

Caring Ambassadors Hepatitis C Program Newsletter
www.HepCChallenge.org
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IN THE NEWS

State seeks new laws following hepatitis outbreak panel

<http://www.lasvegasnow.com/Global/story.asp?S=9884708&nav=168XDWn7>

“State lawmakers were in Las Vegas Saturday trying to pass new laws to strengthen regulations on health care. This comes after nearly 60,000 Clark County residents learned they had been exposed to hepatitis C at local medical clinics. Lawmakers are working on five bills they believe will help prevent the dangerous medical practices that happened at the Endoscopy Center of Southern Nevada. Saturday, a panel heard from victims and the medical community about their concerns and what they believe could be done to prevent a similar outbreak in the future.” [truncated]

Probe attacks NHS 'Bad Blood' scandal

http://news.sky.com/skynews/Home/UK-News/Bad-Blood-Inquiry-Results-Due-Lord-Archers-Report-On-Contaminated-NHS-Transfusions/Article/200902415227755?lpos=UK News First Home Article Teaser Region 0&lid=ARTICLE_15227755_Bad_Blood_Inquiry_Results_Due%3A_Lord_Archers_Report_On_Contaminated_NHS_Transfusions

“An inquiry has criticized the "procrastination" that led to a blood contamination scandal that killed nearly 2,000 people. Nearly 2,000 haemophilia patients died as result of "bad blood" transfusions. Some 4,670 patients who received "bad blood" transfusions during the 1970s and 80s were infected with Hepatitis C - of whom 1,243 were also infected with HIV.” [truncated]

Romark reports promising data from hepatitis C virus study

http://drugdiscovery.pharmaceutical-business-review.com/news/romark_reports_promising_data_from_hepatitis_c_virus_study_200209

“Romark Laboratories, a privately held biopharmaceutical company, has announced encouraging results from international Phase I and II clinical trials evaluating a controlled release version of nitazoxanide in the treatment of chronic hepatitis C virus infection. In the Phase II study in treatment-naive patients infected with hepatitis C virus (HCV) genotype 4, 82% (n=17) and 100% (n=16) of patients receiving low and high doses of controlled release nitazoxanide, respectively, experienced undetectable serum HCV RNA (<12 IU/mL) after 12 weeks of combination therapy with peginterferon and ribavirin.” [truncated]

Free needles for drug users 'good use of NHS money'

<http://www.guardian.co.uk/society/2009/feb/19/needles-nhs-money>

“About 40% of drug users who inject are already infected with Hepatitis C. Providing free needles and syringes to people who inject heroin and cocaine is a cost-effective use of NHS money, the government's medicines watchdog said today. The National Institute for Health and Clinical Excellence (Nice) issued its first guidance on how harm reduction services for addicts should be run throughout England, suggesting combining non-judgmental needle exchange schemes with treatment to help users come off drugs.” [truncated]

Forum addresses sex and hep C

<http://www.ebar.com/news/article.php?sec=news&article=3699>

“No one was more surprised than Tom Kelly when he was diagnosed – not once but twice – with hepatitis C. “I thought I was safe,” he said at a recent community forum on sex and hep C. “I didn't do IV drugs and I thought I couldn't get it, but I got it anyway.” Organized by an informal group of community members with the assistance of the San Francisco Department of Public Health, the January 27 forum at the LGBT Community Center brought out nearly 150 participants, underlining the growing concern about an emerging new epidemic.” [truncated]

Natalie Cole's son to donate kidney to mom

<http://www.actressarchives.com/news.php?id=14562>

“Proving that he's a son that really knows how to step up to the plate for his mom, it's been reported that Natalie Cole's son may give her one of his kidneys. Cole was diagnosed with Hepatitis C about a year ago and now it seems she might need a kidney transplant, which would finally put an end to the dialysis treatments she goes through three times a week.” [truncated]

Vertex will name Emmens to replace Boger as CEO

<http://www.forbes.com/feeds/ap/2009/02/05/ap6015453.html>

“Vertex Pharmaceuticals Inc. said Thursday Matthew Emmens will become president, and eventually chairman and chief executive, of the company when founder Joshua Boger retires. Emmens, 57, takes the president position immediately and will become chairman and CEO in May. He has been a board member at Vertex since 2004.” [truncated]

Tainted blood case study: 'My family believe my brother was murdered'

<http://www.timesonline.co.uk/tol/news/uk/health/article5790676.ece>

“As a result of his hepatitis Mr Fielding developed cirrhosis of the liver and by October 1998 he needed a transplant. Despite a life plagued with ill health after a blood transfusion contaminated with hepatitis B and C, David Fielding, 53, considers himself the lucky one in his family. His brother, also a haemophiliac, contracted HIV after a similar transfusion and died in 1990 at the age of 46.” [truncated]

Liver disease raised need for assistance

<http://www.theledger.com/article/20090221/NEWS/902210315/1410?Title=Liver-Disease-Raised-Need-for-Assistance>

“Liver transplant patient DeWayne Oaks talks about his recovery as he and his wife, Barbara, sit on their patio last week with their dogs in Lake Alfred. Confronted with the frightful diagnosis in 2006, Oaks, a trucker from Lake Alfred, sought medical treatment through the Veterans Administration. He spent the next few years in declining health and it cost him his job. Despite monetary assistance from friends and relatives, Oaks and his wife, Barbara, who stocks shelves at Wal-Mart, find

themselves unable to meet expenses, prompting a request for help through The Ledger's Newspaper with a Heart program.” [truncated]

Abbott and Enanta initiate Phase I hepatitis trial

http://drugdiscovery.pharmaceutical-business-review.com/news/abbott_and_enanta_initiate_phase_i_hepatitis_trial_230209

“Abbott and Enanta Pharmaceuticals, a R&D company, have announced the advancement of their hepatitis C virus collaboration with a first-in-human study evaluating ABT-450, an oral protease inhibitor for the treatment of chronic HCV. The objectives of the trial include assessment of safety, tolerability and pharmacokinetics. ABT-450 was discovered as part of a worldwide alliance between Abbott and Enanta to discover, develop and commercialize protease inhibitors for the treatment of hepatitis C virus (HCV).” [truncated]

In wake of hepatitis C crisis, legislators seek to improve health care

http://www.lvrj.com/news/breaking_news/40036527.html

“Gwendolyn Martin has hepatitis C. Her case was genetically linked to a patient who had underwent a procedure before her on Sept. 21, 2007, at the Endoscopy Center of Southern Nevada. During a special joint meeting of the Assembly Committee on Health and Human Services and Senate Committee on Health and Education today, lawmakers discussed four bills intended to fill gaps in Nevada’s health care system which they say put Martin and other Southern Nevadans at risk for contracting the disease.

“We understand that the public health system in this state depends upon public trust and the public trust was seriously eroded by this public crisis,” said Assemblywoman Sheila Leslie, D-Reno, who sits on the Assembly committee. The introduced bills would prevent retaliation against nurses who report breaches in patient safety, strengthen health authorities’ power during disease investigations and require annual inspections of ambulatory surgery centers and certain physician offices where conscious, general and deep levels of sedation are used.” [truncated]

Hospitalization and disability are higher amongst HIV patients with hepatitis C coinfection

<http://www.aidsmap.com/en/news/59473B4B-EE30-4F2F-BE32-8D48FEC07D02.asp>

“HIV-positive individuals co-infected with hepatitis C virus are hospitalized longer, visit emergency departments more often and spend more days disabled than people with HIV alone, according to new data presented on Tuesday at the Sixteenth Conference on Retroviruses and Opportunistic Infections in Montreal, Canada. An estimated 15% to 30% of HIV positive people also have chronic hepatitis C - though rates as high as 90% have been seen in some groups of injecting drug users. But the burden of disease and utilization of health care by co-infected patients has not been well studied.” [truncated]

Nevada to serve as pilot state for injection safety

<http://www.lasvegassun.com/news/2009/feb/10/nevada-serve-pilot-state-injection-safety/>

“A hepatitis C outbreak in Las Vegas last year led to the discovery of a troubling lack of infection control standards in outpatient clinics nationwide. Now Nevada will be the pilot site for a national program to educate medical providers and patients about proper injection procedures. Sen. Harry Reid and Rep. Shelley Berkley will announce the initiative to promote injection safety Wednesday in Washington. The goal of the "One and Only" campaign is to prevent syringes from being reused -- a dangerous practice that can spread infectious disease.” [truncated]

Infectious diseases kill 600 in China in January.

http://news.xinhuanet.com/english/2009-02/10/content_10796686.htm

“Infectious diseases killed 603 people in China in January, 600 fewer than the previous month, the Health Ministry said here Tuesday. The mainland recorded four deaths from human bird flu in the month and 20 cases of cholera with no fatalities, it said. AIDS, tuberculosis, rabies, hepatitis B and hepatitis C were the top five killers, causing almost 90 percent of the deaths.” [truncated]

Fundraiser for Smithfield's Kurt Beach

http://www.wavy.com/dpp/news/Local_Smithfield_Kurt_Beach_Fund_Raiser_Liver_Transplant_20080208

“SMITHFIELD, Va. - Filling the belly for a good cause. Sunday hundreds showed their love for a Smithfield Police Officer who is in need of a new liver. Friends held a bar-b-que and turnout out was unexpected. "That gentleman in the white shirt will give you a plate," said one worker. The town Smithfield gathered for a good old fashion picnic. "It's more than we ever imagined," said organizer Sonja Pruitt. They're here not just to eat, but to raise money for someone special. "The town has been so generous," said Tracy James. "He has Hepatitis C and he needs a liver transplant," added Pruitt.” [truncated]

Time to lift the federal ban on syringe exchange: Advocates call on Obama to fulfill campaign pledge

<http://threalitycheck.org/node/9302>

“Domestic prevention advocates and members of Congress are calling on President Obama to fulfill a campaign promise by acting swiftly to lift the federal ban on funding for syringe exchange programs. The ban, which has been in place for some 20 years, prevents federal funds from being used to support a health intervention universally recognized as being highly effective in stopping the spread of HIV and hepatitis C, and as a means for reaching drug users for other interventions. It is another in a long line of ideologically-driven restrictions on basic prevention programs which must be removed in US policy, both domestically and internationally.” [truncated]

Negligence spreads hepatitis C in US

<http://www.presstv.ir/detail.aspx?id=84985§ionid=3510203>

“Hepatitis is a virus that causes inflammation of the liver and produces a variety of symptoms. Over 60,000 people have been exposed and 400 infected with hepatitis C in US due to poor injection practices, a federal report says. Several US officials believe that more US citizens could be exposed to hepatitis whose names have not been registered because either they have not reported or they do not know about their illness. Apparently, a number of health care workers believed that discarding used needles was sufficient to prevent the transmission of deadly blood borne diseases, and continued administering injections with the same syringe barrel, thus enabling the potential for infection transmission. Contaminations involved 33 outbreaks and were mostly caused by violations of simple safety standards.” [truncated]

Beaumont Army Medical Center to provide update on shots inquiry

http://www.elpasotimes.com/health/ci_11640886

“ Officials are to meet Thursday at Beaumont Army Medical Center to discuss the progress of an investigation into the possible exposure of more than 2,000 diabetes patients to infectious diseases such as HIV and hepatitis, according to a center official. As of midday Wednesday, 76 percent of the 2,114 patients who might have been exposed through the improper use of an insulin pen had been

contacted, officials said. Of that number, 71 percent have come in for testing to see whether they have contracted any of the diseases, officials said.” [truncated]

Hepatitis C is killing liver cells

http://www.eurekalert.org/pub_releases/2009-02/uoa-hci020409.php

“It has long been thought that liver disease in hepatitis C patients is caused by the patient's immune system attacking the infected liver, ultimately killing the cells. University of Alberta researchers have discovered something different though. Michael Joyce and his team transplanted human liver cells into mice, which lack an adaptive immune system. The researchers then infected the liver cells with the hepatitis C virus. The researchers found that the virus itself damages liver cells and leads to liver cell death. They also found hepatitis C causes inflammation, which is the second step in liver disease. Joyce's finding sheds new light on the virus and gives researchers more targets for therapy.” [truncated]

Local organizations meeting AIDS pandemic head on

<http://www.lawattstimes.com/component/content/article/52-featured/404-local-organizations-meeting-aids-pandemic-head-on.html>

“Laquisha began using drugs and having unprotected sex when she was 15. When she turned 16, she was diagnosed with full-blown AIDS. “At that time in my life, I just didn’t care,” Laquisha said in a testimonial provided to the L.A. Watts Times, not providing her real name. “In the beginning my boyfriend and I didn’t use condoms. I contracted Hepatitis C.” Laquisha soon became homeless, and with no safe place to live the streets became her home, where she did anything to earn money to support her habit. “I ... did all kinds of things to make money for my drugs,” she said. “Often times what I was doing wasn’t safe.” Almost dead from AIDS, Laquisha finally started turning her life around. Now, five years later, she is clean and sober and successfully living with AIDS.” [truncated]

Grant funds liver cancer research

<http://www.press-citizen.com/article/20090204/NEWS01/902040340/1079>

“A University of Iowa assistant research scientist in internal medicine is leading a study funded by a \$30,000 American Cancer Society seed grant through Holden Comprehensive Cancer Center at UI. Dr. Zhaowen Zhu's team will study whether and how three hepatitis C proteins increase the activity of telomerase as a possible explanation for how hepatitis C causes cancer. Hepatitis C affects about four million Americans and causes liver cirrhosis. In some patients with this type of cirrhosis, liver cancer may develop, but how this happens is not clear. Telomerase is an enzyme that promotes the longevity of most cells, including liver cells, and has been associated with the development of cancer.” [truncated]

Experts raise concerns over unsuspected hepatitis C

<http://www.smartbrief.com/news/aabb/storyDetails.jsp?issueid=8B102030-2BDF-4AC0-B96F-2A146D48F3A8©id=66F2B5DF-27D8-418A-A1EF-9A3A7D3D704C>

“An estimated 100,000 people in England are unsuspecting carriers of hepatitis C, according to a British health officer. Experts agree that there is a need for increased public awareness to dispel the myths surrounding hepatitis C and remove the social stigma that comes with the disease.” [truncated]

New York urges testing for possible exposure to HIV

<http://www.emaxhealth.com/2/53/29010/new-york-urges-testing-possible-exposure-hiv.html>

“The New York State Health Department is urging anyone who has had sexual contact with Nassau County resident Robert Musmacker, who has told authorities he is infected with HIV, to be tested for HIV, other sexually transmitted diseases, Hepatitis B and Hepatitis C as soon as possible. Additionally, anyone who has had sexual contact with other persons who may have had sexual contact with Mr. Musmacker should also be tested.” [truncated]

Eleven patients infected with hepatitis C in Bulgarian Hospital

http://www.novinite.com/view_news.php?id=101583

“11 patients were infected with Hepatitis C in the hospital in Bulgaria's Teteven. Eleven patients have been infected with Hepatitis C in the Municipal Hospital in the Bulgarian town of Teteven, Bulgarian National Television reported Friday. The intra-hospital infection most likely resulted from the use of one and the same syringe for arterial transfusion due to negligence on part of the hospital staff, according to Dr. Madlena Boyadzhieva, manager of the hospital.” [truncated]

Eiger BioPharmaceuticals Raises \$7.1 Million 'A' Round

<http://sev.prnewswire.com/health-care-hospitals/20090224/AQTU00624022009-1.html>

Funding to advance novel hepatitis C virus (HCV) therapies against new targets

“Eiger BioPharmaceuticals, Inc., a start-up biotechnology company developing antiviral therapies, announced that it has raised \$7.1 million in a Series A financing co-led by InterWest Partners and Vivo Ventures. The two firms were instrumental in the formation of the company and recruitment of its team and are represented on the board of directors by general partners Nina Kjellson and Dr. Edgar Engelman, respectively. The funding will advance the company's lead program targeted against NS4B, a specific region in the hepatitis C virus (HCV) protein, as well as progress lead identification for other proprietary targets.” [truncated]

Martin County fire-rescue mourns firefighter's death firefighter dies from disease contracted while on duty

<http://www.wpbfl.com/news/18806943/detail.html>

MARTIN COUNTY, Fla. – “The Martin County Fire-Rescue Division is mourning the loss of one of its own. Fred Pierno Jr. died Wednesday at his Port Saint Lucie home due to an illness he contracted on the job. He is the first firefighter to die in the line of duty in the history of the agency. Pierno has been under medical treatment since October 2006 for a Hepatitis C Virus infection he sustained while performing his firefighter duties. He's the 13th firefighter in the United States and the seventh in Florida to be classified as a line of duty death due to a hepatitis infection.” [truncated]

Canadian nurse honored for work with hepatitis C patients

<http://www.smartbrief.com/news/ana/storyDetails.jsp?issueid=A95010D8-AC2D-42F1-A985-761D12F738D1©id=65212C8D-ADFC-4FF0-B731-438501610A83>

“The Canadian Association of Hepatology Nurses is honoring Fran Falconer with its clinical practice award for her 14 years of helping hepatitis C patients. Falconer says she became an advocate for hepatitis C patients when she saw an increase in the number of people seeking treatment for it and the fear and stigma associated with the disease. She continues to work to dispel myths and misconceptions about hepatitis C.” [truncated]

Alcohol, hepatitis C: Dangerous cocktail

http://insciences.org/article.php?article_id=2807

“Patients infected by the virus can develop liver cancer if they drink too much liquor, Keck School researchers find. A new study led by researchers at the Keck School of Medicine of USC found that drinking alcohol greatly increases the chances that a patient infected by the hepatitis C virus will develop a common type of liver cancer.” [truncated]

Infected blood tragedies

<http://www.walesonline.co.uk/news/welsh-politics/welsh-politics-news/2009/02/24/infected-blood-tragedies-91466-22993573/>

“Failures at the heart of Government led to thousands of patients being infected with HIV and Hepatitis C from tainted blood, an independent inquiry concluded yesterday. The Archer inquiry described the scandal as an “horrific human tragedy”, and said public health authorities had been “lethargic” in the 1970s and 1980s. It is estimated 4,670 haemophiliacs – who need regular blood transfusions – became infected with hepatitis C, and 1,243 contracted HIV. Some 1,800 are thought to have died.

The problems date from a 1975 decision to delay making the UK self-sufficient in blood products. But heat treatment of the blood to reduce the chances of infection was only introduced in 1985. During that period the NHS bought blood from US suppliers who used “Skid Row” donors, such as prison inmates, more likely to have HIV and Hepatitis C. The report said: “It is difficult to avoid the conclusion that commercial interests took precedence over public health concerns.” [truncated]

Japan's Toray testing altered interferon for hepatitis C virus

<http://www.tradingmarkets.com/.site/news/Stock%20News/2193625/>

“Toray Industries Inc. and a research team from the University of Tokyo have begun clinical trials on a modified form of interferon beta for treatment of hepatitis C. This version of interferon beta is stabilized with PEG in a targeted manner to cloak the compound from the immune system. In tests using rabbits, unmodified interferon beta was eradicated from the blood in just a day, whereas Toray's PEG-modified interferon beta remained for six days. This suggests it might be possible to treat hepatitis C with weekly subcutaneous injections. Tests in monkeys, mice and cultured human cells have confirmed the compound's safety, durability, and ability to inhibit the proliferation of the hepatitis C virus.” [truncated]

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

The effect of angiotensin-blocking agents on liver fibrosis in patients with hepatitis C.

Corey KE, Shah N, Misraji J, et al. Liver Int. 2009 Feb 6. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19220742?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

ABSTRACT BACKGROUND: Multiple studies implicate the renin-angiotensin system in hepatic fibrogenesis. Few studies have examined the effects of angiotensin blockade on liver fibrosis via human histology. **AIMS:** We studied the histological effect of angiotensin II blocking agents in chronic hepatitis C patients. **METHODS:** This was a retrospective study of 284 chronic hepatitis C patients from 2001 to 2006 who underwent a liver biopsy. Group I was comprised of 143 hypertensive patients who received angiotensin-blocking agents. Group II was comprised of 91

hypertensive subjects who received hypertensive agents other than angiotensin blockers. Group III was comprised of 50 non-hypertensive subjects. **RESULTS:** The groups were similar in age, sex, hepatitis C genotype, viral load and disease duration. They varied significantly in total diabetic patients (Group I, 43; Group II, 10; Group III, 1; $P=0.0001$), consistent with recommended use of angiotensin-converting enzyme inhibitors in hypertensive diabetics. Non-hypertensive patients had significantly less fibrosis than hypertensive patients, regardless of antihypertensive medications (Group I, 3.20; Group II, 3.73; Group III, 2.5; $P=0.0002$). Group I had significantly less fibrosis than Group II ($P=0.02$). This finding persisted in a non-diabetic subgroup of Groups I and II (Group I, 3.07; Group II, 3.69; $P=0.0129$). **CONCLUSION:** Patients with hepatitis C and hypertension have increased fibrosis compared with non-hypertensive patients. Hypertensive patients receiving angiotensin-blocking agents had less fibrosis than hypertensive patients who did not receive angiotensin-blocking agents. This suggests an association with hypertension, possibly via the renin-angiotensin system in the fibrosis development and suggests a beneficial role of angiotensin II blockade in hepatitis C virus-related fibrosis.

Low weight predicts neutropenia and peginterferon alfa-2a dose reductions during treatment for chronic hepatitis C. Rotman Y, Katz L, Cohen M, et al. J Viral Hepat. 2009 Feb 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19220735?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Summary: Treatment-induced neutropenia frequently complicates the treatment course of patients treated with pegylated interferon alfa and ribavirin for chronic hepatitis C. We investigated the effect of weight on the risk for dose reductions caused by neutropenia in patients treated with a weight-independent dose of peginterferon alfa-2a. We retrospectively analysed single centre data for 172 patients enrolled in a multi-centre, open-label trial of peginterferon alfa-2a and ribavirin for chronic hepatitis C. Low body weight was significantly associated with dose reductions due to neutropenia. Patients weighing less than 62 kg had a 35% risk for significant neutropenia as opposed to a 12% risk for heavier patients ($P = 0.001$), and this side-effect occurred earlier during treatment. Low weight was an independent risk factor by multivariate analysis (hazard ratio 0.956/kg). The risk for treatment-induced neutropenia was associated with body surface area more than with the body mass index. **In conclusion**, a low pre-treatment weight strongly predicts the need for peginterferon alfa-2a dose reductions. This apparently reflects overall body size more than body fat content. It is prudent to frequently monitor blood counts for smaller-sized patients, especially during the first weeks of treatment.

Natural course of treated and untreated chronic HCV infection: results of the nationwide Hepnet.Greece cohort study. Manesis EK, Papatheodoridis GV, Touloumi G, et al. Aliment Pharmacol Ther. 2009 Feb 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19222410?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY BACKGROUND-AIMS: Data from the HEPNET.GREECE study were analyzed to investigate the natural course of interferon(IFNa)-based -treated and -untreated patients with chronic hepatitis C (CHC). **METHODS:** We retrospectively analyzed 1738 patients from 25 Greek Centers (median age 40.1; males 57.6%; cirrhosis 9.2%), 734 untreated and 993 treated with IFNa-based regimens (44.7% SVR), followed for median 25.2 and 46.8 months, respectively. **RESULTS:** During follow-up, 48 patients developed liver decompensation and 24 HCC. Older age was significantly related to disease progression (HR=2.6 per 10 years of increasing age). Stratified by baseline cirrhosis Cox analysis showed that patients with SVR, but not without, had significantly

lower hazard for events compared to non-treated patients (HR=0.16; P<0.001), whereas the detrimental effect of older age remained highly significant. Separate group analysis demonstrated that in cirrhosis the beneficial effect of treatment was evident even without SVR. Treatment effect interacted significantly with age, indicating that older patients, mainly non-cirrhotic, gained the most benefit. **CONCLUSIONS:** IFNa-based treatment does alter the natural course of CHC. A protective effect is mostly present in patients with SVR, but older patients, at higher risk of events, gain the greatest benefit. In established cirrhosis treatment carries a protective effect even among those without SVR.

Impact of early viral kinetics on pegylated interferon alpha 2b plus ribavirin therapy in Japanese patients with genotype 2 chronic hepatitis C. Nomura H, Miyagi Y, Tanimoto H, Ishibashi H. *J Viral Hepat.* 2009 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19222743?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: The recommended therapy for genotype-2 chronic hepatitis C is a regimen of pegylated interferon alpha (peginterferon) plus ribavirin. This study was conducted to determine the value of early viral kinetics as a predictive factor for sustained virologic responder (SVR). Peginterferon alpha 2b (1.5 mug/kg/week) plus weight-based ribavirin (600-1000 mg/day) was administered to 51 patients with chronic HCV genotype 2 for 24 weeks. The HCV-RNA loads were measured at the baseline, hour 24, and week 1. The rebound index (RI, an index obtained from the viral load of week 1 divided by that of hour 24) was calculated. Compared with the baseline, the viral load at hour 24 for SVR was reduced by more than 1-log: it continued to decline thereafter, and at week 1 it was significantly lower than at hour 24 (P < 0.05). The viral load for non-SVR increased again between hour 24 and week 1. The SVR of patients with RI <=1.0 was 100% (39/39). The SVR conversion for rapid virologic responders was 92% (35/38). The RI (<=1.0) was the only significant independent factor for SVR by multiple logistic regression analysis and is the first predictive factor in 24-week peginterferon plus ribavirin therapy for patients infected with genotype 2.

Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. Grebely J, Raffa JD, Lai C, et al. *J Viral Hepat.* 2009 Feb 17. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19226330?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: Despite the availability of effective therapy for hepatitis C virus (HCV) infection, there are little data on the uptake of treatment. We evaluated factors associated with HCV infection and the uptake of HCV treatment in a large community-based inner city cohort in Vancouver, Canada. The Community Health and Safety Evaluation is a cohort study of inner city residents recruited from January 2003 to June 2004. HIV and HCV status and information on prescriptions for HCV treatment were determined through linkage with provincial databases. HCV prevalence was calculated and factors associated with HCV infection were identified. HCV treatment uptake and incidence of HCV infection from January 2000 to December 2004 were expressed in terms of person-years of observation. Among 2913 individuals, HCV antibody testing was performed in 2118 and the HCV seroprevalence was 64.2% (1360 of 2118). In total, 1.1% of HCV antibody-positive individuals (15 of 1360) initiated treatment for HCV infection from January 2000 to December 2004 [0.28 cases per 100 person-years (95% CI, 0.15-0.46)]. Three of 15 (20.0%) treated individuals achieved a sustained virological response. During the same period, the incidence of HCV infection was 7.26 cases (95% CI, 5.72-8.80) per 100 person-years. Overall, the rate of new HCV

seroconversions in this cohort in the study period was about 25 times the rate of HCV treatment uptake. There are extremely low rates of HCV treatment initiation and very limited effectiveness, despite a high prevalence of HCV infection in this large community-based cohort of inner city residents with access to universal healthcare.

Occult hepatitis B virus infection increases hepatocellular carcinogenesis by eight times in patients with non-B, non-C liver cirrhosis: a cohort study. Ikeda K, Kobayashi M, Someya T, et al. *J Viral Hepat.* 2009 Feb 13. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19226331?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: An impact of serum hepatitis B virus (HBV) DNA on hepatocarcinogenesis has not been investigated in a cohort of patients with non-B, non-C cirrhosis. Eighty-two consecutive Japanese patients with cirrhosis, who showed negative hepatitis B surface antigen and negative anti-hepatitis C virus, were observed for a median of 5.8 years. Hepatitis B virus core (HBc) region and HBx region were assayed with nested polymerase chain reaction. Both of HBc and HBx DNA were positive in 9 patients (11.0%) and both were negative in 73. Carcinogenesis rates in the whole patients were 13.5% at the end of the 5th year and 24.6% at the 10th year. The carcinogenesis rates in the patients with positive DNA group and negative DNA group were 27.0% and 11.8% at the end of the 5th year, and 100% and 17.6% at the 10th year, respectively ($P = 0.0078$). Multivariate analysis showed that men ($P = 0.04$), presence of HBc and HBx DNA (hazard ratio: 8.25, $P = 0.003$), less total alcohol intake ($P = 0.010$), older age ($P = 0.010$), and association of diabetes ($P = 0.005$) were independently associated with hepatocellular carcinogenesis. Existence of serum HBV DNA predicted a high hepatocellular carcinogenesis rate in a cohort of patients with non-B, non-C cirrhosis.

Course of oral lichen planus: a retrospective study of 808 northern Italian patients. Carbone M, Arduino P, Carrozzo M, et al. *Oral Dis.* 2009 Feb 13. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19222766?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: To undertake a retrospective inspection of the general features, clinical presentation and outcome of 808 Italian patients with oral lichen planus (OLP), followed up from 6 months to 17 years. **RESULTS:** The mean age was 61 years for women ($n = 493$) and 58 years for men ($n = 315$). More than 20% of the total cases had liver abnormalities ($n = 164$) of which 83.5% infected with hepatitis C virus ($n = 137$). The reticular and plaque form were the predominant type, affecting almost 60% of patients. 12.3% of patients had also extraoral manifestation, taking into account the skin ($n = 63$) and genital ($n = 24$). Symptoms were present in 40% of the total patients. Only less than 2.47% of patients underwent remission, whereas 78% still had oral lesions at the end of the follow-up period. Treatment was directed towards almost 42% of the patients, mainly using topical corticosteroids. Oral squamous cell carcinoma developed in 15 patients, commonly arising on the lateral border of the tongue. **CONCLUSION:** This is one of the largest groups of OLP patients with such long a follow-up ever reported. We confirm the chronic nature of this disorder, rarely remissive and the treatment intend for alleviating symptoms. OLP is established to be a disease with small frequency of malignant transformation.

Use of supervised injection facilities and injection risk behaviours among young drug injectors. Bravo MJ, Royuela L, De la Fuente L, et al. *Addiction*. 2009 Feb 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19215603?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIMS: To study the use of supervised injection facilities (SIFs) as a predictor of safer injecting practices. Design Cross-sectional study conducted with face-to-face interview using a structured questionnaire with computer-assisted personal interviewing. Dried blood spot samples were collected for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) antibody testing.

SETTING: All participants were street-recruited by chain referral methods in Madrid and Barcelona. Participants A total of 249 young heroin drug injectors recruited by the ITINERE cohort study in two Spanish cities with SIFs. Measurements The main outcome measures were self-reported injecting behaviors and SIFs attendance. **RESULTS:** SIF users were more marginalized socially than non-users. They were also more often regular injectors (weekly or more versus sporadic) [odds ratio (OR) = 4.9, 95% confidence interval (CI): 2.7-8.8], speedball users (OR = 2.5, 95% CI: 1.5-4.3) and anti-HCV-positive (OR = 3.1, 95% CI: 1.4-7.1). In the logistic regression analysis, using SIFs was associated independently with not borrowing used syringes (OR = 3.3, 95% CI: 1.4-7.7). However, no significant association was found between SIF use and not sharing injection equipment indirectly (OR = 1.1, 95% CI: 0.5-2.2). **CONCLUSIONS:** SIFs attract highly disadvantaged drug injectors who engage none the less in less borrowing of used syringes than non-users of these facilities. The risks of indirect sharing should be emphasized when counseling SIF attendees.

Bacterial infection and neutropenia during peginterferon plus ribavirin combination therapy in patients with chronic hepatitis C with and without baseline neutropenia in clinical practice. Yang JF, Hsieh MY, Hou NJ, et al. *Aliment Pharmacol Ther*. 2009 Feb 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19210290?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Peginterferon-alpha-based therapy frequently leads to neutropenia. It is unclear whether neutropenia is associated with bacterial infection in chronic hepatitis C (CHC). Aim:

Evaluate the risk of bacterial infection and neutropenia in patients with CHC treated with peginterferon-alpha/ribavirin. **METHODS:** 207 patients with CHC with (group A, n=30) and without (group B, n=177) baseline neutropenia treated with peginterferon-alpha/ribavirin.

RESULTS: Group A had significantly higher rates of moderate (<750 cells/ μ L) and severe (<500 cells/ μ L) neutropenia than group B (70.0% and 26.7% vs. 20.3% and 8.5%, respectively, both $P < 0.0001$). The sustained virologic response rate was similar between patients with and without neutropenia, at baseline or during treatment. Bacterial infection occurred in 4.3% of patients. Group A and patients with lower baseline neutrophil counts had substantially higher rates of bacterial infection. Patients with cirrhosis had significantly higher rates of infection during combination therapy than those without cirrhosis (15%, 3 of 20 vs. 3.2%, 6 of 187, $P = 0.045$). Nadir neutrophil counts were not correlated to infection episodes. **CONCLUSIONS:** Bacterial infection during peginterferon-based therapy for CHC was associated with comorbidity of cirrhosis, but not with neutropenia, whether at baseline or during treatment. Neutropenic CHC patients might be treated safely with close monitoring.

Effects of combined interferon alpha and ribavirin therapy on thyroid functions in patients with chronic hepatitis C. Nadeem A, Aslam M, Khan DA, Hussain T, Khan SA. J Coll Physicians Surg Pak. 2009 Feb;19(2):86-9.

http://www.ncbi.nlm.nih.gov/pubmed/19208310?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To determine the frequency of thyroid dysfunction in patients of chronic hepatitis C during treatment with interferon alpha-2b and ribavirin therapy. Study Design: A cohort study. Place and Duration of Study: Army Medical College and Military Hospital, Rawalpindi, from February 2006 to January 2007. **METHODOLOGY:** One hundred and sixty seven non-cirrhotic chronic hepatitis C patients were grouped into treatment group (n=107) and control group (n=60) awaiting treatment. Baseline serum(s) Alanine Transferase (ALT) and S. Aspartate Transferase (AST) were measured by IFCC method. Serum Thyroid Stimulating Hormone (S. TSH), serum free thyroxine (S. Free T4) and serum total triiodothyronine (S.T3) level were determined by chemiluminescence. Study group patients underwent 24 weeks IFN and ribavirin therapy and were followed-up for thyroid dysfunction at weeks 0, 12 and 24. Control group patients underwent the same tests at weeks 0, 12 and 24. Statistical analysis was done on SPSS 15. **RESULTS:** Out of 107 patients of treatment group, 20 patients (18.69%) developed thyroid dysfunction. Females were at higher risk with Relative Risk (RR) of 11.25 and Attributable Risk (AR) of 91%. Hypothyroidism was more common than hyperthyroidism. **CONCLUSION:** Interferon-alpha and ribavirin therapy induces thyroid dysfunction in chronic hepatitis C patients. Hypothyroidism was more common. Females are at a higher risk of developing thyroid dysfunction.

Evaluation of newly developed combination therapy of intra-arterial 5-fluorouracil and systemic pegylated interferon alpha-2b for advanced hepatocellular carcinoma with portal venous invasion: preliminary results. Kasai K, Kuroda H, Ushio A, et al. Hepatol Res. 2009 Feb;39(2):117-25.

http://www.ncbi.nlm.nih.gov/pubmed/19208032?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIM: Prognosis is extremely poor for advanced hepatocellular carcinoma (HCC) in patients with portal invasion. The present study evaluated the efficacy of combined intra-arterial 5-fluorouracil (5-FU) and systemic pegylated interferon (PEG-IFN)alpha-2b in patients with advanced HCC.

METHODS: The subjects comprised nine HCC patients with portal vein thrombosis treated using subcutaneous administration of PEG-IFNalpha-2b (50-100 microg on day 1 of every week, for 4 weeks) and intra-arterial infusion of 5-FU (250 mg/day for 5 h on days 1-5 of every week, for 4 weeks). For four patients with hepatitis C virus (HCV) infection, oral administration of ribavirin (400-800 mg/day) was added. At the end of every cycle, response to therapy was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. **RESULTS:** Partial response (PR) was observed in seven of nine patients, with stable or progressive disease in the remaining two patients. Tumors were resectable in three patients displaying PR after treatment. Tumor markers decreased significantly after therapy. Serum HCV-RNA titers were markedly decreased and became undetectable in all patients with HCV infection. National Cancer Institute-Common Toxicity Criteria: version 3.0 (NCI-CTC) grade 3 thrombocytopenia was seen in one case at the end of treatment, but was resolved with cessation of treatment. Other adverse effects were manageable.

CONCLUSION: Combination therapy with intra-arterial 5-FU and systemic PEG-IFNalpha-2b may be useful as a palliative treatment for patients with advanced HCC. A prospective controlled trial using a larger population of patients with advanced HCC is needed to evaluate this new combination therapy.

Association of genetic polymorphisms with interferon-induced haematologic adverse effects in chronic hepatitis C patients. Wada M, Marusawa H, Yamada R, et al. *Viral Hepat.* 2009 Feb 5. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19200137?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Interferon (IFN)-based combination therapy with ribavirin has become the gold standard for the treatment of chronic hepatitis C virus infection. Haematologic toxicities, such as neutropenia, thrombocytopenia, and anaemia, however, frequently cause poor treatment tolerance, resulting in poor therapeutic efficacy. The aim of this study was to identify host genetic polymorphisms associated with the efficacy or haematologic toxicity of IFN-based combination therapy in chronic hepatitis C patients. We performed comprehensive single nucleotide polymorphism detection in all exonic regions of the 12 genes involved in the IFN signalling pathway in 32 healthy Japanese volunteers. Of 167 identified polymorphisms, 35 were genotyped and tested for an association with the efficacy or toxicity of IFN plus ribavirin therapy in 240 chronic hepatitis C patients. Multiple logistic regression analysis revealed that low viral load, viral genotypes 2 and 3, and a lower degree of liver fibrosis, but none of the genetic polymorphisms, were significantly associated with a sustained virologic response. In contrast to efficacy, multiple linear regression analyses demonstrated that two polymorphisms (IFNAR1 10848-A/G and STAT2 4757-G/T) were significantly associated with IFN-induced neutropenia ($P = 0.013$ and $P = 0.011$, respectively). Thrombocytopenia was associated with the IRF7 789-G/A ($P = 0.031$). In conclusion, genetic polymorphisms in IFN signalling pathway-related genes were associated with IFN-induced neutropenia and thrombocytopenia in chronic hepatitis C patients. In contrast to toxicity, the efficacy of IFN-based therapy was largely dependent on viral factors and degree of liver fibrosis.

Mutations in the interferon sensitivity-determining region of hepatitis C virus genotype 2a correlate with response to pegylated-interferon-alpha 2a monotherapy. Hayashi K, Katano Y, Honda T, et al. *J Med Virol.* 2009 Mar;81(3):459-66

http://www.ncbi.nlm.nih.gov/pubmed/19152412?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The interferon sensitivity-determining region (ISDR) is thought to be inhibited by the double-stranded RNA-dependent protein kinase (PKR). Several studies have reported a relationship between the ISDR and interferon (IFN) responsiveness. However, this relationship is controversial. The aim of this study was to investigate whether genomic heterogeneity of the ISDR among patients with hepatitis C virus (HCV) genotype 2a affects the response to pegylated-IFN-alpha 2a monotherapy. Eighty patients (47 men, 33 women; mean age: 54.2 +/- 12.9 years) infected with HCV genotype 2a were evaluated. HCV viral loads were determined by real-time PCR. The ISDR (amino acids 2193-2228) was examined by direct sequencing. Thirty-one patients received subcutaneous injections of pegylated-IFN-alpha 2a (180 microg) once weekly for 24 weeks, and 35 patients received injections for 48 weeks. Fourteen patients withdrew from treatment. Of the remaining 66 patients, 51 (77.3%) showed a sustained virologic response. Factors related to sustained virologic response on multivariate analysis were rapid virologic response (negative HCV at 4 weeks; odds ratio: 0.033; 95% confidence interval (95% CI) 0.003-0.363; $P = 0.0052$) and the number of mutations in the ISDR (odds ratio: 0.025; 95% CI 0.001-0.476; $P = 0.0141$). There were no significant differences in other factors, including sex, age, aspartate aminotransferase, alanine aminotransferase, platelet count, duration of treatment, and HCV viral load. Rapid virologic response and the ISDR sequence variations are significantly associated with response to pegylated-IFN-alpha 2a monotherapy in Japanese patients with HCV genotype 2a.

A matched case-controlled study of 48 and 72 weeks of peginterferon plus ribavirin combination therapy in patients infected with HCV genotype 1b in Japan: amino acid substitutions in HCV core region as predictor of sustained virological response.

Akuta N, Suzuki F, Hirakawa M, et al. *J Med Virol.* 2009 Mar;81(3):452-8.

http://www.ncbi.nlm.nih.gov/pubmed/19152407?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Substitution of amino acid (aa) 70 and 91 in the core region of HCV genotype 1b is a useful pretreatment predictor of efficacy of 48-week peginterferon (PEG-IFN) plus ribavirin (RBV) therapy. Here, we determined the efficacy of 72-week PEG-IFN/RBV and the predictive factors to such therapy in a case-control study matched for sex, age, and periods from the start of treatment to initial point of HCV RNA-negative. We compared the treatment efficacy of 72-week regimen in 65 patients with that of 48-week in 130 patients, who were infected with HCV genotype 1b and treated with PEG-IFN/RBV. They consisted mainly of late virological responders (LVR) (HCV RNA-positive at 12 weeks and negative at 24 weeks after start of treatment). Sustained virological response (SVR) was achieved by 61.5% and 32.3% of patients of the 72- and 48-week groups, respectively, while non-virological response was noted in 9.2% and 29.2% of the respective groups. Multivariate analysis identified substitution of aa 70 and 91 (Arg70 and/or Leu91) and duration of treatment (72-week) as independent parameters that significantly influenced SVR. For Arg70 and/or Leu91 of core region, SVR rate was significantly higher in 72- (68.0%) than 48-week group (37.8%). For wild-type of ISDR, SVR rate was significantly higher in 72- (61.2%) than in 48-week group (29.3%). We conclude that 72-week PEG-IFN/RBV improves SVR rate for LVR, especially those with Arg70 and/or Leu91 of core region or wild-type of ISDR. Substitution of aa 70 and 91 is also a useful pretreatment predictor of response to 72-week PEG-IFN/RBV. Copyright 2009 Wiley-Liss, Inc.

Long-term follow-up of patients with hepatitis C with a normal alanine aminotransferase.

Kumada T, Toyoda H, Kiriya S, et al. *J Med Virol.* 2009 Mar;81(3):446-51

http://www.ncbi.nlm.nih.gov/pubmed/19152400?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

An attempt was made to identify factors influencing the cumulative probability of an increased alanine aminotransferase (ALT) level and hepatocarcinogenesis in hepatitis C patients with a normal ALT level initially. A total of 398 consecutive patients with a normal ALT level initially for 6 months or more and follow-up period longer than 3 years during the period January 1995 to December 2004 were included. Patients were classified by ALT level into three groups: Group A (3-20 IU/L), Group B (21-30 IU/L), and Group C (31-35 IU/L). Factors associated with the cumulative probability of increased ALT level and hepatocarcinogenesis were evaluated. Women in groups B and C and men in Group C showed high cumulative probabilities of increased ALT levels. Factors associated with increased ALT were a high ALT level (Group B, relative risk; 1.758 [95% confidence interval: 1.290-2.392], $P < 0.001$, Group C, 3.328 [2.256-4.909], $P < 0.001$), high lactate dehydrogenase level (2.352 [1.445-3.829], $P = 0.001$), or low total cholesterol level (1.957 [1.330-2.882], $P = 0.001$). Factors associated with incidence of hepatocellular carcinoma were increased age (3.088 [1.025-9.308], $P = 0.045$), high ALT level (Group C, 5.803 [1.530-22.066], $P = 0.010$), and high total bilirubin level (8.309 [2.235-30.888], $P = 0.002$). In patients with hepatitis C with a normal ALT level initially, an ALT level of 21-35 IU/L is a risk factor for an increased ALT level and hepatocarcinogenesis.

Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. Mangia A, Minerva N, Bacca D, et al. *Hepatology*. 2009 Feb;49(2):358-63

http://www.ncbi.nlm.nih.gov/pubmed/19072829?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

In hepatitis C virus (HCV) genotypes 2 and 3 patients, the high rate of relapse after 12 to 16 weeks of antiviral therapy is the main concern for shortening treatment duration. This study was undertaken to delineate predictors of relapse after short treatment in patients with undetectable HCV RNA at treatment week 4 (RVR), and to report in RVR patients with relapse the sustained virological response (SVR) after a second 24-week course of therapy. RVR patients received pegylated interferon (Peg-IFN) alfa-2b (1.5 microg/kg) and ribavirin (1000-1200 mg/day) for 12 weeks; those who relapsed were re-treated with the same drug doses but for the extended standard duration of 24 weeks. Logistic regression analysis was applied to delineate predictors of relapse by using age, sex, route of transmission, body mass index (BMI), serum alanine aminotransferase (ALT), HCV genotypes, serum HCV RNA levels, and platelet counts as covariates. Of 718 patients with genotypes 2 and 3 who were started on therapy, 496 (69.1%) had undetectable HCV RNA at week 4. Of them, 409 patients (82.5%, CI 79.1-85.8) attained SVR, and 67 (14.1%, CI 10.4-16.5) relapsed. At regression analysis, only platelet count less than 140,000 mm³ [odds ratio, 2.51; confidence interval (CI), 1.49-4.20] and BMI 30 or higher (odds ratio, 1.7; CI, 1.03-2.70) were independently associated with relapse. Forty-three of 67 patients with relapse agreed to be re-treated, and an SVR was achieved in 30 (70.0%) of them. **CONCLUSION:** We recommend 12 weeks course of therapy for patients with undetectable HCV RNA at treatment week 4, providing they present with no advanced fibrosis and low BMI.

Treatment of hepatitis C infection for current or former substance abusers in a community setting. John-Baptiste A, Varenbut M, Lingley M, et al. *J Viral Hepat*. 2009 Feb 23. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22John-Baptiste%20A%22\[Author\]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22John-Baptiste%20A%22[Author]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract)

Substance abusers account for the largest number of hepatitis C infected cases in developed countries. We describe a care model for treating current or former substance abusers with antiviral therapy for hepatitis C virus (HCV) infection. The care model involved hepatitis nurses, a psychologist, infectious disease specialist and primary care physicians. Clients met selection criteria including regular attendance at clinic appointments and social stability. Use of alcohol and illicit substances was monitored with urine toxicology screens. The association between substance use, rates of completion of therapy and rates of response were assessed using multivariable regression analyses. A total of 109 clients (75 with genotype 1/4 and 34 with genotype 2/3) received at least one injection with pegylated interferon between November 2002 and January 2006. Treatment completion rates of 61 and 74% were achieved for genotypes 1/4 and 2/3, respectively. Treatment response rates in an intention to treat analysis were 51% for genotypes 1/4 and 68% for genotypes 2/3. A positive urine toxicology screen indicating use of illicit substances 6 months prior to initiating therapy was significantly associated with lower rates of treatment completion but not lower rates of sustained virological response. A positive urine screen indicating use of alcohol prior to therapy was significantly associated with lower rates of completion and lower rates of response. Rates of completion and response are comparable to non-substance abusing populations. Antiviral therapy for HCV infection can be successful within the context of ongoing care for substance abuse for carefully selected patients.

Never injected, but hepatitis C virus-infected: a study among self-declared never-injecting drug users from the Amsterdam Cohort Studies. van den Berg CH, van de Laar TJ, Kok A, et al. J Viral Hepat. 2009 Feb 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19243497?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The aim of this study was to gain insight in transmission routes of hepatitis C virus (HCV) infection among never-injecting drug users (DU) by studying, incidence, prevalence, determinants and molecular epidemiology of HCV infection. From the Amsterdam Cohort Studies among DU, 352 never-injecting DU were longitudinally tested for HCV antibodies. Logistic regression was used to identify factors associated with antibody prevalence. Part of HCV NS5B was sequenced to determine HCV genotype and for phylogenetic analyses, in which sequences were compared with those from injecting DU. HCV antibody prevalence was 6.3% and HCV incidence was 0.49/1000 PY. HIV-positive status, female sex and starting injection drug use during follow-up (a putative marker of past injection drug use), were independently associated with HCV prevalence. The main genotypes found were genotype 3a (50%) and 1a (30%). Phylogenetic analysis revealed that HCV strains in never-injecting DU did not cluster together and did not differ from HCV strains circulating in injecting DU. We found a higher HCV prevalence in never-injecting DU than in the general population. Phylogenetic analysis shows a strong link with the injecting DU population. The increased risk could be related to underreporting of injecting drug use or to household or sexual transmission from injectors to noninjectors. **Our findings** stress the need for HCV testing of DU who report never injecting, especially given the potential to treat HCV infection effectively.

Outcome of retinopathy in chronic hepatitis C patients treated with peginterferon and ribavirin. Mehta N, Murthy UK, Kaul V, et al. Dig Dis Sci. 2009 Feb 26. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19242801?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The purpose of this study is to evaluate the incidence and outcome of retinopathy in chronic hepatitis C patients treated with peginterferon and ribavirin. A total of 74 hepatitis C patients with baseline eye exams and eye exams during therapy were included. Retinopathy was defined as development of cotton wool spots and/or intra-retinal hemorrhage. Demographics, hepatitis C viral characteristics, treatment and laboratory data, and eye exam findings were compared in groups with and without retinopathy. Retinopathy developed in 28 (38%), early in therapy. Pre-treatment eye exams did not predict risk of retinopathy. Therapy was continued in all but one; cotton wool spots resolved in 24 of 26. All nine patients with intra-retinal hemorrhage had resolution. No patient had retinopathy-related visual deterioration. Retinopathy is common with peginterferon therapy, but the outcome is favorable. Cessation of therapy for retinopathy is not warranted. Severe visual disturbances and scotomas deserve further evaluation.

Coronary artery disease in patients with liver cirrhosis. Kalaitzakis E, Rosengren A, Skommevik T, Björnsson E. Dig Dis Sci. 2009 Feb 26. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19242795?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: The prevalence of coronary artery disease (CAD) has been reported to be low in patients with liver cirrhosis. Previous studies have, however, included mostly patients with cirrhosis due to hepatitis C. **We aimed** to determine the prevalence and predictive factors of CAD in a cohort of consecutive patients with cirrhosis of various etiologies compared to the general population. **Methods** A total of 127 patients with cirrhosis were evaluated for a history of CAD and

cardiovascular risk factors. Arterial blood pressure, fasting plasma glucose, and serum cholesterol were measured. Nutritional status was assessed by anthropometry and estimation of recent weight change. A group of 203 subjects from the general population with similar age and gender distribution, as well as smoking habits as the cirrhotic patients, served as controls. **RESULTS:** CAD was more common in cirrhotics compared to controls (20% vs. 12%, P = 0.001). Compared to controls, cirrhotics had lower mean arterial blood pressure and serum cholesterol and a higher prevalence of diabetes, but did not differ significantly in the prevalence of hypertension or family history for CAD. In regression analysis, CAD was independently related to diabetes (odds ratio [OR] 5.47, 95% confidence interval [CI] 2.44-12.28), but not to liver cirrhosis. In the cirrhosis group, only alcoholic cirrhosis (OR 9.50, 95% CI 1.08-83.4) and age (OR 1.23 per year, 95% CI 1.06-1.43) were independently related to CAD. **CONCLUSIONS:** Liver cirrhosis, per se, does not seem to confer a protective effect against CAD. In cirrhotics, older age and alcoholic etiology were independently related to CAD.

Response to antiviral therapy in liver transplant recipients with recurrent hepatitis C viral infection: a single center experience. Jain A, Sharma R, Ryan C, et al. Clin Transplant. 2009 Feb 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19239480?ordinalpos=10&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

INTRODUCTION: Recurrence of hepatitis C virus (HCV) in hepatic allograft is a major concern after successful liver transplant (LTx). Aim: To examine the response rate to pegylated interferon (PEG-IFN) and ribavirin in post-LTx patients with HCV recurrence. Patients and **METHODS:** Between January 2003 and September 2006, 60 patients with biopsy proven HCV recurrence (46 males and 14 females) received PEG-IFN 2a (n = 40) or IFN 2b (n = 20) with ribavirin. All patients were followed until July 2007. **RESULTS:** Fourteen patients (23.3%) tolerated antiviral therapy for less than six months and 10 (16.7%) discontinued therapy between six and 11 months. PEG-IFN dose was reduced in 21 (35%) patients and ribavirin dose was reduced in 16 (26.7%) patients. Overall, 55% patients achieved end of treatment response (EOT) and 35% sustained virological response (SVR). Mean Hepatitis Activity Index and Fibrosis Score pre-therapy was 5.8 +/- 1.9 and 1.7 +/- 1.3 and post-therapy, it was 4.4 +/- 2.1 and 2.4 +/- 1.6, respectively. Overall, three yr patient and graft survival was 73.9% and 69.2%, respectively. The patients with SVR had significantly lower viral load compared with other groups (p = 0.028). **CONCLUSION:** PEG-IFN and ribavirin therapy achieved 55% EOT and 35% SVR; 60% patients tolerated therapy. Biochemical response was observed in all groups of patients irrespective of virological response.

Factors associated with hepatic fibrosis in patients with chronic hepatitis C: A retrospective study of a large cohort of U.S. patients. Hu SX, Kyulo NL, Xia VW, Hillebrand DJ, Hu KQ. J Clin Gastroenterol. 2009 Feb 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19238091?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

GOALS: To determine the risk factors for stage 3 and 4 fibrosis in a large cohort of U.S. patients with chronic hepatitis C (CHC). **BACKGROUND:** Multiple host and viral factors affect the outcomes of CHC. Further defining the pathogenic roles of these factors in CHC progression will lead to improving management of this disease. **STUDY:** Retrospective study of a large cohort of US patients with CHC. **RESULTS:** Of the 460 patients, 331 were males and 129 were females with mean age of 48.4 +/- 8.0 years, and 191 (41.7%) had stage 3 and 4 fibrosis. Clinically, a multivariate analysis revealed that age of >=60 years at presentation, the estimated duration of hepatitis C virus (HCV) infection >=25 years, a body mass index >=30 kg/m, and a history of diabetes mellitus

were independently associated with stage 3 and 4 fibrosis, after adjusting for history of alcohol use. Laboratorially, a multivariate analysis revealed that aspartate aminotransferase (AST) ≥ 2 upper limit of normal (ULN), alpha fetoprotein ≥ 15 $\mu\text{g/L}$, and presence of grade 2 and 3 steatosis were independently associated with stage 3 and 4 fibrosis, after adjusting for alanine aminotransferase ≥ 2 upper limit of normal, AST/alanine aminotransferase ratio ≥ 1 , HCV genotyping, transferrin saturation, and a histology activity index score ≥ 7 . **CONCLUSIONS:** The present study indicated that elderly, longer duration of HCV infection, obesity, and history of diabetes mellitus are independent clinical parameters associated with advanced fibrosis, whereas elevated AST, alpha fetoprotein, and presence of grade 2 and 3 steatosis are independent laboratorial parameters associated with stage 3 and 4 fibrosis in patients with CHC.

Risk of immune thrombocytopenic purpura and autoimmune hemolytic anemia among 120 908 US veterans with hepatitis C virus infection. Chiao EY, Engels EA, Kramer JR, et al. Arch Intern Med. 2009 Feb 23;169(4):357-63.

http://www.ncbi.nlm.nih.gov/pubmed/19237719?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: There is emerging evidence that hepatitis C virus (HCV) infection play a role in the etiology of immune thrombocytopenia purpura (ITP) and autoimmune hemolytic anemia (AIHA), both of which are severe autoimmune cytopenias. **METHODS:** To determine if HCV infection increases the risk for ITP and AIHA, we calculated the incidence rates of ITP and AIHA among 120 691 HCV-infected and 454 905 matched HCV-uninfected US veterans who received diagnoses during the period 1997 to 2004. After excluding individuals with a prior diagnosis of a lymphoproliferative disease, human immunodeficiency virus, or cirrhosis, we fitted Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) as measures of risks. **RESULTS:** We found 296 ITP and 90 AIHA cases. Among HCV-infected vs HCV-uninfected persons, the overall incidence rates of ITP were 30.2 and 18.5 per 100 000 person-years, and for AIHA they were 11.4 and 5.0 per 100 000 person-years, respectively. Hepatitis C virus was associated with elevated risks for ITP (HR, 1.8; 95% CI, 1.4-2.3) and AIHA (HR, 2.8; 95% CI, 1.8-4.2). The ITP incidence was increased among both untreated and treated HCV-infected persons (HR, 1.7; 95% CI, 1.3-2.2 and HR, 2.4; 95% CI, 1.5-3.7, respectively), whereas AIHA incidence was elevated only among treated HCV-infected persons (HR, 11.6; 95% CI, 7.0-19.3).

CONCLUSIONS: Individuals infected with HCV are at an increased risk for ITP, whereas the development of AIHA seems to be associated with HCV treatment. It may be beneficial to test individuals newly diagnosed as having ITP for HCV infection.

Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. Kirk GD, Astemborski J, Mehta SH, et al. Clin Infect Dis. 2009 Feb 23. [Epub ahead of print]

Spoler C, Fisher C, Allen D, Higgins Y, Moore RD, Afdhal N, Torbenson M, Sulkowski M, Thomas DL.

http://www.ncbi.nlm.nih.gov/pubmed/19236273?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Transient elastography is a novel, noninvasive method for staging liver fibrosis. We compared elastography with histologic methods among hepatitis C virus (HCV)-infected and human immunodeficiency virus (HIV)-HCV-coinfected participants in an urban, predominantly black study population. **METHODS:** Participants recruited from the AIDS Linked to the Intravenous Experience and the Johns Hopkins HIV Clinical Cohort studies underwent elastography to determine liver stiffness measurements. Liver biopsy specimens were staged F0-F4

in accordance with the Metavir score. Diagnostic accuracy and determination of liver stiffness cutoff values, compared with histologic methods, were determined by receiver operating characteristic analysis. Logistic regression methods identified parameters associated with discordant classification status. **RESULTS:** Of 192 participants, 139 (72%) were coinfecting with HIV and HCV, 121 (63%) had insignificant fibrosis, and 48 (25%) had cirrhosis. Overall, the area-under-the-curve receiver operating characteristic was 0.87 for detection of both significant fibrosis (95% confidence interval, 0.82-0.92) and cirrhosis (95% confidence interval, 0.81-0.93). With use of cutoff values of 9.3 kPa for fibrosis and 12.3 kPa for cirrhosis, 79%-83% of participants were correctly classified by liver stiffness measurement (compared with histologic methods); accuracy appeared to be higher among HIV-uninfected participants than among HIV-infected participants. Most discordance occurred when liver stiffness measurements indicated liver disease and histologic examination did not (in 16% of participants); the patients with these discordant results were more likely to have attributes that increased the odds of significant fibrosis, such as elevated serum fibrosis markers or HIV-related immunosuppression, compared with persons in whom low fibrosis was predicted by both examination of a biopsy specimen and elastography. **CONCLUSIONS:** For most HCV-infected persons, fibrosis stage predicted by elastography is similar to that predicted by examination of a biopsy specimen. Elastography-based measurement of liver stiffness holds promise to expand liver disease screening and monitoring, particularly among injection drug users.

Randomized trial of high-dose interferon-alpha-2b combined with ribavirin in patients with chronic hepatitis C: Correlation between amino acid substitutions in the core/NS5A region and virological response to interferon therapy. Mori N, Imamura M, Kawakami Y, et al. *J Med Virol.* 2009 Feb 23;81(4):640-649. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19235866?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The aim of this study was to compare the efficacy of high-dose interferon (IFN)-alpha-2b with standard dose of IFN-alpha-2b in combination with ribavirin (RBV) for patients with chronic hepatitis C virus (HCV) infection, and to investigate the predictive factors associated with virological response. Two hundred Japanese patients with high HCV viral load (>100 KIU/ml) were randomized to 6 or 10 mega units (MU) of 24-week IFN-alpha-2b with RBV. Predictive factors were investigated; including pretreatment amino acid (aa) sequences of the core region and the IFN-sensitive determining region (ISDR). The sustained virological response rate was not different in the two groups (24% vs. 30%) but the incidence of depression was significantly higher in the 10 MU group than 6 MU group (7% vs. 0%, $P = 0.02$). Younger age (<60) and HCV genotype (2a/b) were significant predictors of sustained virological response. In patients infected with genotype 1b, substitutions of core aa 70 and/or 91 were predictive for non-virological response ($P < 0.001$), and substitutions in the ISDR was observed frequently in virological responders. Early viral kinetics study showed that serum HCV core antigen decreased more slowly in both patients with aa 70 and/or 91 substitutions in the core and with absence of substitutions in the ISDR. **In conclusion,** the use of a higher dose of IFN-alpha-2b in combination with RBV did not improve virological response but resulted in higher incidence of depression. Amino acid substitutions in the core and ISDR are predictive of virological response to the therapy in patients with genotype 1b and high viral load.

Severity of liver disease predicts the development of glucose abnormalities in patients with chronic hepatitis B or C following achievement of sustained virological response to antiviral therapy. Chehadeh W, Al-Nakib W. *J Med Virol.* 2009 Feb 23;81(4):610-618. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19235842?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

A higher prevalence of glucose abnormalities has been reported in patients with hepatitis C virus (HCV) infection compared to patients with hepatitis B virus (HBV) infection. However, previous studies considered some confounding factors and ignored others, which might influence the comparative risk assessment between HBV and HCV infections. Fasting plasma glucose concentration, severity of liver disease and viral load were determined in 220 patients with HCV genotype 4 infection, and 200 patients with HBV infection. Patients completing antiviral therapy were followed-up, and the fasting plasma glucose levels were determined in patients with and without sustained virological response. The prevalence of glucose abnormalities in HCV infection (41%) was significantly higher than that in HBV infection (16%). However, when controlling the severity of liver disease and other risk factors, the prevalence of glucose abnormalities in patients with HCV infection was comparable to that in patients with HBV infection. After attaining of sustained virological response, a decrease of the median fasting plasma glucose value was observed only in chronic hepatitis C. In the group of patients with normal fasting plasma glucose levels, an association of nonsustained virological response with the development of impaired fasting glucose was only observed in chronic hepatitis C. The severity of liver disease was a common predictor of impaired fasting glucose in hepatitis B and C infections. These results indicate that high prevalence of glucose abnormalities can be associated with HBV- and HCV-related liver disease, and that clearance of HCV, but not HBV, may improve glucose metabolism.

Proapoptotic IL-18 in patients with chronic hepatitis C treated with pegylated interferon-alpha. Yingli H, Shumei L, Qian Y, Tianyan C, Yingren Z, Wei C. *Clin Exp Med.* 2009 Feb 24. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Yingli%20H%22\[Author\]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Yingli%20H%22[Author]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract)

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide. In mainland of China, It was estimated the population of 1.3 billion infected with HCV. HCV is not cytopathic. Immune response that is essentially conducted by cytokines may play an important role in the pathogenesis of HCV infection. Interleukin (IL)-18, mainly produced by monocytes/macrophages, plays an important role in the immune system by enhancing T cell responses, regulating interferon-gamma (IFN-gamma) production and promoting the development of T helper cell Th1 immune responses. Raised serum levels of IL-18 have recently been reported in patients with chronic hepatitis C before antiviral therapy. Herein we report the IL-18 sequential changes in patients with hepatitis C during the period of pegylated interferon (PEG-IFN) alpha treatment for 48 weeks. We established the correlation of plasma IL-18 level and alanine aminotransferase ($r = 0.77$, $P < 0.05$). Hepatic inflammatory activity in chronic hepatitis C was shown to be closely associated with an increased amount of IL-18. HCV-infected patients had raised IL-18 levels (93.67 ± 23.58 pg/ml versus 59.73 ± 24.06 pg/ml; $P < 0.001$) comparing donor negativity for HCV. PEG-IFN alpha-2a treatment induces a marked decline in IL-18 and remission of hepatic inflammatory in responders at week 24 and week 48 follow-up time point, while increased levels persist in those in whom the HCV

infection was not eliminated by the therapy. We proposed declined IL-18 levels favor for virus solution, while persistent raised IL-18 associated with PEG-IFN treatment failure.

Suppression of hepatitis C virus replication by protein kinase C-related kinase 2 inhibitors that block phosphorylation of viral RNA polymerase. Kim SJ, Kim JH, Sun JM, et al. *J Viral Hepat.* 2009 Feb 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19243496?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Hepatitis C virus (HCV) infection is a serious threat to human health worldwide. In spite of the continued search for specific and effective anti-HCV therapies, the rapid emergence of drug-resistance variants has been hampering the development of anti-HCV drugs designed to target viral enzymes. Targeting host factors has therefore emerged as an alternative strategy offering the potential to circumvent the ever-present complication of drug resistance. We previously identified protein kinase C-related kinase 2 (PRK2) as a cellular kinase that phosphorylates the HCV RNA-dependent RNA polymerase (RdRp). Here, we report the anti-HCV activity of HA1077, also known as fasudil, and Y27632, which blocks HCV RdRp phosphorylation by suppressing PRK2 activation. Treatment of a Huh7 cell line, stably expressing a genotype 1b HCV subgenomic replicon RNA, with 20 μ M each of HA1077 and Y27632 reduced the HCV RNA level by 55% and 30%, respectively. A combination of the inhibitors with 100 IU/mL interferon alpha (IFN-alpha) significantly potentiated the anti-HCV drug activities resulting in approximately a 2-log(10) viral RNA reduction. We also found that IFN-alpha does not activate PRK2 as well as its upstream kinase PDK1 in HCV-replicating cells. Furthermore, treatment of HCV-infected cells with 20 μ M each of HA1077 and Y27632 reduced the levels of intracellular viral RNA by 70% and 92%, respectively. Taken together, the results identify PRK2 inhibitors as potential antiviral drugs that act by suppressing HCV replication via inhibition of viral RNA polymerase phosphorylation.

Evidence for action of ribavirin through the hepatitis C virus RNA polymerase. Cannon NA, Donlin MJ, Mayes LM, et al. *J Viral Hepat.* 2009 Feb 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19243495?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Hepatitis C virus (HCV) infections are treated with interferon alpha plus ribavirin, but it is unknown how ribavirin works against HCV. Ribavirin is a guanosine analogue that can be a substrate for the viral RNA polymerase. HCV is genetically variable, and this genetic variation could affect the polymerase's use of ribavirin triphosphate. Thirteen patients infected with HCV who failed interferon alpha monotherapy and were retreated with interferon alpha plus ribavirin were identified; seven were responders and six were nonresponders to combination therapy. The consensus sequences encoding the 13 polymerases plus seven sequences from treatment-naive controls were determined. The responder sequences were more genetically variable than the nonresponders and controls, the amino acid variations unique to responders had lower BLOSUM90 scores than variations in nonresponders and controls, and the amino acid variations correlated with response to therapy clustered around the RNA-binding channel of the polymerase. These data imply that the responder enzymes were probably more functionally variable than the nonresponder enzymes. Enzymatic activity was measured for 10 recombinant polymerases; RNA synthesis activity varied by over sevenfold and polymerases from two of the responders used GTP much better than UTP, but technical limitations prevented direct measurement of ribavirin triphosphate use. Because response to combination therapy in these patients was primarily due to addition of ribavirin to the treatment

regimen, these data imply that genetic variation in the polymerase may have affected the efficiency of ribavirin incorporation into the viral genome and hence may have modulated ribavirin's efficacy against HCV.

Validation of connective tissue growth factor (CTGF/CCN2) and its gene polymorphisms as noninvasive biomarkers for the assessment of liver fibrosis. Kovalenko E, Tacke F, et al. *J*

Viral Hepat. 2009 Feb 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kovalenko%20E%22\[Author\]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kovalenko%20E%22[Author]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract)

SUMMARY: Clinical and experimental studies have demonstrated that connective-tissue growth factor (CTGF) expression is increased in fibrotic human liver and experimental animal models of liver fibrogenesis. CTGF has been linked to transforming growth factor-beta (TGF-beta) pathways in fibroproliferative diseases and specific polymorphisms within the CTGF gene may predispose for fibrosis in systemic sclerosis. As CTGF is detectable in various human fluids (serum, plasma and urine), it may provide information about fibrotic remodelling processes and reflect hepatic TGF-beta bioactivity. We established a novel ELISA for the measurement of serum CTGF and tested its clinical value in patients with chronic hepatitis C virus (HCV) infection and chronic liver disease (CLD). HCV infected patients (n = 138) had significantly higher serum CTGF levels than healthy controls. CTGF was linked to the histological degree of liver fibrosis. To expand the results to other aetiologies, a separate cohort of CLD patients (n = 129) was evaluated, showing higher serum CTGF than healthy controls and again an association with advanced stages of liver cirrhosis (Child B and C). Although independent of the underlying aetiology, serum CTGF was most powerful in indicating fibrosis/advanced disease states in HCV-related disorders. The genotyping of six polymorphisms (rs6917644, rs9399005, rs6918698, rs9493150, rs2151532 and rs11966728) covering the CTGF locus in 365 patients suffering from chronic hepatitis C revealed that none of these polymorphisms showed a genotypic or allelic association with the severity of hepatic fibrosis. Taken together, serum CTGF is suitable for determination of hepatic fibrosis and most powerful in patients with chronic HCV infection.

A liver slice culture-based ex vivo assay to predict the outcome of antiviral therapy for chronic hepatitis C. Chang ML, Sung KF, Sheen IS, Lin SM, Yeh CT. *J* *Viral Hepat.* 2009

Feb 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Chang%20ML%22\[Author\]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Chang%20ML%22[Author]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract)

SUMMARY: A liver slice culture-based, ex vivo drug suppression assay was developed as a pre-therapeutic predictor for the outcome of antiviral therapy. To investigate its clinical application, 106 consecutive patients with chronic hepatitis C virus (HCV) infection were evaluated. Ex vivo drug suppression assay was performed before administering a standard course of peginterferon plus ribavirin combination therapy. Stepwise logistic regression model was used to estimate sustained virological response (SVR) on the presence of various clinicopathological parameters. Suppression of HCV replication in the ex vivo assay was present in 32 patients, 29 (90.6%) of whom achieved SVR. Stepwise logistic regression analysis indicated that the presence of interferon suppression effect in the ex vivo assay (odds ratio [OR], 5.552; 95% confidence interval [CI], 1.114-27.673; P = 0.036), genotype 1 (OR; 0.045, 95% CI, 0.008-0.259; P = 0.001), HCV-RNA level (OR, 0.739; 95% CI, 0.617-0.885; P = 0.001), the presence of fatty metamorphosis (OR, 0.205; 95% CI, 0.053-0.793; P = 0.022), and albumin (OR, 9.687; 95% CI, 2.237-41.940; P = 0.002) were independent determinants of SVR. Categorical analysis revealed that 17 of 17 (100%) patients with genotype non-

1 and positive ex vivo suppression test achieved SVR, while 20 of 40 (50%) with genotype 1 and negative ex vivo suppression test achieved SVR. In conclusion, the ex vivo drug suppression assay may serve as an independent pre-therapeutic predictor for the SVR in interferon-based antiviral therapy.

Reduced ribavirin antiviral efficacy via nucleoside transporter-mediated drug resistance.

Ibarra KD, Pfeiffer JK. J Virol. 2009 Feb 25. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Ibarra%20KD%22\[Author\]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Ibarra%20KD%22[Author]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVAbstract)

Treatment for hepatitis C virus infection currently consists of pegylated interferon and ribavirin (RBV), a nucleoside analog. Although RBV clearly plays a role in aiding treatment response, its antiviral mechanism is unclear. Regardless of the specific mechanism of RBV, we hypothesize that differences in cellular uptake of RBV may affect antiviral efficacy and treatment success, and that cells may become RBV resistant through reduced uptake. We monitored RBV uptake in various cell lines and determined the effect of uptake capacity on viral replication. RBV-resistant cells demonstrated reduced RBV uptake and increased growth of a model RNA virus, poliovirus, in the presence of RBV. Over-expression of the equilibrative nucleoside transporter 1 (ENT1) or the concentrative nucleoside transporter 3 (CNT3) increased RBV uptake in RBV-sensitive cell lines and restored the uptake defect in most RBV-resistant cell lines. However, CNT3 is not expressed in Huh-7 liver cells, and inhibition of concentrative transport did not affect RBV uptake. Blocking equilibrative transport using the inhibitor nitrobenzylmercaptapurine riboside (NBMPR) recapitulated the RBV-resistant phenotype in RBV-sensitive cell lines, with a reduction in RBV uptake and increased poliovirus growth. Taken together, these results indicate that RBV uptake is primarily restricted to ENT1 in the cell lines examined. Interestingly, some RBV-resistant cell lines may compensate for reduced ENT1-mediated nucleoside uptake by increasing the activity of an alternative nucleoside transporter, ENT2. It is possible that RBV uptake affects antiviral treatment response, either through natural differences in patients or through acquired resistance.

The impact of hepatic steatosis on the natural history of chronic hepatitis C infection.

Cross TJ, Quaglia A, Hughes S., et al. J Viral Hepat. 2009 Feb 5. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19200134?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Since patients with hepatitis C virus (HCV) often have hepatic steatosis, this retrospective analysis aimed to assess whether steatosis influences fibrosis progression. We studied 112 HCV RNA positive subjects (median age 44, IQR 39-51 years), who had two liver biopsies performed (median biopsy interval 50, 34-74 months). Fibrosis was staged using the Ishak method and steatosis by the Kleiner system (<5% steatosis = S0, 5-33% = S1, 33-66% = S2, and >66% = S3). The subjects were untreated because they had mild fibrosis (n = 59), declined therapy (n = 48), or had co-existing disease precluding treatment (n = 5). On first liver biopsy, 60 (54%) had S0, 34 (30%) had S1, 12 (11%) had S2, and 6 (5%) had S3. Steatosis was associated with genotype 3, odds ratio 4.8 (95% CI 1.3-16.7, P = 0.02). Twenty-three patients (21%) had disease progression on the second biopsy, defined as an increase in Ishak score by ≥ 1 stage. On univariate analysis, fibrosis progression was associated with older age (P = 0.004), higher AST (P = 0.04), and steatosis (P = 0.005) but on multivariate analysis, only baseline steatosis was significant, odds ratio 14.3 (2.1-111.1, P = 0.006). Kaplan-Meier analysis demonstrated that steatosis impacted on time to progression to both significant fibrosis (Ishak \geq F3) and cirrhosis (Ishak F5-6) (P = 0.001 and P = 0.049, respectively). The finding that steatosis was significantly associated with fibrosis progression indicates that, independent of baseline fibrosis stage, patients should be considered for anti-viral treatment if

steatosis is present. Furthermore, strategies to reduce steatosis may have a beneficial effect on fibrosis progression and, therefore, patient outcome.

Detection of myxovirus resistance protein A in lichen planus lesions and its relationship to hepatitis C virus. Shaker OG, Hantar N, El-Tahlawi S, et al. *Br J Dermatol.* 2009 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19222461?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY BACKGROUND: Lichen planus (LP) is an inflammatory disease of the skin and oral mucosa. Studies suggested that type I interferons (IFNs) could play an important role in the cytotoxic inflammation in LP. Type I IFNs stimulate the production of several IFN-induced proteins including myxovirus resistance protein A (MxA protein). The association of LP and chronic hepatitis C is well established, with variable prevalence rates among different populations. Many authors have considered hepatitis C virus (HCV) as a possible antigen for inducing cytotoxic immune response in LP. Objectives To investigate the role of type I IFNs in LP through the detection of MxA protein, and to compare the expression of MxA protein between HCV-positive and HCV-negative patients with LP in an attempt to clarify the role of HCV in the pathogenesis of LP. **METHODS:** The study included 33 skin biopsies from patients with LP and 10 control biopsies. MxA mRNA was detected by reverse transcription-polymerase chain reaction. HCV-specific antibodies were detected in patient sera by enzyme-linked immunosorbent assay.

RESULTS: Our analysis revealed a significantly higher level of MxA protein in all the LP skin biopsies compared with controls. The expression was significantly higher in HCV-positive patients than in HCV-negative patients. Conclusions Type I IFNs play a role in the pathogenesis of LP, and HCV could induce LP through increasing the production of type I IFNs.

Serum BLYS/BAFF predicts the outcome of acute hepatitis C virus infection. Tarantino G, Marco VD, Petta S, et al. *J Viral Hepat.* 2009 Feb 5. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19200135?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

B-lymphocyte stimulator/B activating factor (BLYS/BAFF) is a tumour necrosis factor-family cytokine that plays a key role in generating and maintaining the mature B-cell pool. BLYS/BAFF expression by macrophages is stimulated by interferon-gamma and interleukin-10, and its serum levels are increased in chronic hepatitis C (CHC). The aim of this study was to assess serum levels of BLYS/BAFF in patients with acute hepatitis C (AHC) and correlate them with disease outcome. We studied 28 patients with AHC (14 males, mean age 59.3 +/- 15 years), followed for at least 7 months since onset, comparing them with 86 CHC patients and 25 healthy blood donors (HBD).

BLYS/BAFF levels were assessed at baseline (within 4 weeks of onset) and during follow-up. BLYS/BAFF median levels were significantly higher in AHC (1485 pg/mL) than in CHC (1058 pg/mL) and in HBD (980 pg/mL) ($P < 0.001$). BLYS/BAFF levels were higher in AHC patients evolving to chronicity (1980 pg/mL) than in those with a self-limited course (1200 pg/mL), ($P = 0.02$). By logistic regression analysis, higher BLYS/BAFF levels were independently associated with persistence of HCV infection (OR 29.7; 95% CI: 1.73-508.20). High serum levels of BLYS/BAFF at onset of AHC can predict its evolution to chronic infection.

The HCV serum proteome: a search for fibrosis protein markers. Cheung KJ, Tilleman K, Deforce D, et al.. J Viral Hepat. 2009 Feb 15. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19226329?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: Liver fibrosis/cirrhosis is a serious health issue in hepatitis C virus (HCV-) infected patients and is currently diagnosed by the invasive liver biopsy. The aim of this study was to find useful fibrosis markers in HCV-patients' sera of different fibrosis degrees (METAVIR F0-F4) based on proteomics. Serum proteome profiles were created by two-dimensional gel electrophoresis. Profiles were analysed between different degrees of fibrosis (F0-F4) and between early (F0/F1) and late (F2/F3/F4) fibrosis by univariate analyses ($P \leq 0.05$). Differentially expressed proteins were subsequently identified by mass spectrometry. Mac-2-binding protein, alpha-2-macroglobulin and hemopexin were increased in F4 opposite F0/F1. A-1-antitrypsin, leucine-rich alpha-2-glycoprotein and fetuin-A were decreased in F4 opposite F0/F1. Late fibrosis was characterized by an increase in Mac-2-binding protein, alpha-2-macroglobulin and alpha-1B-glycoprotein expression and a decrease in haptoglobin expression. Mac-2-binding protein expression was confirmed by dot blot assay and enzyme-linked immunosorbent assay in a secondary population. In conclusion, serum proteome analysis enabled the detection/identification of existing and new candidate markers in line with fibrosis progression in HCV-patients.

Site-specific cleavage of HCV genomic RNA and its cloned core and NS5B genes by DNAzyme. Kumar D, Chaudhury I, Kar P, et al.. J Gastroenterol Hepatol. 2009 Feb 4. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19220662?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

ABSTRACT BACKGROUND AND AIMS: The 9600 nt hepatitis C virus (HCV) genomic RNA has only one internal ribosome entry site (IRES) for translation to a single polyprotein. In search of nucleic acid-based antiviral agents, two 10-23 DNAzymes were designed to cleave the RNA in IRES and RNA dependent RNA polymerase (RDRP/NS5B) regions to prevent translation and replication of HCV RNA. **METHODS:** In vitro cleavage of HCV RNA by IRES specific DNAzyme, CDz and NS5B specific DNAzyme, NDz was carried out using HCV genomic RNA and in vitro synthesized runoff transcripts of core and NS5B genes. Cleavage of core and NS5B mRNAs by DNAzyme (Dz) in HepG2 cells was assessed by reverse transcription polymerase chain reaction (RT-PCR) using RNA from cells co-transfected with cloned core or NS5B gene and its respective DNAzyme. Suppression of core or NS5B protein expression due to mRNA cleavage by Dz in co-transfected cells was determined by Western blot analysis and fluorescence intensity of fluorescently-tagged expressed protein. Reduction of NS5B protein activity in NDz co-transfected cells was determined by enzymatic assays. **RESULTS:** The designed CDz and NDz cleaved HCV genomic RNA and their respective in vitro generated transcripts. Both mRNA and protein expressions of core or NS5B from their cloned genes reduced substantially when co-transfected with respective Dz. Reduction of RDRP expression by NDz was accompanied with its reduced enzyme activity. Increased RNA cleavage, inhibition of protein expression, and reduction of RDRP activity were observed on increasing Dz concentration. **CONCLUSION:** Core and NS5B targeted DNAzymes can be used in controlling the replication of HCV RNA.

Does fluvastatin favour HCV replication in vivo? A pilot study on HIV-HCV coinfecting patients. Milazzo L, Meroni L, Galazzi M, et al. J Viral Hepat. 2009 Feb 7. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19215577?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Fluvastatin showed anti-hepatitis C virus (HCV) activity in vitro, through the inhibition of geranylgeranylation of cellular proteins, and a synergistic effect with interferon (IFN)-alpha. Nevertheless statins up-regulate low-density lipoprotein (LDL) receptor, required for HCV cell entry, and the closely related scavenger receptors SRBI and CD36; moreover they reduce class II major histocompatibility complex expression on antigen presenting cell, modulating T-cell activation. In vivo LDL levels have been identified as prognostic indicator of sustained viral response to IFN in patients with HCV infection, suggesting that lipid-lowering agents might conversely favour HCV entry into the hepatocytes and translate into higher viral replication. We evaluated the effect of fluvastatin on HCV-RNA levels, CD36 expression and T-cell homeostasis in HCV-RNA positive patients. HCV-RNA was measured at baseline and after 4 weeks in 42 HCV/HIV-1 co-infected patients, randomized to receive either fluvastatin 80 mg qd or no treatment. CD36 expression and markers of T-cell activation were evaluated by means of flow cytometry. Plasma interleukin (IL)-10, IFN-gamma and IL-7 were measured by ELISA. Serum cholesterol and LDL decreased significantly in the treatment group (P = 0.0001 and 0.01, respectively). Surprisingly a significant increase of HCV-RNA levels was seen after 4 weeks of fluvastatin (P = 0.03). The percentages of naive/activated/apoptotic cells and CD36 expression remained unchanged. Fluvastatin did not inhibit HCV-RNA replication in vivo; conversely we observed a significant increase of HCV-RNA levels. CD36 expression on monocytes were not up-regulated by statins as previously reported in vitro. The correlation between HCV infectivity, oxidized-LDL receptor and statins in HCV infection need further evaluation.

Discovery of (R)-6-Cyclopentyl-6-(2-(2,6-diethylpyridin-4-yl)ethyl)-3-((5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl)-4-hydroxy-5,6-dihydropyran-2-one (PF-00868554) as a Potent and Orally Available Hepatitis C Virus Polymerase Inhibitor. Li H, Tatlock J, Linton A, et al. J Med Chem. 2009 Feb 11. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19209845?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The HCV RNA-dependent RNA polymerase has emerged as one of the key targets for novel anti-HCV therapy development. Herein, we report the optimization of the dihydropyrone series inhibitors to improve compound aqueous solubility and reduce CYP2D6 inhibition, which led to the discovery of compound 24 (PF-00868554). Compound 24 is a potent and selective HCV polymerase inhibitor with a favorable pharmacokinetic profile and has recently entered a phase II clinical evaluation in patients with genotype 1 HCV.

Hepatitis C virus infection in hemodialysis patients is not associated with insulin resistance, inflammation and atherosclerosis. Caliskan Y, Oflaz H, Pusuroglu H, et al. Clin Nephrol. 2009 Feb;71(2):147-57.

http://www.ncbi.nlm.nih.gov/pubmed/19203507?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Hepatitis C virus (HCV) infection is associated with increased levels of inflammatory markers and is also a significant risk factor for the development of Type 2 diabetes mellitus (DM) in the general population. In attempt to address this issue in chronic hemodialysis (HD) patients, we evaluated the relation of HCV infection with inflammatory markers, endothelial dysfunction, insulin resistance and atherosclerosis. **METHODS:** In a cohort of 72 HD patients (36

(50%) had a positive HCV EIA test and 36 (50%) had a negative anti-HCV test), we examined HCV antibody status, insulin resistance (HOMA-IR) and beta-cell function (HOMA-beta), serum inflammatory parameters (high sensitive C-reactive protein (CRP), fibrinogen and procalcitonin), and performed echocardiography, high-resolution brachial artery ultrasound and B-mode carotid Doppler examination to assess the vascular functions and atherosclerosis. **RESULTS:** There were no differences in age, gender, body mass index (BMI), primary disease, duration of dialysis, smoking status, laboratory parameters except glucose, total cholesterol and LDL cholesterol between anti-HCV-positive and anti-HCV-negative groups. The serum concentrations of glucose, total cholesterol and LDL cholesterol were significantly lower in the anti-HCV-positive patients than anti-HCV-negative patients ($p = 0.04$, $p = 0.02$, $p = 0.01$, respectively). There were no significant differences in inflammatory parameters, total insulin secretion (HOMA-beta, $p = 0.76$) and insulin resistance (HOMA-R, $p = 0.91$) between anti-HCV-positive and negative patients. The intima media thickness, carotid plaque score and brachial artery endothelium-dependent dilatation did not differ significantly between the two groups ($p = 0.44$, 0.45 , and 0.17 , respectively). **CONCLUSION:** HCV infection was not related to atherosclerosis and insulin resistance in hemodialysis patients. Since hemodialysis patients had a large number of uremia-related cardiovascular risk factors, the effect of HCV infection could disappear in this group of patients.

Boceprevir, an NS3 serine protease inhibitor of hepatitis C virus, for the treatment of HCV infection. Mederacke I, Wedemeyer H, Manns MP. *Curr Opin Investig Drugs*. 2009 Feb;10(2):181-9

http://www.ncbi.nlm.nih.gov/pubmed/19197796?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Boceprevir is an HCV NS3 (non-structural protein 3) serine protease inhibitor being developed by Schering-Plough Corp as a capsule formulation. In pharmacokinetic studies, boceprevir was adequately absorbed, with the most effective mode of administration appearing to be a three-times-daily regimen. In phase I clinical trials, monotherapy with boceprevir led to a distinct viral load reduction. In phase Ib combination trials of boceprevir with PEGylated IFNalpha2b and ribavirin, the reduction in viral replication was further increased. Early data reported from phase II clinical trials have been promising, suggesting a rapid early HCV-RNA reduction. Phase III trials for the drug began in 2008. Results available to date have demonstrated the compound to be well tolerated, with adverse events that were within the range of current standard-of-care therapy. Thus, boceprevir may have the potential to increase sustained virological response rates and possibly also to shorten duration of therapy; data from ongoing clinical trials are awaited.

Impaired plasmacytoid dendritic cell maturation and differential chemotaxis in chronic HCV: Associations with antiviral treatment outcomes. Mengshol JA Md Phd, Golden-Mason L Phd, Castelblanco N, et al. *Gut*. 2009 Feb 4. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Mengshol%20JA%20Md%20Phd%22\[Author\]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HV_Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Mengshol%20JA%20Md%20Phd%22[Author]&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HV_Abstract)

BACKGROUND: DC defects may contribute to chronicity in hepatitis C virus (HCV) infection and determine response to PEG-interferon and ribavirin therapy via poor T cell stimulation. Studies to date have produced inconsistent results regarding DC maturation and function, no large study has examined DCs before and after therapy. **AIMS:** We examined if DC defects in maturation and chemotaxis are present comparing therapeutic responders to non-responders. **METHODS:** We analyzed peripheral DCs of 64 HCV genotype 1-infected patients from the Virahep-C study two weeks before and 24 weeks after therapy. We used flow cytometry to enumerate plasmacytoid DC

(pDC) and myeloid DCs (mDC) and quantify expression of chemokine receptors and maturation markers. Chemotaxis was measured with an in vitro assay. **RESULTS:** Pretreatment frequencies of pDC and mDC were significantly lower in HCV patients than controls and successful therapy normalized pDC. Levels of CXCR3 and CXCR4 on pDC were higher at baseline compared to normal controls and decreased with therapy. Pre therapy levels of co-stimulatory marker CD40 and the maturation marker CD83 were higher on pDC of patients chronically infected with HCV compared to normal patients, and levels of both markers dropped significantly with therapy in the SVR+ group only. Other maturation markers (CD86 and CCR7) were not elevated suggesting a partially activated phenotype. Baseline chemotaxis of pDC to CXCL12 and CXCL10 predicted failure of antiviral response and correlated with the HAI inflammation score. **CONCLUSIONS:** Plasmacytoid DC defects exist in chronic HCV and successful antiviral therapy normalizes many phenotypic and functional abnormalities.

Survival and hepatitis status among Asian Americans with hepatocellular carcinoma treated without liver transplantation. Hwang JP, Hassan MM. BMC Cancer. 2009 Feb 4;9:46

http://www.ncbi.nlm.nih.gov/pubmed/19193234?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) are established causes of HCC. HCC patients are often diagnosed late and receive palliative therapies, however, the survival of Asian American patients with HCC treated without transplantation has not been well studied. We reviewed our institution's experience to determine predictors and rates of survival in Asian American HCC patients treated without transplantation. **METHODS:** We identified Asian American patients with HCC referred to M. D. Anderson Cancer Center. Patients were tested for HBV and HCV. Survival curves were generated by Kaplan-Meier method. Multivariate Cox proportional hazards regression was used to test the relationship between prognostic factors and survival. **RESULTS:** Of 82 Asian American HCC patients, most had advanced disease (65%) and received treatment (68%); however, only 11% had surgical resection. 94% had positive anti-HBc and 61% had positive HBsAg. 20% had positive anti-HCV. There were no significant changes in the rates of HBV and HCV over time. Male gender, high alpha-fetoprotein levels, and stage IV disease were associated with shorter survival. Overall median survival was 9.2 months (95% CI 6.5-11.9), and the survival of HCV and HBV patients was not statistically different. **CONCLUSION:** The survival rate of Asian American patients with advanced HCC, for whom transplantation was not available, was low. Timely hepatitis screening and interventions by primary care physicians may be the most logical solution to reduce the burden of hepatitis-associated HCC among Asian Americans.

Cellular immune responses during high-dose interferon-alpha induction therapy for hepatitis C virus infection. Barnes, E, Gelderblom HC, Semmo N, et al. J Infect Dis. 2009 Feb 1. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19193032?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: The effect that high-dose interferon (IFN)-alpha induction therapy for hepatitis C virus (HCV) infection has on cellular immune responses is currently unknown. **METHODS:** Thirty-one treatment-naive patients with chronic HCV infection received amantadine and ribavirin, combined with 6 weeks of high-dose IFN-alpha-2b induction therapy followed by weekly pegylated IFN-alpha-2b, for 24 or 48 weeks. Using IFN-gamma and interleukin (IL)-2 enzyme-linked immunospot (ELISpot) assays, we analyzed the pattern of cytokine secretion by structural and nonstructural HCV- and cytomegalovirus (CMV)-specific T cells before, during, and after therapy. **RESULTS:** HCV-specific T cell responses, which were predominantly IFN-gamma secreting and

which correlated with alanine transaminase levels ([Formula: see text]; [Formula: see text]), were found before treatment in 10 of 15 patients with a sustained virological response (SVR) and in 11 of 16 in the non-SVR group. There was a striking loss of IFN-gamma and IL-2 HCV-specific T cells during therapy, predominantly in the SVR group. This response recovered after cessation of therapy, regardless of outcome. Suppression of CMV-specific T cell responses, in addition to total lymphocyte counts, was also observed. **CONCLUSIONS:** High-dose IFN-alpha induction therapy leads to a profound decline in IL-2- and IFN-gamma-secreting HCV- and CMV-specific T cells. These data indicate that restoration of T cell responses is unlikely to be causally linked to an early response or SVR to therapy.

Treatment of chronic hepatitis C: anticipated impact of resistance in patients treated with protease inhibitors. Kronenberger B, Zeuzem S.. *Curr Gastroenterol Rep.* 2009 Feb;11(1):15-21. http://www.ncbi.nlm.nih.gov/pubmed/19166654?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

A main target of specifically targeted antiviral therapy for hepatitis C (STAT-C) is the NS3-protease, which has key functions in the hepatitis C virus (HCV) replication cycle. HCV/NS3-protease inhibitors have shown high antiviral activity in vitro and in patients with chronic hepatitis C. Protease-resistant HCV variants occurred rapidly in patients receiving protease-inhibitor monotherapy. The development of resistance can be best explained by selection of preexisting resistant variants, which grow out under selective pressure. Numerous mutations associated with resistance were identified. Clinical trials showed that protease-resistant strains are sensitive to interferon and that a triple combination of protease inhibitors, peginterferon, and ribavirin may improve the sustained virologic response rate compared with standard peginterferon/ribavirin combination therapy. Overall, it can be anticipated that successful treatment with protease inhibitors will require either combination therapy with peginterferon/ribavirin or a combination of STAT-C compounds with distinct modes of action and resistance patterns.

Role of growth factors and thrombopoietic agents in the treatment of chronic hepatitis C. Tillmann HL, Patel K, McHutchison JG.. *Curr Gastroenterol Rep.* 2009 Feb;11(1):5-14. http://www.ncbi.nlm.nih.gov/pubmed/19166653?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Advanced liver disease and interferon-based treatment are both associated with varying degrees of cytopenia in patients with chronic hepatitis C. Growth factors to increase hemoglobin and neutrophils are commonly used in clinical practice, despite the absence of data to indicate benefits in terms of sustained viral response. Thrombocytopenia is observed frequently, is multi-factorial in etiology, and may result in significant limitations on interventional and therapeutic options. A small-molecule thrombopoietin mimetic, eltrombo-pag, has demonstrated a dose-response associated increase in platelet count in a phase 2 study, allowing initiation and completion of a 12-week course of peginterferon plus ribavirin in 36%, 53%, and 65% of patients receiving 30 mg, 50 mg, or 75 mg of eltrombopag daily, respectively, compared with 6% in the placebo arm. Phase 3 studies are currently evaluating whether initiating and maintaining antiviral therapy with eltrombopag will lead to an increase in sustained virologic response in chronic hepatitis C infection.

Comprehensive longitudinal analysis of hepatitis C virus (HCV)-specific T cell responses during acute HCV infection in the presence of existing HIV-1 infection.

van den Berg CH, Ruys TA, Nanlohy NM, et al. J Viral Hepat. 2009 Feb 12. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19222746?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: The aim of this study was to study the development of HCV-specific T cell immunity during acute HCV infection in the presence of an existing HIV-1 infection in four HIV-1 infected men having sex with men. A comprehensive analysis of HCV-specific T cell responses was performed at two time points during acute HCV infection using a T cell expansion assay with overlapping peptide pools spanning the entire HCV genome. Three patients with (near) normal CD4⁺ T cell counts (range 400-970 x 10⁶/L) either resolved (n = 1) or temporarily suppressed HCV RNA. In contrast, one patient with low CD4⁺ T cell counts (330 x 10⁶/L), had sustained high HCV RNA levels. All four patients had low HCV-specific CD8⁺ T cell responses, and similar magnitudes of CD4⁺ T cell responses. Interestingly, individuals with resolved infection or temporary suppression of HCV-RNA had HCV-specific CD4⁺ T cell responses predominantly against nonstructural (NS) proteins. While the individual with high HCV RNA plasma concentrations had CD4⁺ T cell responses predominantly directed against Core. Our data show that an acute HCV infection in an HIV-1 infected person can be suppressed in the presence of HCV-specific CD4⁺ T cell response targeting non-structural proteins. However further research is needed in a larger group of patients to evaluate the role of HIV-1 on HCV-specific T cell responses in relation to outcome of acute HCV infection.

Phenotypic characterization of lymphocytes in HCV/HIV co-infected patients. Roe B, Coughlan S, Dean J, et al. Viral Immunol. 2009 Feb;22(1):39-48.

http://www.ncbi.nlm.nih.gov/pubmed/19210227?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

While hepatitis C virus (HCV)-specific immune responses are attenuated in HCV/HIV co-infected patients compared to those infected with HCV alone, the reasons for this remain unclear. In this study, the proportions of regulatory, naïve, and memory T cells, along with chemokine receptor expression, were measured in co-infected and mono-infected patients to determine if there is an alteration in the phenotypic profile of lymphocytes in these patients. HCV/HIV co-infected patients had increased proportions of CD4(+) naïve cells and decreased proportions of CD4(+) effector cells when compared to HCV mono-infected patients. The proportions of CD4(+) Tregs and CD4(+) CXCR3(+) T cells were also significantly lower in co-infected patients. A decrease in CD4(+) Tregs and subsequent loss of immunosuppressive function may contribute to the accelerated progression to liver disease in co-infected individuals. Dysregulation of immune responses following reduction in the proportions of CD4(+) CXCR3(+) Th-1 cells may contribute to the reduced functional capacity of HCV-specific immune responses in co-infected patients. The findings of this study provide new information on the T-cell immunophenotype in HCV/HIV co-infected patients when compared to those infected with HCV alone, and may provide insight into why cell-mediated immune responses are diminished during HCV infection.

Nonalcoholic fatty liver disease among HIV-infected persons. Crum-Cianflone N, Dilay A, Collins G. et al. *J Acquir Immune Defic Syndr.* 2009 Feb 16. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19225402?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To describe the prevalence and factors associated with nonalcoholic fatty liver disease (NAFLD) among HIV-infected persons not infected with hepatitis C virus (HCV).

DESIGN: A cross-sectional study among HIV-infected patients in a large HIV clinic.

METHODS: NAFLD was defined as steatosis among patients without viral hepatitis (B or C) coinfection or excessive alcohol use. The prevalence of NAFLD was identified by ultrasound examination evaluated by 2 radiologists blinded to the clinic information; liver biopsies were performed on a subset of the study population. Factors associated with NAFLD were evaluated by proportional odds logistic regression models.

RESULTS: Sixty-seven of 216 patients (31%) had NAFLD based on ultrasound evaluation. Among those with NAFLD, steatosis was graded as mild in 60%, moderate in 28%, and severe/marked in 12%. Factors associated with the degree of steatosis on ultrasound examination in the multivariate model included increased waist circumference [odds ratio (OR) 2.1 per 10 cm, $P < 0.001$], elevated triglyceride levels (OR 1.2 per 100 mg/dL, $P = 0.03$), and lower high-density lipoprotein levels (OR 0.7, per 10 mg/dL, $P = 0.03$). African Americans were less likely to have NAFLD compared with whites (14% vs. 35%), although this did not reach statistical significance (OR 0.4, $P = 0.08$). Similar associations were noted for the subset of patients diagnosed by liver biopsy. CD4 cell count, HIV viral load, duration of HIV infection, and antiretroviral medications were not independent risk factors associated with NAFLD after adjustment for dyslipidemia or waist circumference. **CONCLUSIONS:** NAFLD was common among this cohort of HIV-infected HCV-seronegative patients. NAFLD was associated with a greater waist circumference, low high-density lipoprotein, and high triglyceride levels. Antiretroviral medications were not associated with NAFLD; prospective studies are needed to confirm this finding.

Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network (Mortavic 2005 Study in collaboration with the Mortalité 2005 survey, ANRS EN19). Rosenthal E, Salmon-Céron D, Lewden C, et al. *HIV Med.* 2009 Feb 13. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19226410?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: More than 10 years after the introduction of combination antiretroviral therapy (cART), we examined the trend in the proportion of deaths caused by end-stage liver disease (ESLD) in HIV-infected adults in France between 1995 and 2005. **DESIGN AND METHODS:** In 2005, 34 departments prospectively recorded all deaths in HIV-infected patients who were followed in those departments (around 24 000). **Results** were compared with those of four previous cross-sectional surveys conducted since 1995 using the same methodology. Results Among 287 reported deaths in 2005, 100 (35%) were related to AIDS, and 48 (17%) to ESLD. Three out of four patients who died from ESLD-related causes had chronic hepatitis C. Excessive alcohol consumption was reported in approximately half of the patients (48%). At death, 62% of patients had undetectable HIV viral load and the median CD4 count was 237 cells/ μ L. From 1995 to 2005, the proportion of deaths caused by ESLD increased from 2 to 17% ($P < 0.001$). The proportion of deaths caused by hepatocellular carcinoma increased from 5% in 1995 to 25% in 2005 ($P = 0.0337$). **CONCLUSIONS:** Over the 10 years from 1995 to 2005, the proportion of deaths caused by hepatitis C virus-related ESLD has increased in HIV-infected patients. ESLD is currently a leading cause of death in this population, with hepatocellular carcinoma representing a quarter of liver-

related deaths. Recommendations for the detection of hepatocellular carcinoma should be strictly applied in these patients.

Is antiretroviral therapy causing long-term liver damage? A comparative analysis of HIV-mono-infected and HIV/hepatitis C co-infected cohorts. Moodie EE, Pant Pai N, Klein MD.. PLoS ONE. 2009;4(2):e4517. Epub 2009

http://www.ncbi.nlm.nih.gov/pubmed/19223976?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The effects of highly active antiretroviral therapy (HAART) on progression of hepatic fibrosis in HIV-hepatitis C virus (HCV) co-infection are not well understood. Deaths from liver diseases have risen in the post-HAART era, yet some cross-sectional studies have suggested that HAART use is associated with improved fibrosis rates. In a retrospective cohort of 533 HIV mono-infected and 127 HIV/HCV co-infected patients, followed between January 1991 and July 2005 at a university-based HIV clinic, we investigated the relationship between cumulative HAART exposure and hepatic fibrosis, as measured by the aspartate aminotransferase-to-platelet ratio index (APRI). We used a novel methodological approach to estimate the dose-response relationship of the effect of HAART exposure on APRI. HAART was associated with increasing APRI over time in HIV/HCV co-infected patients suggesting that they may be experiencing cumulative hepatotoxicity from antiretrovirals. The estimated median change (95% confidence interval) in APRI per one year of HAART intake was of -0.46% (-1.61% to 0.71%) in HIV mono-infected compared to 2.54% (-1.77% to 7.03%) in HIV/HCV co-infected patients. Similar results were found when the direct effect of HAART intake since the last visit was estimated on the change in APRI. HAART use associated is with increased APRI in patients with HIV/HCV co-infection. Therefore treatment for HCV infection may be required to slow the growing epidemic of end-stage liver disease in this population.

Safety of switching nevirapine twice daily to nevirapine once daily in virologically suppressed patients. Podzamczar D, Olmo M, Sanz J. et al. J Acquir Immune Defic Syndr. 2009 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19214120?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: The strategy of switching nevirapine (NVP) twice daily to once daily was evaluated. **METHODS:** Forty-eight-week randomized, open, multicenter trial. Stable HIV-infected patients on NVP twice daily for >12-18 weeks with alanine aminotransferase (ALT) <2.5, the upper normal limit were randomized to continue their regimen or switch to NVP 400 mg once daily. Primary end point was the proportion of ALT/aspartate transaminase (AST) \geq grade 3.

RESULTS: Two hundred eighty-nine patients were included, mean CD4 620 cells per microliter. Noninferiority was demonstrated in the per protocol analysis, with 97.9% (once daily) and 99.3% (twice daily) of patients event free (difference, 1.4%; 95% confidence interval, -1.95% to 5.4%), whereas 81.8% vs. 93.8% were event free by intent-to-treat switch = toxicity analysis (difference, 12%; 95% confidence interval, 4.6% to 19.4%). Only 4 patients (3 once daily, 1 twice daily) had NVP-related grade 3/4 ALT/AST increases, but in 2 of them (once daily), transaminases decreased despite continuation with NVP. Two other once daily patients presented grade 3/4 ALT/AST increase due to well-documented acute hepatitis A virus or hepatitis C virus infection. Grade 2 ALT/AST increases occurred in 11.2% (once daily) vs. 10.3% (twice daily) of patients (P = 0.80). A larger number of once daily patients were lost to follow-up/violated protocol (15% vs. 5%).

CONCLUSIONS: In patients on standard twice daily NVP-containing regimens for at least 12-18

weeks, per protocol analysis showed that switching to once daily NVP was not inferior to continued twice daily NVP in terms of the predefined noninferiority margin of 10% for hepatotoxicity.

High seroprevalence but low incidence of HCV infection in a cohort of patients with sexually transmitted HIV in Andalusia (South of Spain). Palacios R, Mata R, Aguilar I, et al.

J Int Assoc Physicians AIDS Care (Chic Ill). 2009 Feb 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19211932?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

PURPOSE: To analyze the prevalence and the incidence of hepatitis C virus (HCV) seropositivity in sexually transmitted human immunodeficiency virus (HIV) patients. **METHODS:** Observational study of 1468 sexually transmitted HIV-infected patients from 7 hospitals (Southern Spain).

Characteristics of HCV cases, and incidence of HCV seroconversion was assessed. **RESULTS:**

Seroprevalence of HCV was 16.1%, higher among heterosexual than homosexual patients, and similar between heterosexual men and women. Seroincidence was 0.16 cases per 100 patient-years, similar between homosexual and heterosexual patients. HCV patients had a mean CD4 of 523

cells/microL, 82.0% were on highly active antiretroviral therapy (HAART), and 72.0% had undetectable HIV viral load. Serum HCV-RNA was positive in 79.0% cases, and only 16.0% had

ever received HCV treatment. **CONCLUSIONS:** HCV seroprevalence among sexually transmitted HIV-infected patients is more frequent than in the general population; however, incidence of HCV infection is currently low. Patients with sexually transmitted HIV coinfecting with HCV have their HIV infection well controlled, but HCV infection was treated in few cases.

HIV-related liver disease: ARV drugs, coinfection, and other risk factors. Puoti M, Nasta P,

Gatti F, et al. J Int Assoc Physicians AIDS Care (Chic Ill). 2009 Feb 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19211929?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Highly-active antiretroviral therapy (HAART) has proven remarkably effective for prolonging the life of patients with human immunodeficiency virus (HIV). However, while most HAART agents are safe, many have the potential to cause liver toxicity. Physicians must therefore consider the possibility of drug-induced liver injury in the management of HIV-infected patients, especially those with certain risk factors such as coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV), female gender, alcohol abuse, older age, or obesity. Understanding how, when, and why drug-related liver damage occurs is key to managing these patients safely and effectively. Knowledge of HAART-related liver effects will help ensure that patients receive the most benefit with the least toxicity from any given drug regimen. As more information about the mechanisms of drug related liver injury is known, clinicians will be better able to tailor therapies to suit individual situations, resulting in greater patient safety and outcomes.

Hyaluronic acid, transforming growth factor-beta1 and hepatic fibrosis in patients with chronic hepatitis C virus and human immunodeficiency virus co-infection. Sanvisens A,

Serra I, Tural C, et al. J Viral Hepat. 2009 Feb 5. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19200132?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Chronic hepatitis C virus (HCV) infection follows an accelerated course in patients co-infected with human immunodeficiency virus (HIV); establishing the extent of liver fibrosis is crucial for disease staging and determining treatment strategy in these patients. The utility of noninvasive markers of fibrosis as alternatives to liver biopsy has not been well-studied in these patients. We evaluated the predictive value of serum transforming growth factor-beta1 (TGF-beta1) and hyaluronic acid (HA)

levels for determining the extent of liver fibrosis. Liver biopsies and blood samples were collected from 69 consecutive patients (74% male; median age, 41 years) between May 2005 and November 2006. Serum TGF-beta1 and HA were analysed using commercial kits. Aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transpeptidase levels were elevated in 81%, 70% and 60% of patients, respectively. Fifty-three patients (90%) were on highly active antiretroviral therapy and the median CD4-positive cell count was 422 cells/ μ L. The extent of fibrosis according to Scheuer's scoring was 32% F0 (no fibrosis), 16.5% F1, 16.5% F2, 26% F3 and 7% F4 (cirrhosis). Mean serum TGF-beta1 was 36.1 +/- 14.4 ng/mL; mean serum HA was 75.2 +/- 85.0 μ g/L. Serum HA was positively associated and significantly correlated with the stage of fibrosis ($r = 0.56$; $P < 0.05$). The area under the curve for discriminating mild (F0-F2) from significant (F3-F4) fibrosis in receiver operating analysis using HA was 0.83 (sensitivity, 87%; specificity, 70%). These data suggest that HA is clinically useful for predicting liver fibrosis and cirrhosis in patients co-infected with HCV/HIV. However, serum TGF-beta1 was not predictive of histological damage in co-infected individuals treated with HAART.

Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trial in acute hepatitis C. Matthews GV, Hellard M, Haber P, et al. Clin Infect Dis. 2009 Mar 1;48(5):650-8.

http://www.ncbi.nlm.nih.gov/pubmed/19191653?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: The Australian Trial in Acute Hepatitis C (ATAHC) is a National Institutes of Health-funded prospective cohort study of the natural history and efficacy of treatment in individuals with recently acquired hepatitis C. Enrollment is open to both human immunodeficiency virus (HIV)-infected and -uninfected individuals. The aim of this article was to evaluate characteristics and virological outcomes among HIV-infected individuals enrolled in ATAHC.

METHODS: Eligibility criteria included the first positive result of testing for anti-hepatitis C virus (HCV) antibody within 6 months and either clinical hepatitis diagnosed within the past 12 months or documented anti-HCV seroconversion within the past 24 months. **RESULTS:** Of the initial 103 patients enrolled, 27 (26%) were HIV infected. HIV-infected patients were more likely to be older, to have HCV genotype 1 infection and high levels of HCV RNA at baseline than were HCV-monoinfected patients. Sexual acquisition accounted for the majority (56%) of HCV infections among HIV-infected patients, compared with only 8% of HCV-monoinfected patients. The median duration from estimated HCV infection to treatment was 30 weeks. Treatment with 24 weeks of pegylated interferon and ribavirin resulted in rates of undetectability of HCV RNA of 95%, 90%, and 80% at weeks 12, 24, and 48, respectively. Undetectability at week 4 was achieved in 44% of patients and yielded positive and negative predictive values for sustained virological response of 100% and 33%, respectively. **CONCLUSIONS:** Significant differences were demonstrated between HIV-infected and HIV-uninfected individuals enrolled in ATAHC. Treatment responses among HIV-infected individuals with both acute and early chronic infection are encouraging and support regular HCV screening of high-risk individuals and early treatment for recently acquired HCV infection.

Involvement of hepatoma-derived growth factor in the growth inhibition of hepatocellular carcinoma cells by vitamin K(2). Yamamoto T, Nakamura H, Liu W, et al. *J Gastroenterol.* 2009;44(3):228-35. Epub 2009 Feb 13.

http://www.ncbi.nlm.nih.gov/pubmed/19214667?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Vitamin K(2) has been reported to suppress the growth of human hepatocellular carcinoma (HCC) in vitro and hepatocarcinogenesis in hepatitis C virus (HCV)-related cirrhosis in vivo. Hepatoma-derived growth factor (HDGF) is a unique nuclear targeting growth factor that is highly expressed in HCC cells and is a possible prognostic factor for patients with HCC. We investigated the regulation of HDGF expression by vitamin K(2). **METHODS:** Three HCC-derived cell lines, HepG2, HuH-7, and SK-Hep-1, were used. Cell number was determined with the MTT assay. The expression levels of HDGF mRNA and protein were measured by the real-time reverse transcriptase-polymerase chain reaction (PCR) method and ELISA and Western blot analysis, respectively. The HDGF promoter activity was measured by a dual luciferase-reporter assay. **RESULTS:** Vitamin K(2) suppressed the growth of the three HCC cell lines in a dose-dependent manner. Vitamin K(2) significantly suppressed the expression of the HDGF protein and mRNA in three cell lines. By a luciferase assay, vitamin K(2) significantly suppressed the promoter activity of the HDGF protein. Based on some luciferase-reporter plasmids containing truncated promoter regions, the possible responsive site of vitamin K(2) seems to reside in the region -1 to -150 bp of the HDGF gene. **CONCLUSIONS:** These findings suggested that regulation of the HDGF gene expression is one of the crucial mechanisms of vitamin K(2)-induced cell growth suppression for HCC.

Hepatic fatty acid composition differs between chronic hepatitis C patients with and without steatosis. Arendt BM, Mohammed SS, Aghdassi E, et al. *J Nutr.* 2009 Feb 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19211827?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Hepatic fatty acid (FA) composition may influence steatosis development in patients with chronic hepatitis C (CHC). In a cross-sectional study, we compared the hepatic FA profile in hepatitis C patients with (n = 9) and without (n = 33) steatosis (>/=5% of hepatocytes involved). FA composition of hepatic and RBC total lipids was measured by gas chromatography. Lipid peroxidation and antioxidants in liver and plasma, blood biochemistry, and nutritional status were also assessed. Patients with steatosis had more fibrosis, higher necroinflammatory activity of their hepatitis C infection, were more often infected with genotype 3, and had lower serum cholesterol. Monounsaturated FA in the liver were higher and trans FA were lower in patients with steatosis. Lower stearic acid and higher oleic acid in hepatic total lipids suggested higher Delta9-desaturase activity. alpha-Linolenic acid in the liver was higher and the ratios of long-chain PUFA:essential FA precursors were lower for (n-3) and (n-6) PUFA. Plasma vitamin C was lower in steatosis, but RBC FA composition and other parameters did not differ. We conclude that hepatic FA composition is altered in patients with hepatitis C and steatosis, probably due to modulation of enzymatic elongation and desaturation. Oxidative stress or nutritional status does not seem to play a predominant role for development of steatosis in CHC.

Isoflavone consumption and subsequent risk of hepatocellular carcinoma in a population-based prospective cohort of Japanese men and women. Kurahashi N, Inoue M, Iwasaki M, et al. *Int J Cancer*. 2009 Apr 1;124(7):1644-9.

http://www.ncbi.nlm.nih.gov/pubmed/19089922?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The incidence of hepatocellular carcinoma (HCC) is much higher in men than in women. Several experiment and epidemiological studies have suggested that estrogen might play an inhibitory role in the development of HCC. Because isoflavones have a similar structure as 17beta-estradiol and appear to have an anti-estrogenic effect in women and estrogenic effect in men, we hypothesized that the effect of isoflavones on HCC differs by sex. We investigated the association between isoflavones (genistein and daidzein) and soy products and HCC in Japan in a population-based prospective study in 19,998 Japanese (7,215 men and 12,783 women) aged 40-69 years. During 11.8 years of follow-up, 101 subjects (69 men and 32 women) were newly diagnosed with HCC. Case patients were grouped according to consumption of isoflavones and soy products and stratified by hepatitis virus infection. Hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC were calculated by Cox proportional-hazards modeling. In women, genistein and daidzein were dose-dependently associated with an increased risk of HCC, with multivariable HRs for the highest versus lowest tertile of 3.19 (95%CI = 1.13-9.00, p(trend) = 0.03) and 3.90 (95% CI = 1.30-11.69, p(trend) = 0.01), respectively. No association between isoflavones and HCC was observed in men. These results persisted when analysis was restricted to subjects positive for either or both hepatitis C and B virus. In conclusion, isoflavone consumption may be associated with an increased risk of HCC in women. Women with hepatitis virus infection may be advised to abstain from isoflavone consumption. Further studies are warranted to confirm these findings.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Hepatocellular carcinoma after sustained virologic response in hepatitis C patients without cirrhosis on a pretreatment liver biopsy. Sewell JL, Stick KM, Monto A. *Eur J Gastroenterol Hepatol*. 2009 Feb;21(2):225-9.

http://www.ncbi.nlm.nih.gov/pubmed/19212213?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Among hepatitis C patients, lack of cirrhosis and sustained virologic response (SVR) reduce the risk of hepatocellular carcinoma (HCC). Japanese studies document multiple cases of HCC among these patients, but only one case has been reported outside of Asia. We identified five patients with hepatitis C in our university-based hepatology practice who developed HCC despite SVR and lack of cirrhosis on their pretreatment liver biopsy. At the time of HCC diagnosis, two remained noncirrhotic, one had clearly progressed to cirrhosis, and two lacked repeat histology. We present these patients in a case series format and discuss several important implications of their cases. Physicians often base screening and treatment decisions on an initial liver biopsy performed years earlier. As fibrosis may advance, and because SVR and lack of cirrhosis do not fully protect against HCC, future study should further evaluate the risk of HCC among hepatitis C patients after sustained virologic response.

Risky sexual behavior, bleeding caused by intimate partner violence, and hepatitis C virus infection in patients of a sexually transmitted disease clinic. Russell M, Chen MJ, Nochajski TH, et al. Am J Public Health. 2009 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19218181?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: We sought to investigate independent contributions of risky sexual behaviors and bleeding caused by intimate partner violence to prediction of HCV infection. **Methods.** We conducted a case-control study of risk factors among patients of a sexually transmitted disease clinic with and without HCV antibodies, group-matched by age. **RESULTS:** Multivariate analyses indicated that Black race (odds ratio [OR]=2.4; 95% confidence interval [CI]=1.3, 4.4), injection drug use (OR=20.3; 95% CI=10.8, 37.8), sharing straws to snort drugs (OR=1.8; 95% CI=1.01, 3.0), sharing razors (OR=7.8; 95% CI=2.0, 31.0), and exposure to bleeding caused by intimate partner violence (OR=5.5; 95% CI=1.4, 22.8) contributed significantly to the prediction of HCV infection; risky sexual behavior and exposure to blood or sores during sexual intercourse did not.

CONCLUSIONS: HCV risk among patients of a sexually transmitted disease clinic can be explained by direct blood exposure, primarily through injection drug use. Exposure to bleeding caused by intimate partner violence may be a previously unrecognized mechanism for HCV transmission associated with risky sexual behavior.

Screening for non-alcoholic fatty liver disease (NAFLD), hepatitis B (HBV) and hepatitis C (HCV): A survey of community-based physicians. Kallman JB, Arsalla A, Park V, et al. Aliment Pharmacol Ther. 2009 Feb 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19220207?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

ABSTRACT BACKGROUND: Screening guidelines for hepatitis B (HBV) and C (HCV) as well as a position statement for non-alcoholic fatty liver disease (NAFLD) have been put forth by different sources but awareness of these guidelines and their impact on the physician practices have not been assessed. **AIM:** To assess the attitudes of primary care physicians (PCPs), gastroenterologists (GEs) and hepatologists (HEPs) regarding screening for HBV, HCV and NAFLD. **Design:** A survey was sent to PCPs, GEs and HEPs to assess issues related to HBV, HCV and NAFLD. The survey contained 10 items related to demographic and practice patterns of these physicians, 35 items related to HBV, 35 items related to HCV and 29 items related to NAFLD.

RESULTS: A total of 214 physicians [103 primary care physicians (PCPs), 59 gastroenterologists (GEs), and 52 hepatologists (HEPs)] completed the survey. The majority of PCPs, GEs, and HEPs agreed on most screening issues for these causes of liver disease. Nevertheless, within group comparison of physicians (guideline aware versus guideline unaware) showed significant differences in accurate response between those who were aware of guidelines versus those who were not aware.

CONCLUSIONS: A large percentage of PCPs and GEs were unaware of official guidelines for viral hepatitis B and C. Those aware of guidelines were more likely to screen appropriately and avoid unnecessary testing. More needs to be done to assess awareness and the impact implementation of official guidelines in hepatology.

Detection of hepatocellular carcinoma using glycomic analysis. Goldman R, Resson HW, Varghese RS, et al. Clin Cancer Res. 2009 Feb 17. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19223512?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

PURPOSE: Hepatocellular carcinoma (HCC) represents an increasing health problem in the United States. Serum alpha-fetoprotein, the currently used clinical marker, is elevated in only approximately

60% of HCC patients; therefore, the identification of additional markers is expected to have significant public health impact. The objective of our study was to quantitatively assess N-glycans originating from serum glycoproteins as alternative markers for the detection of HCC.

EXPERIMENTAL DESIGN: We used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for quantitative comparison of 83 N-glycans in serum samples of 202 participants (73 HCC cases, 77 age- and gender-matched cancer-free controls, and 52 patients with chronic liver disease). N-glycans were enzymatically released from serum glycoproteins and permethylated before mass spectrometric quantification. **RESULTS:** The abundance of 57 N-glycans was significantly altered in HCC patients compared with controls. The sensitivity of six individual glycans evaluated for separation of HCC cases from population controls ranged from 73% to 90%, and the specificity ranged from 36% to 91%. A combination of three selected N-glycans was sufficient to classify HCC with 90% sensitivity and 89% specificity in an independent validation set of patients with chronic liver disease. The three N-glycans remained associated with HCC after adjustment for chronic viral infection and other known covariates, whereas the other glycans increased significantly at earlier stages of the progression of chronic viral infection to HCC. **CONCLUSION:** A set of three identified N-glycans is sufficient for the detection of HCC with 90% prediction accuracy in a population with high rates of hepatitis C viral infection. Further evaluation of a wider clinical utility of these candidate markers is warranted.

Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size.

Craine N, Hickman M, Parry JV, et al. *Epidemiol Infect.* 2009 Feb 19:1-11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19224654?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: A prospective cohort study estimated the incidence of hepatitis C virus (HCV) in drug injectors in South Wales (UK). In total, 286/481 eligible seronegative individuals were followed up after approximately 12 months. Dried blood spot samples were collected and tested for anti-HCV antibody and behavioural data were collected at baseline and follow-up. HCV incidence was 5.9/100 person-years [95% confidence interval (CI) 3.4-9.5]. HCV incidence was predicted by community size [incident rate ratio (IRR) 6.6, 95% CI 2.11-20.51, $P=0.001$], homelessness (IRR 2.9, 95% CI 1.02-8.28, $P=0.047$) and sharing injecting equipment (IRR 12.7, 95% CI 1.62-99.6, $P=0.015$). HCV incidence was reduced in individuals in opiate substitution treatment (IRR 0.34, 95% CI 0.12-0.99, $P=0.047$). In order to reduce follow-up bias we used multiple imputation of missing data using switching regression; after imputation estimated HCV incidence was 8.5/100 person-years (95% CI 5.4-12.7). HCV incidence varies with community size, equipment sharing and homelessness are associated with increased HCV incidence and opiate substitution treatment may be protective against HCV.

Hepatitis C virus (HCV)-specific T-cell responses among recombinant immunoblot assay-3-indeterminate blood donors: a confirmatory evidence of HCV exposure.

Bes M, Esteban JI, Casamitjana N, et al. *Transfusion.* 2009 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19222816?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Blood donors are routinely screened for hepatitis C virus (HCV) infection. Some show weak anti-HCV responses, often restricted to a single antigen on confirmatory immunoblot (recombinant immunoblot assay [RIBA]) testing. The aim of this study was to investigate the extent to which such RIBA-indeterminate donors had previously been exposed to HCV. **STUDY DESIGN AND METHODS:** T-cell responses to HCV recombinant proteins (core,

NS3, and NS3 helicase) were analyzed using an interferon-gamma (IFN-gamma) enzyme-linked immunospot (ELISpot) assay and quantification of cytokines in culture supernatants in 27 RIBA-indeterminate donors, 60 RIBA-confirmed donors (48 with and 12 without HCV RNA), and 30 RIBA-negative donors. **RESULTS:** HCV-specific T-cell responses were identified in 13 (48%) RIBA-indeterminate donors, 33 (55%) RIBA-confirmed donors, and 4 (13%) RIBA-negative controls ($p = 0.008$ and $p < 0.001$, respectively). The magnitude of the T-cell response among indeterminate donors was similar to that of RIBA-confirmed donors for all HCV antigens and the specificity of the ELISpot results was confirmed by antigen-specific cytokine production (interleukin-2 and IFN-gamma) in short-term culture supernatants. **CONCLUSIONS:** These findings confirm that approximately half of RIBA-indeterminate donors have resolved a previous HCV infection and suggest that ELISpot might be a useful tool to clarify the status of such donors and help in their counseling and management.

Advanced recipient age (>60 years) alone should not be a contraindication to liver retransplantation. Schmitt TM, Kumer SC, Pruett TL, Argo CK, Northup PG. *Transpl Int.* 2009 Feb 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19220825?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

SUMMARY: Advanced age has been shown to be a risk factor for survival in primary liver transplantation. We sought to determine the independent influence of recipient age on retransplantation survival. The UNOS dataset was analyzed for adult, nonstatus 1, liver retransplantations since February 27, 2002. The univariate effect of age on 90-day and 1-year survival was analyzed. Multivariate survival models were used to determine 90-day, 1-year, and overall survival. Recipient age, donor age, model for end-stage liver disease (MELD) score, and hepatitis C status were used to construct multivariable survival models. Some 2141 liver retransplantations were analyzed. Overall, increasing recipient age was independently predictive of increasing mortality after liver retransplantation. In recipients between 18 and 60, there remained a direct relationship between age and mortality. However, in recipients aged over 60, increasing age was not independently associated with 90-day mortality ($P = 0.88$) and 1-year mortality ($P = 0.74$), despite adjusting for donor age, MELD score, and viral hepatitis status, suggesting that their original liver condition, their co-morbidities or perioperative condition plays an important role in retransplantation survival. Increasing recipient age up to 60, adversely affects liver retransplantation survival. After 60, there are no additional risks. Advanced age alone should not be an exclusionary factor when considering liver retransplantation; only the overall ability of the patient to tolerate a major surgery should be the determining factor.

Hepatocellular carcinoma in the Asia Pacific region. Yuen MF, Hou JL, Chutaputti A. *J Gastroenterol Hepatol.* 2009 Feb 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19220670?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Primary liver cancer, particularly hepatocellular carcinoma (HCC) remains a significant disease worldwide. It is among the top three causes of cancer death in the Asia Pacific region because of the high prevalence of its main etiological agents, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. In this region, the incidence of HCC has been static over recent decades. Older age is a major risk factor; the incidence increasing sharply after age 40 years. There is a male predilection, with male to female ratio of 3:1, except in elderly Japanese with equal sex incidence or female predominance. In most Asia-Pacific countries, chronic HBV infection accounts for 75-80% of cases; Japan, Singapore and Australia/New Zealand are exceptions because of higher prevalence

of HCV infection. In spite of advances in surgery, liver transplantation and newer pharmacological/biological therapies, the survival rate has improved only slightly over recent decades, and this could be attributable to earlier diagnosis ('lead-time bias'). The majority of patients present with advanced diseases, hence reducing the chance of curative treatment. The importance of HCC may decrease in two to three decades when the prevalence of chronic HBV infection decreases as a result of the universal HBV vaccination programs implemented in late 1980s in most Asia-Pacific countries, and because of reduced incidence of medical transmission of HCV. However, transmission of HCV by injection drug use, and rising prevalence of obesity and diabetes, both independent risk factors for HCC, may partly offset this decline.

Long-term outcomes of donation after cardiac death liver allografts from a single center.

Nguyen JH, Bonatti H, Dickson RC, et al. Clin Transplant. 2009 Feb 11. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19220366?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Long-term outcomes of donation after cardiac death liver allografts from a single center. Clin Transplant 2009 DOI: 10.1111/j.1399-0012.2009.00968.x (c) 2009 Wiley Periodicals, Inc. Abstract: Organ shortage continues to be a major challenge in transplantation. Recent experience with controlled non-heart-beating or donation after cardiac death (DCD) are encouraging. However, long-term outcomes of DCD liver allografts are limited. In this study, we present outcomes of 19 DCD liver allografts with follow-up >4.5 years. During 1998-2001, 19 (4.1%) liver transplants (LT) with DCD allografts were performed at our center. Conventional heart-beating donors included 234 standard criteria donors (SCD) and 214 extended criteria donors (ECD). We found that DCD allografts had equivalent rates of primary non-function and biliary complications as compared with SCD and ECD. The overall one-, two-, and five-yr DCD graft and patient survival was 73.7%, 68.4%, and 63.2%, and 89.5%, 89.5%, and 89.5%, respectively. DCD graft survival was similar to graft survival of SCD and ECD in non hepatitis C virus (HCV) recipients ($p > 0.370$). In contrast, DCD graft survival was significantly reduced in HCV recipients ($p = 0.007$). In conclusion, DCD liver allografts are durable and have acceptable long-term outcomes. Further research is required to assess the impact of HCV on DCD allograft survival.

Effects of a hepatitis C virus educational intervention or a motivational intervention on alcohol use, injection drug use, and sexual risk behaviors among injection drug users.

Zule WA, Costenbader EC, Coomes CM, Wechsberg WM. Am J Public Health. 2009 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19218179?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: We compared the effects of 2 interventions on alcohol use, use of a new syringe at last injection, and condom use at last sexual encounter in a community sample of injection drug users. **METHODS:** Between 2003 and 2006, 851 out-of-treatment injection drug users were recruited in Raleigh, NC, and Durham, NC, through street outreach and were randomly assigned to either a 6-session educational intervention or a 6-session motivational intervention. Intervention effects were examined at 6 and 12 months after enrollment. **RESULTS:** In multiple logistic regression analyses adjusted for baseline alcohol use and HCV status, participants assigned to the motivational intervention were significantly less likely than were participants in the educational intervention to be drinking at the 6-month follow-up (odds ratio=0.67; 95% confidence interval=0.46, 0.97). There were no significant between-group differences in use of a new syringe at last injection or condom use at last sexual encounter at either follow-up. **CONCLUSIONS:** Reducing alcohol use among persons with HCV may slow disease progression and provide

important health benefits. Additional strategies are needed for slowing HCV disease progression until more effective HCV treatments are available.

Doing harm reduction better: syringe exchange in the United States. Des Jarlais DC, McKnight C, Goldblatt C, Purchase D. *Addiction*. 2009 Feb 10. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19215605?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To trace the growth of syringe exchange programs (SEPs) in the United States since 1994-95 and assess the current state of SEPs. **METHODS:** Annual surveys of US SEPs known to North American Syringe Exchange Network (NASEN). Surveys mailed to executive directors with follow-up interviews by telephone and/or e-mail. Response rates have varied between 70% and 88% since surveys were initiated in 1996. **RESULTS:** The numbers of programs known to NASEN have increased from 68 in 1994-95 to 186 in 2007. Among programs participating in the survey, numbers of syringes exchanged have increased from 8.0 million per year to 29.5 million per year, total annual budgets have increased from \$6.3 to \$19.6 million and public funding (from state and local governments) has increased from \$3.9 to \$14.4 million. In 2007, 89% of programs permitted secondary exchange and 76% encouraged it. Condoms, referrals to substance abuse treatment, human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) counseling and testing and naloxone for overdose were among the most commonly provided services in addition to basic syringe exchange. Each of these services was provided by 40% or more of SEPs in 2007. **CONCLUSIONS:** While syringe exchange has remained controversial in the United States, there has been very substantial growth in numbers of programs, syringes exchange and program budgets. Utilizing secondary exchange to reach large numbers of injecting drug users and utilizing SEPs as a new platform for providing health and social services beyond basic syringe exchange have been the two major organizational strategies in the growth of SEPs in the United States.

Should Brazilian patients with chronic hepatitis C virus infection be vaccinated against hepatitis A virus? Villar LM, de Melo MM, Calado IA, et al. *J Gastroenterol Hepatol*. 2009 Feb;24(2):238-42

http://www.ncbi.nlm.nih.gov/pubmed/19215334?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND AND AIM: Hepatitis A virus (HAV) superinfection is associated with a high risk of liver failure and death in patients with hepatitis C virus (HCV) infection. The aim of this study was to investigate the presence of serological and molecular HAV markers in a population of HCV-infected patients in order to determine a cost-effective strategy to vaccinate against HAV. **METHODS:** The presence of total and immunoglobulin (Ig)M anti-HAV antibodies was investigated in 399 patients (median age, 50 years; range, 4-81) referred to the Public Health Central Laboratory of Pernambuco State who tested positive for anti-HCV antibodies and HCV RNA. HAV RNA was investigated by reverse transcription-nested polymerase chain reaction in these patients. **RESULTS:** Three hundred and eighty-four (96%) patients were positive for anti-HAV total and negative for IgM anti-HAV antibodies (immune patients). Three patients had IgM (and total) anti-HAV antibodies, showing an acute infection, and two of them had HAV RNA detected in serum samples. HAV RNA was also found in another patient in the absence of detectable anti-HAV antibodies. By nucleotide sequencing, it was demonstrated that the HAV isolates infecting these patients belonged to subgenotype 1B. **CONCLUSION:** This study provides valuable new data on anti-HAV prevalence among HCV carriers in Brazil. In the present study, we found a high proportion of patients with anti-HAV positivity, indicating that anti-HAV testing of HCV-infected patients is a cost-effective strategy and should be carried out before vaccination against HAV in

these patients, particularly in regions such as our geographical area with high total anti-HAV prevalence.

A novel diagnostic target in the hepatitis C virus genome. Drexler JF, Kupfer B, Petersen N, et al. PLoS Med. 2009 Feb 10;6(2):e31. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19209955?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Detection and quantification of hepatitis C virus (HCV) RNA is integral to diagnostic and therapeutic regimens. All molecular assays target the viral 5'-noncoding region (5'-NCR), and all show genotype-dependent variation of sensitivities and viral load results. Non-western HCV genotypes have been under-represented in evaluation studies. An alternative diagnostic target region within the HCV genome could facilitate a new generation of assays. **METHODS AND FINDINGS:** In this study we determined by de novo sequencing that the 3'-X-tail element, characterized significantly later than the rest of the genome, is highly conserved across genotypes. To prove its clinical utility as a molecular diagnostic target, a prototype qualitative and quantitative test was developed and evaluated multicentrically on a large and complete panel of 725 clinical plasma samples, covering HCV genotypes 1-6, from four continents (Germany, UK, Brazil, South Africa, Singapore). To our knowledge, this is the most diversified and comprehensive panel of clinical and genotype specimens used in HCV nucleic acid testing (NAT) validation to date. The lower limit of detection (LOD) was 18.4 IU/ml (95% confidence interval, 15.3-24.1 IU/ml), suggesting applicability in donor blood screening. The upper LOD exceeded 10⁽⁻⁹⁾ IU/ml, facilitating viral load monitoring within a wide dynamic range. In 598 genotyped samples, quantified by Bayer VERSANT 3.0 branched DNA (bDNA), X-tail-based viral loads were highly concordant with bDNA for all genotypes. Correlation coefficients between bDNA and X-tail NAT, for genotypes 1-6, were: 0.92, 0.85, 0.95, 0.91, 0.95, and 0.96, respectively; X-tail-based viral loads deviated by more than 0.5 log₁₀ from 5'-NCR-based viral loads in only 12% of samples (maximum deviation, 0.85 log₁₀). The successful introduction of X-tail NAT in a Brazilian laboratory confirmed the practical stability and robustness of the X-tail-based protocol. The assay was implemented at low reaction costs (US\$8.70 per sample), short turnover times (2.5 h for up to 96 samples), and without technical difficulties. **CONCLUSION:** This study indicates a way to fundamentally improve HCV viral load monitoring and infection screening. Our prototype assay can serve as a template for a new generation of viral load assays. Additionally, to our knowledge this study provides the first open protocol to permit industry-grade HCV detection and quantification in resource-limited settings.

Serum ferritin as a predictor of treatment outcome in patients with chronic hepatitis C.

Ferrara F, Ventura P, Vegetti A, et al. Am J Gastroenterol. 2009 Feb 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19209167?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: Antiviral treatment in chronic hepatitis C (CHC) involves ribavirin, a hemolytic agent. We planned a prospective study to evaluate whether drug-induced iron perturbation is clinically relevant as it relates to therapeutic outcome. **METHODS:** Iron variables were sequentially assessed in 206 CHC patients undergoing antiviral therapy and were correlated with pretreatment iron status and histology, hemolysis, and therapeutic outcome. **RESULTS:** At week 1 of therapy, serum iron (SI), transferrin saturation (TS), and serum ferritin (SF) increased markedly in all patients. All iron parameters correlated with hemolysis up to week 4; this correlation was lost for SF at later time points. SF rise during treatment was inversely related to baseline SF and iron deposits in hepatic mesenchymal/Kupffer cells. Both baseline SF and mesenchymal iron significantly correlated

with fibrosis at multivariate analysis ($P=0.015$ and 0.008 , respectively). Interestingly, baseline SF, despite good specificity (89%), had low sensitivity in predicting siderosis (25%). During therapy, SI, TS, and hemolysis parameters did not correlate with sustained virological response (SVR), whereas SF rise became an independent predictor of therapeutic response: a 2.5-fold increase of SF at week 12 associated with higher likelihood of SVR (odds ratio 1.91, $P=0.032$). Accordingly, lack of mesenchymal iron deposits at the baseline biopsy correlated with SVR (odds ratio 3.02, $P=0.043$). **CONCLUSIONS:** In CHC, SF is a useful marker for assessing disease duration and progression before starting treatment and for predicting therapeutic response while on therapy. SF rise during antiviral therapy is largely independent of hemolysis and likely indicates activation of macrophages in response to antivirals. *Am J Gastroenterol* advance online publication, 10 February 2009; doi:10.1038/ajg.2008.126.

Improving survey methods in sero-epidemiological studies of injecting drug users: a case example of two cross sectional surveys in Serbia and Montenegro. Judd A, Rhodes T, Johnston LG, et al. *BMC Infect Dis.* 2009 Feb 9;9(1):14. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19203380?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Little is known about the prevalence of HIV or HCV in injecting drug users (IDUs) in Serbia and Montenegro. We measured prevalence of antibodies to HIV (anti-HIV) and hepatitis C virus (anti-HCV), and risk factors for anti-HCV, in community-recruited IDUs in Belgrade and Podgorica, and determined the performance of a parallel rapid HIV testing algorithm. **METHODS:** Respondent driven sampling and audio-computer assisted survey interviewing (ACASI) methods were employed. Dried blood spots were collected for unlinked anonymous antibody testing. Belgrade IDUs were offered voluntary confidential rapid HIV testing using a parallel testing algorithm, the performance of which was compared with standard laboratory tests. Predictors of anti-HCV positivity and the diagnostic accuracy of the rapid HIV test algorithm were calculated. **RESULTS:** Overall population prevalence of anti-HIV and anti-HCV in IDUs were 3% and 63% respectively in Belgrade ($n=433$) and 0% and 22% in Podgorica ($n=328$). Around a quarter of IDUs in each city had injected with used needles and syringes in the last four weeks. In both cities anti-HCV positivity was associated with increasing number of years injecting (eg Belgrade adjusted odds ratio (AOR) 5.6 (95% CI 3.2-9.7) and Podgorica AOR 2.5 (1.3-5.1) for ≥ 10 years v 0-4 years), daily injecting (Belgrade AOR 1.6 (1.0-2.7), Podgorica AOR 2.1 (1.3-5.1)), and having ever shared used needles/syringes (Belgrade AOR 2.3 (1.0-5.4), Podgorica AOR 1.9 (1.4-2.6)). Half (47%) of Belgrade participants accepted rapid HIV testing, and there was complete concordance between rapid test results and subsequent confirmatory laboratory tests (sensitivity 100% (95%CI 59%-100%), specificity 100% (95%CI 98%-100%)). **CONCLUSION:** The combination of community recruitment, ACASI, rapid testing and a linked diagnostic accuracy study provide enhanced methods for conducting blood borne virus sero-prevalence studies in IDUs. The relatively high uptake of rapid testing suggests that introducing this method in community settings could increase the number of people tested in high risk populations. The high prevalence of HCV and relatively high prevalence of injecting risk behaviour indicate that further HIV transmission is likely in IDUs in both cities. Urgent scale up of HIV prevention interventions is needed.

Alcohol and other drug treatment experiences of hepatitis C-positive and negative clients: implications for hepatitis C treatment. Brener L, Treloar CJ. Aust Health Rev. 2009 Feb;33(1):100-6.

http://www.ncbi.nlm.nih.gov/pubmed/19203339?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

To assess whether HCV-positive clients perceive that alcohol and other drug (AOD) staff discriminate against them, this study compared the treatment experiences of 120 HCV-positive clients with those of 120 HCV-negative clients attending the same AOD treatment facility. Despite the overall findings of favourable attitudes of HCV-positive clients toward their health care workers, these attitudes were less positive than those of their HCV-negative counterparts. Clients with HCV also rated their interpersonal treatment by their health care workers less favourably. These findings suggest that HCV-positive clients' attitudes towards their health care workers and their experiences of differential treatment by these health care workers might be a barrier to HCV treatment uptake in AOD treatment facilities.

Amidinoanthracyclines - a new group of potential anti-hepatitis C virus compounds.

Krawczyk M, Wasowska-Lukawska M, Oszczapowicz I, et al. Biol Chem. 2009 Feb 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19199832?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Hepatitis C virus (HCV) infections represent one of the major and still unresolved health problems because the current therapy is effective in only 50-80% of the cases, depending on viral genotype. A large group of amidinoanthracyclines, with decreased acute toxicity and cardiotoxicity compared to the parent antibiotics, was tested in a high-throughput fluorometric HCV helicase assay. Here we report the selection of more than fifty potent inhibitors of helicase activity that inhibit the enzyme with IC₅₀ values in the range of 0.03-10 μM; four of these compounds are the most potent inhibitors of helicase activity described in literature. The activity of these inhibitors is highly dependent on their chemical structure, mainly on the substituent at the amidino carbon atom and on the orientation of the hydroxyl group at the 4' position of the daunosamine moiety. The most effective compounds act not solely via intercalation into the double-stranded DNA substrate, but also compete with the enzyme for access to the substrate, impeding formation of the active helicase complex. Selected amidinoanthracyclines were tested in the subgenomic HCV replicon system. These experiments confirmed the antiviral activity of two selected inhibitors (EC₅₀ values below 0.2 μM with selectivity indices of 19 and 33) and proved that they may be considered as potential anti-HCV drugs.

Temporal dynamics of a predominant protease inhibitor-resistance mutation in a treatment-naive, hepatitis C virus-infected individual. Kim AY, Timm J, Nolan BE, et al. J Infect Dis. 2009 Mar 1;199(5):737-41.

http://www.ncbi.nlm.nih.gov/pubmed/19199553?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The dramatic antiviral activities of drugs that specifically inhibit hepatitis C virus replication can be tempered by baseline mutations that confer resistance. We describe the kinetics of an R155K mutation in hepatitis C virus (HCV) NS3 protease known to confer resistance to specific protease inhibitors in an individual coinfecting with human immunodeficiency virus-1 and HCV. Longitudinal sequences revealed changes in the relative frequency with which this variant was observed independent of HCV replication levels, illustrating that this mutation coexists with wild-type strains

in vivo in the absence of drugs. The persistence of drug-resistance mutations argues for baseline resistance genotyping at the time therapy is initiated to accurately predict the efficacy of treatment.

Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection. Sroczynski G, Esteban E, Conrads-Frank A, et al. *Eur J Public Health*. 2009 Feb 5. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19196737?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Hepatitis C virus (HCV) infection is an emerging problem in public health. In most countries, the majority of HCV infected people are yet undiagnosed. Early detection and treatment may result in better health outcomes and save costs by preventing future advanced liver disease. The evidence for long-term effectiveness and cost-effectiveness of HCV screening was systematically reviewed. **METHODS:** We performed a systematic literature search on long-term health-economic effects of HCV screening and included Health Technology Assessment (HTA) reports, systematic reviews, long-term clinical trials, full health economic and decision-analytic modelling studies with a sufficiently long time horizon and patient-relevant long-term outcomes such as life-years gained (LYG) or quality-adjusted life years (QALY) gained. Economic results were converted to 2005 Euros. **RESULTS:** Seven studies were included. Target population, HCV prevalence, study perspective, discount rate, screening and antiviral treatment mode varied. The incremental effectiveness of HCV screening and early treatment compared to no screening and standard care varied from 0.0004 to 0.066 LYG, and from 0.0001 to 0.072 QALY. Incremental cost-effectiveness and cost-utility ratios of HCV screening vs. no screening were 3900-243 700 euro/LYG and 18 300-1 151 000 euro/QALY. HCV screening seems to be cost-effective in populations with high HCV prevalence, but not in low HCV prevalence populations.

CONCLUSIONS: HCV screening and early treatment have the potential to improve average life-expectancy, but should focus on populations with elevated HCV prevalence to be cost-effective. Further research on the long-term health-economic impact of HCV screening when combined with appropriate monitoring strategies in different European health care systems is needed.

Antiviral treatment for hepatitis C virus infection: Effectiveness at general population level in a highly endemic area. Mariano A, Caserta C, Pendino GM, et al. *Dig Liver Dis*. 2009 Feb 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19196557?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Peginterferon plus ribavirin treatment induced a sustained virological response in >50% of HCV-RNA-positive individuals enrolled in published clinical trials. **AIM:** To determine anti-HCV treatment effectiveness at a general population level. **PATIENTS AND METHODS:** In 2002, a 1:5 random sample of >11 years old inhabitants of a small Italian town (Cittanova) was invited for HCV screening. HCV-RNA-positive individuals were evaluated for antiviral treatment. **RESULTS:** 1645 of 1924 invited individuals (85.5%) participated in the screening. 84 HCV-RNA-positive individuals were detected: median age was 65 years (range: 32-87); 67% was infected with genotype 1 or 4. Antiviral treatment was judged unnecessary for 43 (51.2%), due to persistently normal alanine aminotransferases, mild disease at liver biopsy or age >70 years without cirrhosis. Twenty-eight of the remaining 41 patients (68.3%) were ineligible for treatment, because of medical/psychiatric contraindications (42.9%), alcohol/drug abuse (17.9%), decompensated cirrhosis/hepatocellular carcinoma (17.9%), not attending official appointments (10.7%), previous intolerance/non-response to interferon plus ribavirin (10.7%). 5 of 13 eligible patients (38.5%) did not receive treatment (4 refused and 1 accidental death). 3 of 8 treated patients (37.5%) reached a

sustained virological response. **CONCLUSIONS:** Although efficacy of anti-HCV therapy improved in recent years, we found that low eligibility to treatment still limited its effectiveness at general population level in a highly endemic town.

Epidemiological and genetic analyses of Hepatitis C virus transmission among young/ short- and long-term injecting drug users from Rio de Janeiro, Brazil. Oliveira MD, Bastos FI, Telles PR, et al. J Clin Virol. 2009 Feb 3. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19195927?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Injecting drug users (IDU) have a key role in Hepatitis C Virus (HCV) epidemiology. Young/short-term IDUs constitute a target group for preventive/harm reduction interventions. **OBJECTIVES:** To investigate HCV transmission among young/short-term (ST) and long-term (LT) IDUs, from the perspective of epidemiology and molecular biology. **STUDY DESIGN:** Cross-sectional study assessing the prevalence of HCV infection/genotypes, as well as risk behaviours/practices among IDUs from Rio de Janeiro. Phylogenetic analyses were performed and the extent of segregation between sequences was quantified by the Association Index. **RESULTS:** ST were more likely to engage into needle-sharing ($p=.021$) and LT to attend Needle Exchange Programs ($p=.006$). HCV prevalence was 10.1% vs. 23.4% among initiates and LT, respectively ($p<.001$). Older age vs. imprisonment and longer duration of IDU career were independent predictors for HCV infection among ST and LT, respectively. Among the latter, NEP attendance was inversely associated with viral infection. HCV3a infections were the most prevalent. A moderate extent of phylogenetic segregation between sequences was found, suggestive of transmission between IDU subgroups. **CONCLUSIONS:** The lower HCV prevalence among young/short-term IDUs cannot be viewed with complacency, due to their frequent engagement into direct/indirect sharing practices and the ongoing transmission between IDU subsets. To avert new infections, preventive/harm reduction policies must be tailored to empirical findings.

Use of specialty care versus standard retail pharmacies for treatment of hepatitis C (February). Cohen SM, Kwasny MJ, Ahn J. Ann Pharmacother. 2009 Feb 3. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19193591?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Treatment for hepatitis C virus (HCV) is associated with significant adverse events. Improved adherence increases the probability of achieving sustained virologic response (SVR). Despite a lack of supporting literature, the use of specialty care pharmacies has increased in recent years in an attempt to improve HCV treatment outcomes. **OBJECTIVE:** To compare specialty care versus standard retail pharmacies in HCV treatment outcomes, utilization of office resources, and the use of supplemental medications. **METHODS:** A retrospective chart review was performed at a single academic institution for adults with HCV infection treated between 2001 and 2006. SVR was the primary endpoint. Secondary endpoints included therapy completion rates, HCV treatment dose reductions, additional phone calls and clinic visits, and the use of supplemental medications. **RESULTS:** One hundred ninety-seven patients were identified (102 standard and 95 specialty care pharmacy). There were no differences in baseline demographics between the groups, except for a higher proportion of African Americans using specialty care pharmacies. Overall SVR was 103/197 (52%). SVR was 57/102 (56%) in the standard pharmacy group and 46/95 (48%) in the specialty care pharmacy group. There were no statistically significant differences with regard to SVR (even after accounting for differences in ethnicity), the use of supplemental medications, additional clinic phone calls and visits required, and the reasons for HCV therapy discontinuation. There was a statistically significantly higher incidence of HCV medication dose reductions in the

standard retail pharmacy group (45% vs 28%; $p = 0.016$). **CONCLUSIONS:** The use of specialty care pharmacies for the treatment of HCV was not associated with higher SVR rates. Patients using specialty care pharmacies had a lower incidence of interferon and/or ribavirin dose reductions, but there was no difference between the groups in therapy completion rates, use of additional office resources, or use of supplemental medications.

Viral Nucleic Acid Testing (NAT) and OPO-level disposition of high-risk donor organs.

Kucirka LM, Alexander C, Namuyinga R, et al. Am J Transplant. 2009 Feb 3. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19191766?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The use of Public Health Service/Centers for Disease Control and Prevention (PHS/CDC) high-risk donor (HRD) organs remains controversial, especially in light of a recent high-profile case of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission. Nucleic acid testing (NAT), while more expensive and time consuming, reduces infectious risk by shortening the period between infection and detectability. The purpose of this study was to characterize HRDs and disposition of their organs by organ procurement organization (OPO), to measure NAT practices by OPO and to examine associations between NAT practices and use of HRD organs. We analyzed 29 950 deceased donors (2574 HRDs) reported to UNOS since July 1, 2004 and May 8, 2008. We then surveyed all OPO clinical directors about their use of NAT, average time to receive NAT results, locations where NAT is performed and percentage of the time NAT results are available for allocation decisions. In total, 51.7% of OPOs always perform HIV NAT, while 24.1% never do. A similar pattern is seen for HCV NAT performance, while the majority (65.6%) never perform HBV NAT. AIDS prevalence in an OPO service area is not associated with NAT practice. OPOs that perform HIV NAT are less likely to export organs outside of their region. The wide variation of current practice and the possibility that NAT would improve organ utilization support consideration for a national policy.

Lay management of chronic disease: a qualitative study of living with hepatitis C infection.

Stoller EP, Webster NJ, Blixen CE, et al. Am J Health Behav. 2009 Jul-Aug;33(4):376-90. http://www.ncbi.nlm.nih.gov/pubmed/19182983?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: To examine management strategies and goals reported by people diagnosed with chronic hepatitis C. **METHODS:** We analyzed data from semistructured interviews ($N = 42$) and from electronic sources [illness narratives ($N = 79$) and Internet threaded discussions ($N = 264$)]. Line-by-line coding, comparisons, and team discussions generated catalogs of lay management strategies and goals. We analyzed code-based files to identify informants' selection of specific strategies for each goal. **RESULTS:** We classified lay management strategies into 3 categories: medical self-care, behavior change, and coping. These strategies were used selectively in addressing multiple goals, categorized as fighting the virus, strengthening the body, and managing consequences. **CONCLUSIONS:** Results underscore the diversity of strategies for living with a disease characterized by uncertain prognosis and variable expression of symptoms.

Development and characterization of hepatitis C virus genotype 1-7 cell culture systems: role of CD81 and scavenger receptor class B type I and effect of antiviral drugs. Gottwein JM, Scheel TK, Jensen TB, et al. *Hepatology*. 2009 Feb;49(2):364-77

http://www.ncbi.nlm.nih.gov/pubmed/19148942?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Six major hepatitis C virus (HCV) genotypes and numerous subtypes have been described, and recently a seventh major genotype was discovered. Genotypes show significant molecular and clinical differences, such as differential response to combination therapy with interferon-alpha and ribavirin. Recently, HCV research has been accelerated by cell culture systems based on the unique growth capacity of strain JFH1 (genotype 2a). By development of JFH1-based intergenotypic recombinants containing Core, envelope protein 1 and 2 (E1, E2), p7, and nonstructural protein 2 (NS2) of genotype 6a and 7a strains, as well as subtype 1b and 2b strains, we have completed a panel of culture systems for all major HCV genotypes. Efficient growth in Huh7.5 cells depended on adaptive mutations for HK6a/JFH1 (6a/2a, in E1 and E2) and J4/JFH1 (1b/2a, in NS2 and NS3); viability of J8/JFH1 (2b/2a) and QC69/JFH1 (7a/2a) did not require adaptation. To facilitate comparative studies, we generated virus stocks of genotype 1-7 recombinants with infectivity titers of $10^{3.7}$ to $10^{5.2}$ 50% tissue culture infectious dose/mL and HCV RNA titers of $10^{7.0}$ to $10^{7.9}$ IU/mL. Huh7.5 cultures infected with genotype 1-6 viruses had similar spread kinetics, intracellular Core, NS5A, and lipid amounts, and colocalization of Core and NS5A with lipids. Treatment with interferon-alpha2b but not ribavirin or amantadine showed a significant antiviral effect. Infection with all genotypes could be blocked by specific antibodies against the putative coreceptors CD81 and scavenger receptor class B type I in a dose-dependent manner. Finally, neutralizing antibodies in selected chronic phase HCV sera had differential effects against genotype 1-7 viruses. **CONCLUSION:** We completed and characterized a panel of JFH1-based cell culture systems of all seven major HCV genotypes and important subtypes and used these viruses in comparative studies of antivirals, HCV receptor interaction, and neutralizing antibodies.

Transmission of hepatitis C virus in an orthopedic hospital ward. Ross RS, Viazov S, Khudyakov YE, et al. *J Med Virol*. 2009 Feb;81(2):249-57

http://www.ncbi.nlm.nih.gov/pubmed/19107970?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Healthcare-associated infections with hepatitis C virus (HCV) hitherto have been observed mainly in hemodialysis settings as well as in hematology and oncology wards. In this communication, molecular and epidemiologic investigations to elucidate an HCV outbreak in an orthopedic ward are reported. One hundred and thirty-five patients hospitalized in the ward and 104 staff members were tested. In addition to extensive epidemiologic reviews and hygienic inspections, direct sequencing of HCV PCR fragments and phylogenetic analysis of more than 300 partial HCV sequences obtained by end-point limiting-dilution real-time PCR assay were carried out. Six patients were infected with very closely related HCV variants. Patient-to-patient spread of the virus was inferred to have started from one patient with previous HCV infection to the other five patients during their hospital stay. Inspections did not reveal substantial breaches in basic infection control practices and did not identify a specific activity that might have led to nosocomial transmission. As a result of the investigations, the hospital corrected the documentation of all medical and nursing activities undertaken in the ward, abandoned the use of all multidose saline and other medication vials, and included explicitly recommendations for the safe preparation and administration of injectable drugs into internal infection control guidelines. Thereafter, no further nosocomial transmissions of HCV have been recorded in the orthopedic ward. The events observed suggest that nosocomial

transmission of HCV is not limited to hemodialysis, hematology or oncology settings, and they also reinforce the mandatory adherence to basic infection control practices. (c) 2008 Wiley-Liss, Inc.

Serum aminotransferase level and the risk of hepatocellular carcinoma: a population-based cohort study in Japan. Ishiguro S, Inoue M, Tanaka Y, et al. *Eur J Cancer Prev.* 2009 Feb;18(1):26-32.

http://www.ncbi.nlm.nih.gov/pubmed/19077561?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Aminotransferase level is presumed to be a marker of hepatic inflammation, but uncertainty remains whether elevated aminotransferase levels are associated with an increased risk of hepatocellular carcinoma (HCC). We evaluated the incidence of HCC by aminotransferase level in 19 812 middle-aged and older individuals with and without hepatitis virus infection from a large-scale population-based cohort study (JPHC Study cohort II) in Japan. Hepatitis virus infection was identified at baseline in 1236 participants, namely 737 (3.7%) with hepatitis C virus, 479 (2.4%) with hepatitis B virus, and 20 (0.1%) with both. By the end of follow-up, a total of 109 newly arising HCC cases were diagnosed (71 men, 38 women), of which 87 (79.8%) had evidence of viral etiology. Alanine aminotransferase (ALT) was concentration-dependently associated with an increased risk of HCC in both virus-positive and virus-negative participants. Compared with virus-negative participants with ALT levels of less than 30 IU/l, a significant increase in the risk of HCC was observed in virus-negative participants with an ALT level greater than 30 IU/l, and in virus-positive participants with an ALT less than 30 IU/l, 30-69 IU/l, and ≥ 70 IU/l [Hazard ratio (95% confidence interval): 9.4 (3.9-22.3), 15.2 (6.1-37.6), 180.5 (89.4-364.2), 454.2 (221.5-931.2), respectively; P for trend < 0.001]. In conclusion, our findings suggest that elevated ALT levels are strongly associated with the incidence of HCC regardless of hepatitis virus positivity. This finding indicates that ALT level is a good independent determinant of the need for intervention. Clinical application of these findings may help decrease HCC-associated mortality in hepatitis virus-endemic regions.

Little evidence that hepatitis C virus leads to a higher risk of mortality in the absence of cirrhosis and excess alcohol intake: the Swiss Hepatitis C Cohort Study. Prasad L, Spicher VM, Negro F, Rickenbach M, Zwahlen M; the Swiss Hepatitis C Cohort Study Group. *J Viral Hepat.* 2009 Feb 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19243494?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The objective of this study was to describe the all-cause mortality of participants in the Swiss Hepatitis C Cohort compared to the Swiss general population. Patients with hepatitis C virus (HCV) infection attending secondary and tertiary care centres in Switzerland. One thousand six hundred and forty-five patients with HCV infection were followed up for a mean of over 2 years. We calculated all-cause standardized mortality ratios (SMR) and 95% confidence intervals (CI) using age, sex and calendar year-specific Swiss all-cause mortality rates. Multivariable Poisson regression was used to model the variability of SMR by cirrhotic status, HCV genotype, infection with hepatitis B virus or HIV, injection drug use and alcohol intake. Sixty-one deaths were recorded out of 1645 participants. The crude all-cause SMR was 4.5 (95% CI: 3.5-5.8). Patients co-infected with HIV had a crude SMR of 20 (95% CI: 11.1-36.1). The SMR of 1.1 (95% CI: 0.63-2.03) for patients who were not cirrhotic, not infected with HBV or HIV, did not inject drugs, were not heavy alcohol consumers (≤ 40 g/day) and were not genotype 3, indicated no strong evidence of excess mortality. We found little evidence of excess mortality in hepatitis C infected patients who were not cirrhotic, in the absence of selected risk factors. Our findings emphasize the importance of

providing appropriate preventive advice, such as counselling to avoid alcohol intake, in those infected with HCV.

Access to sterile injecting equipment is more important than awareness of HCV status for injection risk behaviors among drug users.

Cox J, Morissette C, DE P, Tremblay C, Allard R, Graves L, Stephenson R, Roy E. *Subst Use Misuse*. 2009 Feb 25:1. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19242863?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Awareness of hepatitis C virus (HCV) infection status is expected to influence risk behaviors. In 2004-2005, injection drug users (IDUs) recruited from syringe exchange programs (SEPs) and methadone clinics in Montreal, Canada, were interviewed on drug use behaviors (past 6 months) and HCV testing. Subjects (n = 230) were classified as low/intermediate risk (20.4% borrowed drug preparation equipment only) and high risk (19.6% borrowed syringes), and 54.5% reported being HCV positive. Logistic regression modeling showed that compared to no risk (60% borrowed nothing), low/intermediate risk was associated with fewer noninjecting social network members, poor physical health, and problems obtaining sterile injecting equipment. High risk was associated with all of these factors except social networks. HCV status was not associated with any level of risk. Improved access to sterile injecting equipment may be more important than knowledge of HCV status in reducing injection risks among this IDU population. The study limitations are noted and recommendations discussed.

Viral hepatitis in incarcerated adults: A medical and public health concern. Hunt DR, Saab S. *Am J Gastroenterol*. 2009 Feb 24. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19240708?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Viral hepatitis is a common problem in the incarcerated population. It causes significant morbidity and mortality, and incarcerated inmates receive their health care almost exclusively from corrections-based health systems. The seroprevalence of hepatitis B and C infections is increased in this population, and a number of risk factors for viral hepatitis are particularly common and confer higher risk among inmates, including injection drug use (IDU), high-risk sexual activity, and tattoos. IDU, in particular, has been identified as an important and common risk factor for viral hepatitis in inmates, and variable rates of IDU among inmates have been found to be the most important cause of the marked variability of seroprevalence rates for exposure to hepatitis C virus. A number of risk reduction and management strategies have been identified that can decrease transmission to other inmates. Prison-based hepatitis A and hepatitis B vaccination programs, needle exchange programs, methadone maintenance programs, risk education programs, and hepatitis C virus antiviral programs, for example, have been shown to be safe and effective risk reduction and management strategies. Preliminary studies have shown that these strategies are underutilized in the United States. Reasons for this phenomenon are multifactorial, involving financial as well as ethical and political considerations. Additional funding, research, and formal consideration / discussion of the complex issues involving viral hepatitis in the US incarcerated population are clearly important for the sake of inmates and the community at large. In this article, the published medical literature regarding this important topic is reviewed.

Health-related quality of life in methadone maintenance patients with untreated hepatitis C virus infection. Batki SL, Canfield KM, Smyth E, Ploutz-Snyder R. Drug Alcohol Depend. 2009 Feb 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19233573?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To assess health-related quality of life (HRQOL) in methadone maintenance treatment (MMT) patients with untreated chronic HCV infection and to determine the clinical factors that predict HRQOL. **METHOD:** HRQOL was measured in 100 MMT patients entering an HCV treatment trial. Subjects were mostly male (61%) and white (81%) with a mean age of 43 (+/- 10). 57% had a current non-substance use psychiatric disorder. 55% had a current (past 12 months) substance use disorder, including 44% with current opioid or cocaine abuse/dependence. HRQOL in our sample was compared to published reports for the general population as well as for non-MMT HCV patients. To assess predictors of SF-36 HRQOL, hierarchical multiple regression techniques were used to assess model improvement with four blocks of baseline predictors: Demographics, Medical Severity, Addiction Severity, and Depression Severity. **RESULTS:** HRQOL scores were significantly lower than scores for the general population and were also lower than scores reported for untreated HCV patients not in MMT. Regression analysis demonstrated a consistent pattern whereby Depression Severity increased predictive accuracy for HRQOL measures over simpler models. Beck Depression Inventory scores significantly predicted quality of life across both the mental and physical composite scores and all eight sub-scales of the SF-36.

CONCLUSIONS: Untreated HCV patients in MMT had lower HRQOL than HCV patients not in MMT. Depression Severity was associated with significantly lower quality of life measures, suggesting that psychiatric evaluation and intervention prior to the start of HCV treatment may improve overall quality of life and could influence HCV treatment outcomes in MMT patients.