health care and for liver-related disease outcomes in HCV-positive persons.

Tracing the evolution of hepatitis C virus in the United States, Japan, and Egypt by using the molecular clock. Mizokami M, Tanaka Y. Clin Gastroenterol Hepatol. 2005 Oct;3(10 Suppl 2):S82-5.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16234067&query_hl=2

The molecular clock has been a very powerful tool in looking back at the epidemic spread of HCV infection in the United States (US) and Japan, as well as in Egypt. This analysis estimates that the growth of the US HCV genotype 1a (HCV-1a)-infected population occurred around 1960, at least 30 years later than the widespread introduction of HCV-1b into the Japanese population. In Japan, the estimated effective number of HCV infections indicated a rapid exponential growth in the 1920s among patients with schistosomiasis, which coincides with injection treatment for schistosomiasis since 1921 in previously schistosomiasis-endemic areas. In Egypt, the spread of HCV-4a would have increased exponentially during the 1940s through 1980, which was also consistent with the duration of intravenous antimony campaigns for the treatment of schistosomiasis in that country. The implications are that Japan has set the model for HCV-related HCC, and that the high HCC incidence in Japan might be replicated by the rest of the world as their HCV-infected population ages and the duration of HCV infection approaches that currently observed in Japan.

Genotyping of hepatitis C virus by Taqman real-time PCR. Lindh M, Hannoun C. J Clin Virol. 2005 Oct;34(2):108-14.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16157261&query_hl=3

BACKGROUND: Genotype of hepatitis C virus (HCV) is of major importance for the outcome of treatment. The response rate is considerably lower for genotype 1, the predominant genotype in western countries. **OBJECTIVES:** To develop and evaluate a new, simple method for genotyping of HCV based on real-time polymerase chain reaction (PCR) and Taqman probes targeting the 5' non-coding region. **STUDY DESIGN:** The method was compared with Innolipa on 220 serum samples representing genotypes 1-4, and was applied on a further 614 clinical samples. **RESULTS:** Taqman typing of the 220 samples showed genotype 1 in 69, genotype 2 in 58, genotype 3 in 57 and genotype 4 in 19, while 17 were non-reactive. There was a complete concordance with Innolipa with the exception of seven samples, which were of genotype 1 by Taqman, but genotype 4 by Innolipa. Sequencing of these samples showed a subtype 4 variant which differed at two positions compared with subtypes 4b/c/d, which are targeted by the probe. By adding a modified probe, these genotype 4 variants could also be identified. Out of 614 consecutive clinical samples, 524 could be typed by the Taqman assay; 45.2% were genotype 1, 19.3% genotype 2, 33.8% genotype 3 and 1.7%, genotype 4. **CONCLUSION:** The method was overall accurate

and provides an attractive alternative for genotyping because processing time and costs are significantly reduced. Inclusion of probes targeting genotypes 5 and 6 is required for the method to be useful in areas where these genotypes are present.

Cost-efficacy analysis of peginterferon alfa-2b plus ribavirin compared with peginterferon alfa-2a plus ribavirin for the treatment of chronic hepatitis C. Malone DC, Tran TT, Poordad FF. *J Manag Care Pharm.* 2005 Oct;11(8):687-94.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16194133&query_hl=3

OBJECTIVE: Combination therapy with pegylated interferon (Peg) and ribavirin (RBV) is the standard of care for the treatment of chronic hepatitis C virus (HCV) infection. This analysis compares the cost efficacy of treatment with pegylated interferon alfa-2b plus ribavirin (Peg-2b plus RBV) with pegylated interferon alfa-2a plus ribavirin (Peg-2a plus RBV) in hypothetical cohorts of 100 chronic HCV patients comprised 75% of genotype 1.

METHODS: A decision analysis model was constructed from the viewpoint of a managed care organization to compare Peg-2b plus RBV (1.5 mcg per kilogram per week plus RBV 800 mg per day) and Peg-2a plus RBV (180 mcg per week plus RBV 1,000-1,200 mg per day) pursuant to the label dosing approved by the U.S. Food and Drug Administration. The model also included the so-called weight-based dosing regimen with Peg-2b plus RBV (1.5 mcg per kilogram per week plus RBV 10.6 mg/kg per day). Patient weight was assumed to be 80 kg. For purposes of this analysis, early virologic response (EVR), defined as viral negative or 2-log drop in viral load, was assessed at 12 weeks for only genotype 1 patients, and nonresponders were assumed to discontinue therapy. The positive predictive value (PPV) was calculated for each treatment group for genotype 1 patients, which is determined from the values for EVR and sustained viral response (SVR). Genotype 2 and genotype 3 patients were assumed to be treated for 24 weeks. Treatment duration and efficacy data were obtained from the published literature. Product pricing was based on average wholesale price, October 2004, and sensitivity analysis was performed using prices from the Federal Supply Schedule. Economic outcomes were determined from hypothetical 100-patient cohorts assumed to be comprised 75% of genotype 1 HCV. **RESULTS:** Taking into account both EVR and SVR, the PPV for genotype 1 patients was 0.63 and 0.57 for Peg-2b plus RBV and Peg-2a plus RBV, respectively. The proportion of treated patients achieving SVR would be nearly identical, (53.6%) and (53.8%) for Peg-2a plus RBV and Peg-2b plus flat RBV, respectively. For Peg- 2b plus weight-based RBV, the proportion of patients achieving SVR was higher (61.4%). Consequently, this leads to fewer overall treatment weeks for the Peg- 2b plus RBV cohorts. Therefore, the cost per successful treatment (defined as SVR) was 19.4% less (37,638 US dollars) for Peg-2b plus flat dosing of RBV as compared with Peg-2a plus RBV (46,717 US dollars). When Peg-2b plus RBV was dosed 1.5 mcg per kilogram per week plus RBV 10.6 mg/kg/day, then the cost per SVR was 39,045 US dollars. The cost for the 100-patient cohort was 2,024,846 US dollars for Peg-2b plus RBV, 2,397,529 US dollars for Peg-2b plus weight-based RBV, and 2,505,317 US dollars for Peg-2a plus RBV. This difference is due to a lower PPV in the Peg-2a plus RBV groups and hence more patients treated in spite of a low probability of achieving SVR. **CONCLUSION:** The results of this cost-efficacy analysis suggest that treating HCV genotype 1 patients with Peg-2b plus RBV may result in savings to a health care system because fewer of these patients are treated beyond 12 weeks when achieving sustained viral clearance is unlikely.