Caring Ambassadors Hepatitis C Program Newsletter

www.HepCChallenge.org
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IN THE NEWS

The program: Cumberland County's Treatment Court
http://www.pennlive.com/news/patriotnews/index.ssf?/base/news/123092341044570.xml&coll=1
Judge Skip Ebert smiled as Brian, a husky guy in a muscle shirt, walked to the front of his Cumberland County courtroom. "How's the interferon going?" Ebert asked. Brian, a recovering addict in the county's treatment court program, had just begun that therapy to combat the Hepatitis C that imperiled his health. "I'm just glad I'm finally getting this started," he told the judge. "That's my goal. If I'm not drinking and doing drugs that'll save my life.

"Hepatitis affects your liver. If you drink, that can really kill you." Lives hang in the balance in treatment court, or "drug court" as its promoters and participants call it. Some clients might really die if they don't end their spirals of addiction. For others, prison is their only future. [truncated]

U.S. government sets infection control goals
http://www.reuters.com/article/healthNews/idUSTRE5055ZA20090106
WASHINGTON (Reuters) - Urinary infections caused by improper use and placement of catheters are the top cause of infections among hospital patients, but simple measures can prevent them, the U.S. government said on Tuesday. The Health and Human Services Department released a plan to reduce hospital infections, which kill an estimated 99,000 people a year, affect 1.7 million patients and cost nearly $20 billion.

Besides catheter-linked urinary infections, the most common causes of infections linked with hospitals are surgical site infections, bloodstream infections from intravenous lines and pneumonia from ventilators, HHS said in the report. [truncated]

A dose of reality
An increase in cases of hepatitis C among injecting drug users has led to calls to reverse the dramatic fall in needle exchanges.
http://www.guardian.co.uk/society/2009/jan/07/drugs-hepatitis-c-society-needle-exchange
In terms of its public profile, hepatitis C is a poor relation of the HIV virus. However, an estimated 170 million people worldwide are infected with the blood-borne virus, and many of them have no idea they are walking around with it until years or even decades later. Twenty years after becoming infected, one in six people develop serious liver damage; after 30 years, the figure is nearly a quarter.

New figures published by the Health Protection Agency show that there has been an increase in hepatitis C among injecting drug users. In the late 1990s, a fifth of injectors became infected within three years of starting to inject, but now around 50% of injectors have the virus. Because the virus is able to survive outside the body for longer than HIV, it is relatively easy to become infected with it, and the main route of transmission in this country is among drug users who share injection paraphernalia.

It is with this group that the most effective harm reduction work can be done and the Department of Health, the National Treatment Agency and Exchange Supplies have launched a campaign urging drug users not to share injecting equipment. However, Sara McGrail, an independent drug policy specialist, is concerned about a dramatic fall in the number of needle exchanges. She says: "I'd like to see more of these needle exchanges, and they should offer extended access and support. At the moment, a lot of needle exchanges are open only from 9am to 5pm. [truncated]

Hepatitis C can't slow down Natalie Cole
The Cole must go on
http://www.mydesert.com/article/20090108/LIFESTYLES0101/901070384
Last year, Natalie Cole did something she's rarely had to do in her long career. She canceled a number of shows. "In 30 years, I think I've canceled five, maybe 10 shows," she said. "That's just something I don't do."

The singer had to back out because she was recovering from the effects of treatment she received for Hepatitis C. Cole had known for months that something wasn't quite right physically. Last April, a series of blood tests revealed she had been infected with the liver virus, which she most likely contracted by sharing needles as a heroin user during the 1970s and '80s. [truncated]

Get tested now, says hepatitis C survivor Susan
http://www.theboltonnews.co.uk/news/4029164.Get_tested_now__says_hepatitis_C_survivor_Susan/
A former teacher who has overcome the blood disease hepatitis C has made a fresh plea to people who think they may be at risk to get tested. Susan Wright discovered she had the potentially fatal illness during a medical check-up for an insurance company in 2003.

Mrs Wright, aged 51, stopped drinking, went through a programme of treatment in 2006-07 and has now been declared free of the virus. Last year, she became the face of a publicity campaign in a bid to dispel the stigma surrounding the blood disease. Now the mother of four wants to warn others that they could have the condition without knowing it.

Mrs Wright, of Hulton Lane, Deane, said: "It was only by chance that I found out I had hepatitis C. I got it because I dabbled with drugs when I was younger. In my early 20s I did some pretty crazy stuff, not knowing there were such risks. [truncated]

Hepatitis C drug from Anadys shows quick virus-killing punch
http://www.xconomy.com/san-diego/2009/01/08/anadys-hepatitis-c-drug-shows-quick-virus-killing-punch-in-small-study/
An early peek at data from Anadys Pharmaceuticals suggests the company may have a promising new drug in the works for hepatitis C. The San Diego-based biotech is announcing results today from the first eight patients with the chronic liver infection, which shows its drug has more viral

killing pop in the first three days of treatment than was seen in other drugs studied in its class, with minimal side effects.

The company found that its experimental medicine was able to wipe out 99 percent of the virus from the blood (known as a 2.5 logarithmic reduction) within 72 hours at the lowest dose tested in a Phase I clinical trial, says CEO Steve Worland. This finding was in the first group of patients who took a 200 milligram, twice-daily dose of ANA598. It is just the first slice of data available, and the trial is continuing to enroll patients at two higher doses, Worland says. The company hopes to present full data at the European Association for the Study of the Liver meeting in Copenhagen, Denmark in April. [truncated]

Joseph Bolduc Jr., 56, activist and former firefighter
http://www.philly.com/philly/obituaries/20090110_Joseph_Bolduc_Jr___56__activist_and_former_firefighter.html
Joseph J. Bolduc Jr., 56, of Port Richmond, a neighborhood activist and a former Philadelphia firefighter and paramedic, died of complications from liver cancer Wednesday at Northeast Hospital.

Mr. Bolduc believed he contracted hepatitis C while serving in the Fire Department from 1984 to 1988, his son Christopher said. The disease led to liver cancer, which was diagnosed in 2005. He had a liver transplant in 2006, but the cancer returned the following year. Mr. Bolduc was active in the Philadelphia firefighters' union's effort to seek improved health benefits and testing for members exposed to hepatitis C, his son said. [truncated]

Human Genome Sciences announces initiation of phase 2b trial of Albuferon(R) dosed monthly in chronic hepatitis C
http://news.prnewswire.com/DisplayReleaseContent.aspx?ACCT=104&STORY=/www/story/01-12-2009/0004952729&EDATE=
Human Genome Sciences, Inc. today announced that Novartis has initiated dosing in a Phase 2b trial that will evaluate the safety and efficacy of Albuferon(R) (albinterferon alfa-2b) administered monthly in combination with ribavirin in treatment-naive patients with genotypes 2 and 3 chronic hepatitis C. Albuferon is being developed by HGS and Novartis under an exclusive worldwide co-development and commercialization agreement entered into in June 2006.

"Patients undergoing treatment for chronic hepatitis C often find it challenging to participate in normal daily activities, especially in the days following dose administration," said Stephen Pianko, M.D., F.R.A.C.P., Ph.D., Monash University, Melbourne, Australia. "Pegylated interferons, the current standard of care, require administration once every week. Albinterferon alfa-2b dosed every four weeks with a total of six injections could offer an important treatment option, if it demonstrates comparable safety and efficacy vs. peginterferon alfa-2a dosed weekly with a total of 24 injections." [truncated]

Colorado testing campaign finds link between HIV, hepatitis C
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=56375
A Western Colorado AIDS Project HIV and hepatitis C testing campaign has found an average 12% positive rate for hepatitis C among HIV-positive people and injection drug users who access the organization's services.

The hepatitis C positive rate, which is the highest in the state, has remained constant since last fiscal year despite an increase in the number of people being tested, Rabeeha Ghaffar, prevention resource director at WestCAP, said. "Usually when you increase the tests the positivity rate goes down, so that is telling me that it is a very alarming concern," Ghaffar said. The testing program began in 2005 after WestCAP staff noticed that 10% of HIV-positive clients also had hepatitis C. [truncated]

Hep C inquiry chairman appointed (Scotland)
http://news.bbc.co.uk/2/hi/uk_news/scotland/7824901.stm
A chairman has been appointed to lead a public inquiry into the deaths of two people who contracted Hepatitis C through NHS blood products. Lord Penrose will chair the probe into how Eileen O'Hara and Rev David Black contracted the virus while in NHS care. It follows complaints by relatives of the victims over the length of time it has taken to start the inquiry. The Scottish Government said the withdrawal of the original chair, judge Lady Cosgrove, had led to the delay.

Health Secretary Nicola Sturgeon told the Scottish Parliament the inquiry will be known as the Penrose Inquiry. She said: "I have every sympathy with those who have suffered or lost loved ones as a result of Hepatitis C or HIV infection through NHS treatment with blood or blood products. "I hope the Penrose Inquiry can provide answers and the closure which I know they so desperately want. "This inquiry will also ensure that all possible lessons are learned to prevent such a tragedy occurring again." [truncated]

InterMune shares rise on hepatitis C study data
http://www.forbes.com/feeds/ap/2009/01/12/ap5908791.html
Shares of biotechnology company InterMune Inc. rose Monday after the company reported positive results from early-stage studies of its hepatitis C drug candidate in combination with two other treatments. Calif.-based InterMune said results from all six completed Phase 1b clinical trials shows ITMN-191 treated the virus, or reduced the viral load in patients. Early-stage studies are not often used to measure a drug's effectiveness, as they are typically too small to yield sufficient results. The studies are typically only used to assess safety and dosing, though investors were looking out for any indication the drug might be competitive in what could be a crowded field of treatments. [truncated]

New phase of national hepatitis C awareness campaign launched for GPs (England)
http://www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=5445
The Department of Health is gearing up to launch a hepatitis C public health campaign to improve detection and diagnosis among the 100,000 people in England who are thought to be unaware they have the infection. The campaign will get underway at the start of next month with radio and press advertising to remind the public of life experiences that could have exposed them to infection.

GPs will be encouraged to support the campaign by offering information and testing for patients in at risk groups. The campaign coincides with the 20th anniversary of the virus being identified and follows a recent letter from the Chief Medical Officer and Chief Nursing Officers to Primary Care Trusts on improving the detection and diagnosis of hepatitis C in primary care. [truncated]

Hep C scandal (Ireland)
http://www.irishtimes.com/newspaper/opinion/2009/0114/1231738222559.html
There is something deeply disturbing about a decision by the Director of Public Prosecutions (DPP) to drop all charges in the last remaining case involving the infection of women with hepatitis C.

Nobody will now be prosecuted for the injuries and deaths visited on more than 1,000 people by contaminated blood products over a period of 15 years. This public failure is part of a pattern whereby prominent individuals charged with serious offences have not been tried as a result of a culture of official apathy, excessive delays and legal challenges.

It has taken more than 10 years and a succession of legal actions to reach this unsatisfactory conclusion. No wonder the surviving women who were infected by hepatitis C are angry. We should be angry too. Without accountability in public life, dangerous practices, inadequate services and political corruption will persist. At this time of economic transition, the opportunity for root and branch reform of our administrative and legal structures must be taken. [truncated]

Hepatitis C action plan 'delayed'
http://news.bbc.co.uk/2/hi/uk_news/wales/7826955.stm
An action plan drawn up to tackle the growing threat posed by hepatitis C in Wales is three years behind schedule, according to a group of MPs. A parliamentary report claims the Welsh Assembly Government has drafted the plan, originally due in 2006, but has failed to publish it.

The Hepatitis C Trust accused ministers in Wales of "ignoring" sufferers. The assembly government said Health Minister Edwina Hart was expected to publish the plan shortly. Hepatitis is an inflammation of the liver and hepatitis C is one of several viruses that can causes the illness. [truncated]

Hepatitis C ups liver cancer risk, study confirms
http://uk.reuters.com/article/healthNews/idUKTRE50E6QJ20090115
(Reuters Health) - The risk of a rare form of liver cancer called intrahepatic cholangiocarcinoma, which occurs in the bile ducts of the liver, is significantly elevated in individuals who are infected with hepatitis C virus (HCV), according to a large "case-control" study of US veterans. HCV-infected individuals are also at increased risk for another type of liver cancer called hepatocellular carcinoma, the study shows. Liver cancer is the third leading cause of cancer deaths worldwide.

The findings stem from a look at 146,394 HCV-infected and 572,293 uninfected adults, mostly men, who were followed for an average of more than 2 years. When comparing HCV-infected with HCV-uninfected subjects, the risk of hepatocellular carcinoma was 15-fold higher in the infected group and the risk of intrahepatic cholangiocarcinoma was 2.5-fold higher. The risk of pancreatic cancer was 23 percent higher. [truncated]

Bristol Myers Squibb: strengthening the hepatitis C pipeline
http://www.tradingmarkets.com/.site/news/Stock%20News/2125000/
Bristol-Myers Squibb has acquired the rights to co-develop PEG-Interferon lambda for the treatment of hepatitis C from ZymoGenetics. Although current interferon alpha therapy is relatively successful in treating hepatitis C infection, it has several drawbacks, leaving significant room for the development of alternative interferon products as well as novel classes.

Bristol-Myers Squibb (BMS) has formed a global partnership with ZymoGenetics to develop PEG-Interferon lambda, which is currently in Phase Ib development for the treatment of hepatitis C virus (HCV). Having successfully penetrated the hepatitis B and HIV markets, this collaboration indicates that BMS is keen to expand its presence into the HCV field. The company also has two small molecule antivirals in early stage development for the treatment of HCV. [truncated]

Manhattan dialysis center notifies patients of possible exposure to infections
http://www.emaxhealth.com/2/24/28604/manhattan-dialysis-center-notifies-patients-possible-exposure-infections.html
A Manhattan dialysis center is notifying patients after the facility identified, and a State Department of Health (DOH) investigation confirmed, one patient who contracted hepatitis C after undergoing dialysis there. Approximately 170 patients of the Upper Manhattan Dialysis Center of Beth Israel Medical Center at 2465-67 Broadway in Manhattan are being notified in person or by mail that they may have been exposed to hepatitis C and possibly other bloodborne viruses while being treated at the facility.

"This situation is an example of infection prevention guidelines in action: frequent testing can quickly identify a problem. Steps can be taken right away to correct possible problems, and patients can be notified and tested," said Health Commissioner Richard F. Daines, M.D. He commended the facility on the completeness of testing and response. Patients who receive care at Upper Manhattan Dialysis Center are routinely screened for hepatitis B and C, both bloodborne viruses.
The transmission was identified after routine testing conducted by the facility identified a patient who became infected with hepatitis C while receiving treatment at the facility. DOH's investigation concluded that transmission had occurred at the dialysis center. The facility and DOH each conducted a thorough investigation that included an assessment of infection control procedures by a panel of independent experts. Neither assessment found major deficiencies, and the facility incorporated all of the experts' recommendations immediately. [truncated]

Hepatitis task force fights to keep funding
http://www.hometownannapolis.com/cgi-bin/read/2009/01_30-17/LIF
A law that provided about $10,000 annually to prevent the spread of hepatitis in Anne Arundel County is set to expire by the end of the year. Members of the Maryland Viral Hepatitis Task Force said they hope to maintain the funding by educating lawmakers about the liver disease. The group hosted its first Hepatitis C Education Day at the House of Delegates building in Annapolis on Wednesday in an attempt to keep the law on the books.

In Maryland, an estimated 100,000 people have the illness and a majority are unaware they have it, according to the group. According to the latest figures available from the county Health Department, in 2007, 595 people in the county were diagnosed with acute or chronic hepatitis C, while another 166 people had acute or chronic hepatitis B. [truncated]

Study supports early initiation of HIV treatment by HIV/hepatitis C co-infected patients
http://www.aidsmap.com/en/news/05E6437D-5633-4BC4-9666-2F0E4CE6831A.asp
Early initiation of HIV treatment can help prevent liver damage in HIV/hepatitis C co-infected patients, French investigators report in the February edition of the Journal of Acquired Immune Deficiency Syndromes. The investigators suggest that, in co-infected patients who have not responded to treatment for hepatitis C, "early highly active antiretroviral therapy may help to protect the liver".

The study adds to a growing body of research suggesting that HIV treatment can help reduce the risk of liver-related illness and death in co-infected patients. Current UK HIV treatment guidelines state that co-infected patients should be encouraged to start treatment when their CD4 cell count is

in the region of 350 cells/mm3. A separate Danish study reported here on aidsmap.com showed that the preservation of a functioning immune system reduced the risk of liver-related death for co-infected patients to such an extent that it was no different to that seen in patients only infected with hepatitis C. [truncated]

In fight for his life, Isle of Wight officer needs help from the law
http://www.tidewaternews.com/news/2009/jan/30/fight-his-life-isle-wight-officer-needs-help-law/
Kurt Beach, a Smithfield police officer, has the undying loyalty of his wife, Kathie, as he waits and hopes for a lifesaving liver transplant.For many of the townspeople of Smithfield, Kathie's husband, Kurt Beach, is just that as a veteran of the Smithfield Police Department. But now, the well-known lieutenant is fighting for his life and fighting the law.

Twenty years ago, in February 1988, Beach responded to an emergency call for an infant who wasn't breathing. Basic CPR techniques were futile due to obstructing particles in the child's throat, so Beach had to suck out the clogging blood and mucous particles. Doing that, says Beach, "I got the airway to open up and started to give CPR."

It wasn't until 1994 that police officers and first responders in Smithfield were instructed about the potential for contracting diseases via blood-borne pathogens. Beach immediately had himself tested for two common blood-borne diseases: hepatitis and HIV. The tests came back negative. But when Beach tried to donate blood to the American Red Cross later in the year, he received a letter saying that his blood had been detected as having "non-A, non-B Hepatitis." [truncated]

Schering-Plough completes enrollment of boceprevir registration studies in treatment-naive and treatment-experienced HCV patients
http://news.prnewswire.com/DisplayReleaseContent.aspx?ACCT=104&STORY=/www/story/01-27-2009/0004960935&EDATE=
Schering-Plough Corporation today reported that it has completed patient enrollment in the boceprevir HCV SPRINT-2 study, a pivotal Phase III study in treatment-naive patients. Together with the HCV RESPOND-2 study, a pivotal Phase III study in patients who failed prior treatment that completed enrollment in November 2008, the Company has fully enrolled its registration studies for boceprevir, its lead investigational oral hepatitis C protease inhibitor. A total of more than 1,500 patients were enrolled in these studies at U.S. and international sites.

"We believe boceprevir has the potential to be a first-in-class and best-in-class protease inhibitor for treating chronic hepatitis C," said Thomas P. Koestler, Ph.D., executive vice president and president, Schering-Plough Research Institute. "We are very encouraged by the boceprevir study results reported to date and look forward to the completion of these registration studies." The Company expects to complete the studies in mid-2010. [truncated]

Rights ruling for hep C sufferer
http://www.vocm.com/news-info.asp?id=33905
The Human Rights Commission is heralding a recent decision involving a young woman who's struggle with drug addiction has brought her to public attention. Sonya Harvey filed a complaint against a local esthetics training centre, charging discrimination. The Board of Inquiry ruled that

Harvey was discriminated against as a result of being diagnosed with hepatitis C. Human Rights Commission Executive Director Carey Majid says while it's not common, issues surrounding discrimination based on being diagnosed with a communicable disease do come up from time to time.

Majid says Harvey was refunded her tuition fee and a copy of the decision has been provided to the department of education in order to seek changes to the entry requirements for private training institutions regarding medical certification. There may still be an appeal of the case. Sharon Woodford told VOCM Night Line with Ryan Cleary that Harvey withdrew from their aesthetics training program on the advice of her doctor. She says Sonya left on good faith that she could return when her treatment was finished. [TRUNCATED]

Clinical update - Debio 025 in hepatitis C
Debiopharm starts phase iib triple therapy study, a promising therapeutic avenue
http://news.prnewswire.com/DisplayReleaseContent.aspx?ACCT=104&STORY=/www/story/01-26-2009/0004959980&EDATE=
Debiopharm Group, a global biopharmaceutical development specialist that focuses on serious medical conditions and particularly oncology, announced today the randomisation of its first patient in a phase IIb clinical study with Debio 025, a selective cyclophilin (Cyp) inhibitor with a potent anti-hepatitis C (HCV) effect. This multinational, double blind, placebo-controlled, parallel-group study will investigate the efficacy and safety of three different treatment regimens combining Debio 025 with Peg interferon alpha 2a (peg-IFNalpha2a) and ribavirin in treatment-naive chronic HCV genotype 1 patients.

During this 72 week trial, on top of the Standard of Care (SOC) treatment consisting of peg-IFNalpha2a 180 microgram once weekly and ribavirin 1000 or 1200 mg/day, patients will receive an oral dose of 600 mg of Debio 025. Three different triple combination regimens will be compared to the SOC treatment. The Company aims to evaluate whether there is an increase in the proportion of patients who achieve a sustained viral response (HCV RNA < 10 U/mL 24 weeks after treatment end) with Debio 025, compared to the SOC treatment. The trial will include 272 treatment-naive chronic HCV genotype 1 patients. Results of the study are expected in Q1 2011.

"We believe that the future of chronic HCV treatment lies in the combination of drugs with different mechanisms of action and potential additive or synergistic antiviral effects. For this reason we are investigating the use of Debio 025 combined with the current peg-IFNalpha2a/ribavirin dual therapy. We are optimistic that this combination will reduce the risk of treatment failure for HCV patients and maximise their chances of sustained viral response," said Rolland-Yves Mauvernay, President and Founder of Debiopharm Group. [truncated]

Natalie Cole to undergo kidney transplant to fight hepatitis C
http://www.medindia.net/news/Natalie-Cole-To-Undergo-Kidney-Transplant-To-Fight-Hepatitis-C-46647-1.htm
Natalie Cole's sister has reportedly decided to donate her kidney to the singer, who is suffering from the chronic liver disease Hepatitis C. The eight-time Grammy Award-winner was believed to have contracted the condition owing to her drug addiction during the 80s and has been treated for kidney failure since September last year. It was claimed that the doctors had told Cole that she needed a transplant and her sister Timolin's kidney was said to have been a match for her ailing sister.

"After (she learned of the match), Natalie kept saying, 'I can't believe this! I'm so blessed," Contact music quoted a source as telling the National Enquirer. "My sister's giving me a tomorrow. She's saving my life,'" the source added.

Homemade tattoo risks
http://www.wytv.com/mostpopular/story/Homemade-Tattoo-Risks/LDvFAR3xSU-WRRkB3LQstQ.cspx
When done right, tattooing is an art form, but in the wrong hands, the results could leave you with a skin infection or be downright deadly. "The worst case scenario,"says Dr. John Ven Glarcik, "you could get things like blood born pathogens; HIV, Hepatitis B, Hepatitis C, all of which have serious if not potentially fatal complications."

Debbie Lenz has worked as a tattoo artist for three decades and owns Artistic Dermagraphics in Boardman. She says she hears horror stories of people getting tattooed out of someone's house or garage everyday. "My prediction, you know, being around this business for more than 30 years, is that eventually, you know, within the next 10 years or so, there's going to be a surge of Hepatitis C cases which is going to be devastating." [truncated]

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Clinical expression of insulin resistance in hepatitis C and B virus-related chronic hepatitis: Differences and similarities. Persico M, Masarone M, La Mura V, et al. World J Gastroenterol. 2009 Jan 28;15(4):462-466.
http://www.ncbi.nlm.nih.gov/pubmed/19152451?ordinalpos=1&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
AIM: To investigate the prevalence of the clinical parameters of insulin resistance and diabetes in patients affected by chronic hepatitis C (CHC) or chronic hepatitis B (CHB). **METHODS**: We retrospectively evaluated 852 consecutive patients (726 CHC and 126 CHB) who had undergone liver biopsy. We recorded age, sex, ALT, type 2 diabetes and/or metabolic syndrome (MS), body mass index (BMI), and apparent disease duration (ADD). **RESULTS**: Age, ADD, BMI, prevalence of MS and diabetes in patients with mild/moderate liver fibrosis were significantly higher in CHC. However, the degree of steatosis and liver fibrosis evaluated in liver biopsies did not differ between CHC and CHB patients. At multivariate analysis, age, sex, BMI, ALT and diabetes were independent risk factors for liver fibrosis in CHC, whereas only age was related to liver fibrosis in CHB. We also evaluated the association between significant steatosis (> 30%) and age, sex, BMI, diabetes, MS and liver fibrosis. Diabetes, BMI and liver fibrosis were associated with steatosis > 30% in CHC, whereas only age and BMI were related to steatosis in CHB. **CONCLUSION**: These data may indicate that hepatitis C virus infection is a risk factor for insulin resistance.

Long-term follow-up of patients with hepatitis C with a normal alanine aminotransferase. Kumada T, Toyoda H, Kiriyama S, et al. J Med Virol. 2009 Jan 16;81(3):446-451. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19152400?ordinalpos=5&itool=Email.EmailReport.Pubmed_ReportSelector.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 hepotocarcinogenesis 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.

Unboosted fosamprenavir is associated with low drug exposure in HIV-infected patients with mild-moderate liver impairment resulting from HCV-related cirrhosis. Gatti F, Nasta P, Loregian A, et al. J Antimicrob Chemother. 2009 Jan 16. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19151039?ordinalpos=6&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
OBJECTIVES The **AIM** of this study was to compare amprenavir pharmacokinetics in HIV/hepatitis C virus (HCV)-co-infected cirrhotic patients receiving non-boosted fosamprenavir 700 mg twice daily with HCV/HIV-co-infected non-cirrhotic subjects and HIV-mono-infected subjects receiving fosamprenavir/ritonavir 700/100 mg twice daily. Liver stiffness at baseline and alanine aminotransferase levels at baseline and during follow-up were measured in order to find a correlation between drug levels and liver fibrosis or hepatotoxicity. **METHODS** Amprenavir plasma concentration was determined by HPLC. Liver stiffness was measured by transient elastometry. Liver function tests were determined every 1-3 months during follow-up. **RESULTS** Nineteen HIV-infected patients were included. Eight had chronic HCV hepatitis (group NC), five had HCV-related liver cirrhosis (group C) and six were HIV-mono-infected (group M). In group C patients, amprenavir C(trough), AUC(0-12) and half-life were 86%/83%, 64%/55% and 58%/59% lower when compared with controls and co-infected subjects without cirrhosis, respectively; conversely, drug clearance in cirrhotics was 181%/124% higher. In 3/5 cirrhotic patients (60%) and in 2/14 non-cirrhotic patients (14%), C(trough) was below the minimum target concentration of 400 ng/mL; nonetheless, in all these patients, HIV viral load was undetectable. No correlation was found between amprenavir pharmacokinetics and liver stiffness or hepatotoxicity at follow-up. **CONCLUSIONS** On the basis of these data, it seems reasonable to boost fosamprenavir with ritonavir even in cirrhotic patients; amprenavir pharmacokinetics could not be predicted by liver stiffness and seem not to predict hepatotoxicity at follow-up.

Diabetes mellitus is associated with impaired response to antiviral therapy in chronic hepatitis C infection. Elgouhari HM, Zein CO, Hanouneh I, Feldstein AE, Zein NN. Dig Dis Sci. 2009 Jan 16. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19148751?ordinalpos=13&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Insulin resistance may promote hepatic fibrosis in chronic hepatitis C (HCV) and has emerged as a cofactor in failure to achieve sustained viral response (SVR). Aims (1) To assess the association of diabetes mellitus (DM) in HCV patients to the severity of hepatic fibrosis and to the response to antiviral treatment. (2) To assess the safety of pegylated interferon and ribavirin combination therapy (Peg IFN/RBV) in diabetic HCV patients. **METHODS** HCV diabetics (n = 61) were identified. A

2:1 matching control group was used to identify independent factors of advanced fibrosis and treatment failure. **RESULTS** Compared to HCV non-diabetics, HCV diabetics were more likely to have steatosis ($P < 0.0001$) and advanced fibrosis ($P = 0.003$). Patients' age, Caucasian ethnicity, obesity, and histologic activity index were independently associated with advanced fibrosis ($P < 0.05$). Only 23% of HCV diabetics achieved SVR compared to 46% of HCV non-diabetics ($P = 0.003$). DM, genotype 1, high baseline viral load, and African-American ethnicity were independently associated with less SVR ($P < 0.05$). Significant adverse events were more common in HCV diabetics compared to HCV non-diabetics ($P = 0.001$). Side effects did not increase in patients receiving PEG IFN/RBV and insulin sensitizers. **CONCLUSION** DM was associated with impaired virologic response to PEG IFN/RBV in HCV patients. Adverse events during therapy were more frequent in diabetic compared to non-diabetic HCV patients.

Hepatitis C virus infection in haemodialysis: The 'no-isolation' policy should not be generalized. Agarwal SK, Dash SC, Gupta S, Pandey RM. Nephron Clin Pract. 2009 Jan 16;111(2):c133-c140. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19147995?ordinalpos=14&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Hepatitis C virus (HCV) infection is the most common blood-borne viral infection in haemodialysis. It causes significant morbidity and long-term mortality. Practice of universal precautions has been reported to be sufficient to prevent HCV seroconversion in dialysis units. However, the seroconversion rate remains very high in many dialysis units. A previous study from 1995 to 1998 at our own hospital without isolation showed that nosocomial transmission is the major cause of HCV seroconversion. The present study was therefore conducted with the **AIM** to study the impact of isolation on HCV seroconversion. In this prospective cohort study, with non-probability consecutive sampling, patients with HCV infection were dialysed in an isolated room. In addition, standard universal precautions were practiced. HCV seroconversion rate was compared with the previous study. All patients with end-stage kidney disease (ESKD) admitted to our hospital for renal replacement therapy were included in the present study. At the time of admission, HCV screening was done. All anti-HCV-positive patients were dialysed in an isolated room. While on maintenance haemodialysis, all patients were monthly tested for anti-HCV, aspartate aminotransferase and alanine aminotransferase. Any patient who had HCV seroconversion was transferred to an isolated room for maintenance haemodialysis. Patients with HCV infection were managed by further testing for HCV-RNA and liver biopsy. Every patient who ultimately received renal transplantation at our hospital was also tested for HCV just prior to renal transplantation as well as 3 months after renal transplantation. HCV infection was diagnosed by detecting anti-HCV antibodies using an ELISA-based third-generation diagnostic test kit. Serum bilirubin, aspartate aminotransferase and alanine aminotransferase were assayed using standard laboratory techniques. From March 2003 to February 2006, 1,417 patients were admitted for haemodialysis in our unit. Of these 1,077 (76%) had ESKD. Mean age of patients was 42.47 +/- 16.2 (14-94) and 70.39% were males. Patients with ESKD had had more dialysis sessions (10.9 +/- 39.5 vs. 4.4 +/- 5.95, $p = 0.009$), more blood transfusions and more pre-existing HCV infections (4.72 vs. 1.5%, $p = 0.009$) than patients with acute renal failure. Of the ESKD patients, 65.7% were discharged, 9.47% died, 1.85% were shifted to chronic ambulatory peritoneal dialysis and 22.46% patients received renal transplantation. Of the patients who received renal transplantation, HCV seroconversion was detected in 2.75%. In the previous study without isolation practices, the HCV seroconversion rate in transplanted patients was 36.2%. The hazard of HCV seroconversion was 0.97 (95% CI 0.93-1.02, $p = 0.2$) for each additional dialysis and 1.09 (95% CI 0.88-1.36, $p = 0.37$) for each additional blood transfusion. **The study concludes**

that isolation of HCV-infected patients during haemodialysis significantly decreases the HCV seroconversion rate.

Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. Rodriguez-Torres M, Jeffers LJ, et al. N Engl J Med. 2009 Jan 15;360(3):257-67.
http://www.ncbi.nlm.nih.gov/pubmed/19144941?ordinalpos=16&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND: Race has been shown to be a factor in the response to therapy for hepatitis C virus (HCV) infection, and limited data suggest that ethnic group may be as well; however, Latinos and other ethnic subpopulations have been underrepresented in clinical trials. We evaluated the effect of Latino ethnic background on the response to treatment with peginterferon alfa-2a and ribavirin in patients infected with HCV genotype 1 who had not been treated previously.
METHODS: In a multicenter, open-label, nonrandomized, prospective study, 269 Latino and 300 non-Latino whites with HCV infection received peginterferon alfa-2a, at a dose of 180 microg per week, and ribavirin, at a dose of 1000 or 1200 mg per day, for 48 weeks, and were followed through 72 weeks. The primary end point was a sustained virologic response. We enrolled Latinos whose parents and grandparents spoke Spanish as their primary language; nonwhite Latinos were excluded.
RESULTS: Baseline characteristics were similar in the Latino and non-Latino groups, although higher proportions of Latino patients were 40 years of age or younger, had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of more than 27 or more than 30, and had cirrhosis. The rate of sustained virologic response was higher among non-Latino whites than among Latinos (49% vs. 34%, P<0.001). The absence of HCV RNA in serum was more frequent in non-Latino whites at week 4 (P=0.045) and throughout the treatment period (P<0.001 for all other comparisons). Latino or non-Latino background was an independent predictor of the rate of sustained virologic response in an analysis adjusted for baseline differences in BMI, cirrhosis, and other characteristics. Adherence to treatment did not differ significantly between the two groups. The numbers of patients with adverse events and dose modifications were similar in the two groups, but fewer Latino patients discontinued therapy because of adverse events.
CONCLUSIONS: Treatment with peginterferon alfa-2a and ribavirin for 48 weeks resulted in rates of sustained virologic response among patients infected with HCV genotype 1 that were lower among Latino whites than among non-Latino whites. Strategies to improve the sustained virologic response in Latinos are needed. (ClinicalTrials.gov number, NCT00107653.) 2009 Massachusetts Medical Society

Sorafenib for the treatment of unresectable hepatocellular carcinoma. Kane RC, Farrell AT, Madabushi R, et al. Oncologist. 2009 Jan 14. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19144678?ordinalpos=17&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Purpose. To describe the U.S. Food and Drug Administration (FDA) review and approval of sorafenib (Nexavar(R); Bayer Pharmaceuticals Corp., Montville, NJ, and Onyx Pharmaceuticals Corp., Emeryville, CA), an oral kinase inhibitor, for the treatment of patients with unresectable hepatocellular carcinoma (HCC). Experimental Design. The FDA independently analyzed an international, double-blind, placebo-controlled trial comparing the effect of best supportive care plus sorafenib or matching placebo on overall survival. Eligible patients had unresectable, biopsy-proven HCC and had not received prior systemic therapy. **RESULTS**. Among the 602 randomized patients (placebo, 303; sorafenib, 299), baseline characteristics were well balanced, and 97% were Child-Pugh score A. HCC was "advanced" in 70% overall, as defined by extrahepatic metastases or by tumor radiographically visible in venous structures outside the liver. Underlying liver diseases

included hepatitis B (18%), hepatitis C (28%), and alcohol-related (26%). The trial was stopped following a prespecified second interim analysis showing a statistically significant survival advantage for sorafenib [median, 10.7 vs 7.9 months; hazard ratio, 0.69 (95% confidence interval, (0.55, 0.87)), p = 0.00058]. Adverse events in sorafenib-treated patients included diarrhea in 55% (grade 3, 10%), hand-foot syndrome in 21% (grade 3, 8%), rash in 19% (grade 3, 1%), and cardiac ischemia or infarction in 2.7% (versus 1.3% for placebo). On sorafenib, treatment-emergent hypertension occurred in 9% of patients (placebo, 4%) and was grade 3 in 4% (placebo, 1%); elevated serum lipase occurred in 40% (placebo, 37%); hypophosphatemia occurred in 35% (placebo, 11%). **CONCLUSIONS**. Sorafenib is the first systemic therapy to demonstrate a survival benefit in a randomized trial for unresectable HCC and has received FDA approval for this indication.

Hepatitis status and mortality in hemodialysis population. Santoro D, Mazzaglia G, Savica V, Li Vecchi M, Bellinghieri G. Ren Fail. 2009;31(1):6-12.
http://www.ncbi.nlm.nih.gov/pubmed/19142803?ordinalpos=19&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The role of hepatitis B (HBV) and C (HCV) virus infection in mortality among MHD patients is poorly understood. Recent studies have shown that HCV positivity is associated with significantly higher cardiovascular mortality, especially in dialysis patients younger than 65 years. However, little information is available in European renal registries about mortality among HBV and HCV positive MHD patients. We prospectively followed all patients (prevalents and incidents) attending the dialysis center in the Sicilian region since January 1, 1999, up to December 31, 2000. Those who died for any cause after the starting point were identified and included in the cases population. In all, 698 eligible cases were found. For each case, three controls extracted from the Registry were matched by age at death (within five years) and sex. We calculated the sample size of 698 cases and three controls for each case, assuming the power of the study to be 80%, with an estimated prevalence of exposure among controls of 3.0%. The chi(2) and the t-test were used to evaluate possible differences among cases and controls for the different variables under investigation. The ORs of the association between hepatitis infection and mortality, adjusted for each of the possible confounding factors, was calculated using the Mantel-Haenszel test. The prevalence of Hepatitis C (HCV) was much higher among case compared with controls, both in males (23.4% vs. 17.7 %) and females (25.0% vs. 22.4%). In the multivariate model, the association between HCV and mortality maintained a significant association only among women aged <65 years with an OR of 1.77 (95% CI: 1.12-2.79). We also observed a correlation between increased risk of mortality in hemodialysis and HCV-positive patients with a longer time on dialysis. Our **RESULTS** suggest that HCV positivity among MHD patients is associated with significantly higher mortality in female aged <65 years. For this reason we should be more aggressive in identifying, preventing, and treating HCV infection among patients with end stage renal disease.

HCV response in patients with end stage renal disease treated with combination pegylated interferon alpha-2a and ribavirin. Hakim W, Sheikh S, Inayat I, et al. J Clin Gastroenterol. 2009 Jan 12. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19142165?ordinalpos=20&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
GOALS: To determine the efficacy and safety of combination therapy in patients with hepatitis C virus (HCV) and end-stage renal disease (ESRD). **BACKGROUND**: There is little data on the treatment of ESRD patients with pegylated interferon and ribavirin. We designed a pilot study to determine the initial and 12-week posttreatment viral response. **STUDY:** A nonrandomized, prospective observational study of adjusted-dose combination therapy. Twenty patients were

enrolled and began pegylated interferon at 135 mug/wk SC, and 4 weeks later ribavirin was started at 200 mg PO weekly, increasing gradually to 3 times a week for a total of 48 weeks. **RESULTS**: Twenty patients: M:F 18:2; mean age 52.4 years; genotype 1: 18, non-genotype 1: 2. Of the 20 patients, 5 withdrew before starting treatment. Of the 11 patients who reached 3 months, 6 had early virologic response, defined as at least a 2-log drop in their HCV count (54.5%). Of the 5 patients who were treated for 1-year, only 1 patient had a response 12 weeks after treatment. Side effects included 4 cases of anemia and 1 patient with headache. **CONCLUSIONS**: The initial response rate in individuals taking 3 months of treatment in our study is comparable with studies in non-ESRD patients with no serious adverse side effects. However, the sustained posttreatment rate was low. This demonstrates that combination therapy is a safe therapeutic option in the ESRD population with HCV infection which needs further testing to determine if increasing the length of treatment and/or the dose of ribavirin will affect posttreatment rates.

Predictors of sustained virological response to a 48-week course of pegylated interferon alfa-2a and ribavirin in patients infected with hepatitis C virus genotype 4. Al Ashgar H, Helmy A, Khan MQ, et al. Ann Saudi Med. 2009 January-February;29(1):4-14.
http://www.ncbi.nlm.nih.gov/pubmed/19139619?ordinalpos=27&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND AND OBJECTIVES: Knowledge of the predictors of sustained viral response (SVR) to pegylated interferon (PEG-INF) alfa-2a and ribavirin (RBV) therapy in patients with hepatitis C genotype-4 (HCV-4) is crucial for selecting patients who would benefit most from therapy. We assessed the predictors of SVR to this combination therapy in Saudi patients with chronic HCV-4 infection. PATIENTS AND **METHODS**: This retrospective study included 148 patients with HCV-4 infection who underwent clinical, biochemical and virological assessments before treatment and at 12, 24, 48 and 72 weeks post-treatment. **RESULTS**: Of the 148 patients, 90 (60.8%) were males. Mean (SD) for age was 48.5 (12.7) years and BMI was 27.9 (7.5) kg/m(2). Seventy-nine of 148 (60.1%) patients were treatment naA ve and 110 (74.3%) underwent pre-treatment liver biopsy. Eighteen (12.2%) patients did not complete therapy because of side effects or they were lost to follow up. Early virological response was achieved in 84 of 91 (92.3%) patients. In the 130 (87.8%) patients who completed therapy, 34 (26.2%) were non-responders and 96 (63.8%) achieved end-of-treatment virological response (ETVR). SVR and virological relapse (24 weeks after ETVR) occurred in 66/130 (50.7%) and 30/130 (31.2%) patients, respectively. Compared to relapsers, sustained responders were significantly younger (P=.005), non-diabetic (P=.005), had higher serum albumin (P=.028), lower alpha-fetoprotein level (P=.026), lower aspartate aminotransferase (AST) (P=.04) levels, and were treatment-naA ve (P=.008). In a multivariate regression analysis, the independent predictors of SVR were younger age (P=.016), lower serum AST (P=.012), and being treatment naA ve (P=.021). **CONCLUSION**: Approximately half of HCV-4 patients who complete the course of combination therapy achieve an SVR, especially if they are young, treatment naA ve and have lower AST levels.

Management of psychiatric disorders and addictive behaviors in patients with viral hepatitis C in France. Lang JP, Michel L, Melin P, et al. Gastroenterol Clin Biol. 2009 Jan;33(1 Pt 1):1-7. Epub 2009 Jan 8.
http://www.ncbi.nlm.nih.gov/pubmed/19135326?ordinalpos=34&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
INTRODUCTION: Guidelines concerning the management of psychiatric disorders and addictive behaviors in patients with chronic hepatitis C and the conditions of collaboration between hepatogastroenterologists, infectiologists, psychiatrists and psychologists have not been published.

This has a negative influence on optimal therapeutic management of chronic hepatitis C virus (HCV) infection. The **AIM** of this study was to describe the current clinical practices for ambulatory management of psychiatric disorders and addictions, and the influence of a possible psychiatric and/or psychological collaboration. **PATIENTS AND METHODS**: A retrospective survey was conducted among 101 clinicians treating patients with chronic hepatitis C. Data were collected from personal interviews with the managing clinicians and from the files of patients with chronic hepatitis C patients who presented psychiatric disorders. **RESULTS**: Analysis of the 101 interviews and 598 patient files showed that 19% of patients had not received an optimal treatment for their HCV infection because of a psychiatric problem, and that less than 50% of the managing clinicians were working in collaboration with a psychiatrist or a psychologist. In **CONCLUSION**, lack of collaboration between hepatogastroenterologists and psychiatrists could be deleterious for the optimal treatment of HCV infected patients. Improvement is required.

The cognitive effects of hepatitis C in the presence and absence of a history of substance use disorder. Huckans M, Seelye A, Parcel T, et al. J Int Neuropsychol Soc. 2009 Jan;15(1):69-82.
http://www.ncbi.nlm.nih.gov/pubmed/19128530?ordinalpos=45&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The **AIM** of the study was to determine whether infection with the hepatitis C virus (HCV) is associated with cognitive impairment beyond the effects of prevalent comorbidities and a history of substance use disorder (SUD). Adult veterans were recruited from the Portland Veterans Affairs Medical Center into three groups: (1) HCV+/SUD+ (n = 39), (2) HCV+/SUD- (n = 24), and (3) HCV-/SUD- (n = 56). SUD+ participants were in remission for > or =90 days, while SUD- participants had no history of SUD. Groups did not significantly differ in terms of rates of psychiatric or medical comorbidities. Procedures included clinical interviews, medical record reviews, and neuropsychological testing. Significant group differences were found in the domains of Verbal Memory, Auditory Attention, Speeded Visual Information Processing, and Reasoning/Mental Flexibility (p <or = .05). Post hoc comparisons indicated that HCV+/SUD- patients performed significantly worse than HCV-/SUD- controls on tests measuring verbal learning, auditory attention, and reasoning/mental flexibility, but only HCV+/SUD+ patients did worse than HCV-/SUD- controls on tests of speeded visual information processing. **RESULTS** indicate that chronic HCV is associated with cognitive impairment in the absence of a history of SUD. The most robust deficits appear to be in verbal learning and reasoning/mental flexibility.

Influence of occult hepatitis B virus coinfection on the incidence of fibrosis and hepatocellular carcinoma in chronic hepatitis C. Matsuoka S, Nirei K, Tamura A, et al. Intervirology. 2009 Jan 7;51(5):352-361. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19127078?ordinalpos=49&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
We examined prospectively the influence of occult hepatitis B virus (HBV) infection on the histopathological features and clinical outcome of HCV RNA-positive chronic hepatitis (CH-C) and detected hepatitis B core (HBc) particles in hepatocytes. The subjects were 468 patients with CH-C or liver cirrhosis (LC) who were negative for serum hepatitis B surface antigen (HBsAg) by enzyme-linked immunosorbent assay. HBV DNA was detected in serum by nested PCR. HBsAg and HBc antigen (HBcAg) in liver were investigated using immunohistochemical techniques and light (LM) and electron microscopy (EM). Serum HBV DNA was detected in 43.6% of the patients studied. There were no significant differences between HBV DNA-positive and DNA-negative patients in terms of their clinical profiles. For HBV DNA-positive patients, the degree of inflammatory cell infiltration and irregular regeneration of hepatocytes was significantly greater than for HBV DNA-

negative patients. The cumulative probability of development of hepatocellular carcinoma (HCC) was significantly higher for HBV DNA-positive patients than for HBV DNA-negative patients. HBV DNA positivity was a risk factor for the occurrence of HCC according to multivariate analysis. HBsAg and HBcAg were detected in 8.5 and 72.3%, respectively, of the livers of serum HBV DNA-positive individuals. Core particles were detected in the nuclei of the hepatocytes by IEM. The histopathological features and long-term outcome of CH-C or LC could be affected by occult HBV infection.

Impact of donor graft steatosis on overall outcome and viral recurrence after liver transplantation for hepatitis C virus cirrhosis. Briceño J, Ciria R, Pleguezuelo M, et al. Liver Transpl. 2009 Jan;15(1):37-48.
http://www.ncbi.nlm.nih.gov/pubmed/19109846?ordinalpos=63&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The **AIM** of this study was to determine the influence of donor graft steatosis on overall outcome, viral recurrence, and fibrosis progression in orthotopic liver transplantation (OLT) for hepatitis C virus (HCV) cirrhosis. One hundred twenty patients who underwent OLT for HCV cirrhosis between 1995 and 2005 were included in the study. Donor steatosis was categorized as absent (0%-10%; n = 40), mild (10%-30%; n = 32), moderate (30%-60%; n = 29), or severe (>60%; n = 19). A Cox multivariate analysis for marginal donor variables and a Model for End-Stage Liver Disease index were performed. Fibrosis evolution was analyzed in liver biopsies (fibrosis < 2 or > or =2) 3, 6, and 12 months post-OLT and in the late post-OLT period. Fifty-six grafts were lost (46%). The survival of the grafts was inversely proportional to donor liver steatosis: 82%, 72%, and 72% at 1, 2, and 3 years post-OLT in the absence of steatosis; 73%, 63%, and 58% with mild steatosis; 74%, 62%, and 43% with moderate steatosis; and 62%, 49%, and 42% with severe steatosis (P = 0.012). HCV recurrence was earlier and more frequent in recipients with steatosis > 30% (46% versus 32% at 3 months, P = 0.017; 58% versus 43% at 6 months, P = 0.020; 70% versus 56% at 12 months, P = 0.058; and 95% versus 69% at 3 years post-OLT, P = 0.0001). Graft survival was lower in alcoholic liver disease recipients versus HCV recipients when steatosis was >30% at 3, 6, and 12 months post-OLT (P = 0.042) but not when steatosis was <30% (P = 0.53). A higher fibrosis score was obtained 3 months post-OLT (P = 0.033), 6 months post-OLT (P = 0.306), 12 months post-OLT (P = 0.035), and in the late post-OLT period (P = 0.009). In **CONCLUSION**, donor graft steatosis influences the outcome of OLT for HCV cirrhosis. HCV recurrence is more frequent and earlier in recipients of moderately and severely steatotic livers. Fibrosis evolution is higher when graft steatosis is >30%. OLT with >30% steatotic donor livers should be precluded in HCV recipients.

Long-term antiviral therapy for recurrent hepatitis C after liver transplantation in nonresponders: biochemical, virological, and histological impact. Walter T, Scoazec JY, Guillaud O, et al. Liver Transpl. 2009 Jan;15(1):54-63
http://www.ncbi.nlm.nih.gov/pubmed/19109834?ordinalpos=66&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
More than 50% of patients with a recurrent posttransplant hepatitis C virus infection fail to respond to antiviral treatment. The **AIM** of this study was to evaluate the interest of a long-term antiviral treatment maintained for more than 48 weeks. Seventy treated patients, with a histological follow-up > 1 year, were enrolled in this observational, retrospective study. The duration of antiviral treatment, tolerance, and occurrence of virological, biochemical, and histological responses were recorded. Thirty-two patients were nonresponders after 48 weeks of treatment. Combined antiviral therapy was maintained for >12 months in 26 and for >18 months in 21. Twelve patients had to discontinue

their treatment. At 48 weeks, the rates of virological response and sustained virological response were 37% and 24.3%, respectively; at the end of the follow-up, they were 48.5% and 35.7%. Virological response was significantly associated with a higher incidence of biochemical and histological response, regardless of its time of occurrence (before or after 6 months). Even in the absence of virological response, the rate of progression of fibrosis was significantly slowed in patients treated for more than 6 months. Our **RESULTS** show the feasibility, safety, and efficacy of long-term antiviral therapy in nonresponder patients with a recurrent posttransplant hepatitis C virus infection.

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A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C. Ide T, Hino T, Ogata K, et al. Am J Gastroenterol. 2009 Jan;104(1):70-5http://www.ncbi.nlm.nih.gov/pubmed/19098852?ordinalpos=75&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

OBJECTIVES: The treatment of patients with hepatitis C virus (HCV) genotype 1 with peginterferon plus ribavirin treatment for more than 48 weeks demonstrated high sustained virological response (SVR) rates. Although many studies extended the duration of therapy from 48 weeks to 72 weeks, the optimal duration has not yet been determined. **METHODS**: A total of 113 genotype 1b patients with high viral load were randomized at baseline to the standard (n=56) or extended (n=57) treatment group. The standard group patients received 48 weeks of peginterferon plus ribavirin treatment. In the extended group, the treatment was performed for 44 weeks after patients became negative for HCV RNA (total duration 48-68 weeks).**RESULTS**: The SVR rate of the standard and extended group was 36% (20 of 56) and 53% (30 of 57; P=0.07). However, the extended group patients who became negative for HCV RNA between weeks 16 and 24 had a significantly higher SVR rate (78%; 7 of 9) than that of standard group (9%, 1 of 11; P=0.005). The predictive factors for the SVR were the treatment regimen (the standard vs. extended treatment) and the time to HCV RNA negative-status. **CONCLUSIONS**: The extended treatment significantly increased the SVR rate in patients who were HCV RNA negative at 16-24 weeks.Am J Gastroenterol 2009; 104:70-75; doi:10.1038/ajg.2008.60.

Adherence to hepatitis C virus therapy and early virologic outcomes. Lo Re V 3rd, Amorosa VK, Localio AR, O'Flynn R, et al. Clin Infect Dis. 2009 Jan 15;48(2):186-93.
http://www.ncbi.nlm.nih.gov/pubmed/19086908?ordinalpos=81&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

BACKGROUND: Suboptimal drug exposure attributable to physician-directed dosage reductions of pegylated interferon and/or ribavirin are associated with decreased sustained virologic response rates. However, data are limited with regard to suboptimal drug exposure that is attributable to missed doses by patients with chronic hepatitis C virus (HCV) infection. We examined the relationship between adherence to pegylated interferon and ribavirin therapy, measured by pharmacy refill, and HCV suppression during the initial 12 weeks of therapy. **METHODS**: We conducted a cohort study involving 188 patients with chronic HCV infection who were treated with pegylated interferon plus ribavirin. Adherence was calculated using pharmacy refill data and could exceed 100%. The primary outcome was decrease in HCV load at 12 weeks; early virologic response was a secondary outcome. Mixed-effects regression models estimated the association between adherence and HCV suppression during the initial 12 weeks. Subanalyses were performed among patients who received optimal weight-based dosages. **RESULTS**: The mean decrease in HCV load at 12 weeks was 0.66 log IU/mL greater for patients with > or =85% adherence than for those with <85% adherence (3.23 vs. 2.57 log IU/mL; P = .04). When patients who received a suboptimal ribavirin

dosage were excluded, the decrease in viral load was 1.00 log IU/mL greater for persons with > or =85% adherence (3.32 vs. 2.32 log IU/mL; P = .01). Early virologic response was more common among patients with > or =85% adherence than it was among those with <85% adherence to treatment with pegylated interferon (73% vs. 29%; P = .02) and ribavirin (73% vs. 55%; P = .08). **CONCLUSIONS**: Adherence of > or =85% to pegylated interferon and ribavirin treatment was associated with increased HCV suppression. Decreases in HCV load became greater when patients with > or =85% adherence to their regimen continued to receive their recommended weight-based ribavirin dosage

Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. El-Serag HB, Engels EA, Landgren O, et al. Hepatology. 2009 Jan;49(1):116-23.http://www.ncbi.nlm.nih.gov/pubmed/19085911?ordinalpos=82&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Hepatitis C virus (HCV) may increase the risk of hepatopancreaticobiliary tumors other than hepatocellular carcinoma (HCC). Previous case control studies indicated a possible association between HCV and intrahepatic cholangiocarcinoma (ICC). Little is known about the association between HCV and extrahepatic cholangiocarcinoma (ECC) or pancreatic cancer. We conducted a cohort study including 146,394 HCV-infected and 572,293 HCV-uninfected patients who received care at Veterans Affairs health care facilities. Patients with two visits between 1996 and 2004 with HCV infection were included, as were up to four matched HCV-uninfected subjects for each HCV-infected subject. Risks of ICC, ECC, pancreatic cancer, and HCC were assessed using proportional hazards regression. In the 1.37 million person-years of follow-up, which began 6 months after the baseline visit, there were 75 cases of ECC, 37 cases of ICC, 617 cases of pancreatic cancer, and 1679 cases of HCC. As expected, the risk of HCC associated with HCV was very high (hazard ratio [HR], 15.09; 95% confidence interval [95% CI], 13.44, 16.94). Risk for ICC was elevated with HCV infection 2.55; 1.31, 4.95), but risk for ECC was not significantly increased (1.50; 0.60, 1.85). Adjustments for cirrhosis, diabetes, inflammatory bowel disease, hepatitis B, alcoholism, and alcoholic liver disease did not reduce the risk for ICC below twofold. The risk of pancreatic cancer was slightly elevated (1.23; 1.02, 1.49), but was attenuated after adjusting for alcohol use, pancreatitis, and other variables. **CONCLUSIONS**: Findings indicated that HCV infection conferred a more than twofold elevated risk of ICC. Absence of an association with ECC was consistent in adjusted and unadjusted models. A significant association with pancreatic cancer was erased by alcohol use and other variables.

Characterization of hepatocellular carcinoma developed after achieving sustained virological response to interferon therapy for hepatitis C. Sanefuji K, Kayashima H, Iguchi T, et al. J Surg Oncol. 2009 Jan 1;99(1):32-7.
http://www.ncbi.nlm.nih.gov/pubmed/18985618?ordinalpos=164&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND: Interferon (IFN) reduces the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC). However, HCC develops in the some patients who have achieved a sustained virological response (SVR). The **AIM** of this study was to clarify the features and prognosis of SVR patients who developed HCC. **MATERIALS AND METHODS**: Twenty-six patients who underwent curative hepatectomy for initial HCC after IFN therapy were closely investigated. Twenty patients who were seropositive for HCV-RNA (non-SVR), and a further 6 patients who achieved SVRs (SVR) were included. We analyzed the clinicopathological features, immunological expression levels of p53 and whether HCV-RNA is present in the excised liver.

RESULTS: The liver functions of the SVR group were almost better than those of the non-SVR group. However, there was no significant difference in pathological features, surgical factors and prognosis between the groups. In one case with SVR out of eight specimens tested was HCV-RNA detected in the non-cancerous tissue. Immunohistochemistry revealed overexpression of p53 in eight HCCs (100%) from SVR patients. **CONCLUSION**: Recurrent HCC still developed after the curative hepatectomy, even if viral elimination had been successful. And molecular alterations in hepatocarcinogenesis of SVR patients might be different from those of CHC patients.

Perihepatic lymph nodes as markers of disease response in patients with hepatitis C-related liver disease: a prospective clinical evaluation. Grier S, Patel N, Kuo YT, et al. Eur J Gastroenterol Hepatol. 2009 Jan 27. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19177027?ordinalpos=5&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
AIM: To assess the clinical feasibility of utilizing the presence of perihepatic lymphadenopathy, seen on ultrasound, as a marker of response to antiviral treatment in patients with hepatitis C virus (HCV)-related liver disease. **METHODS**: Eighty-five patients with HCV-related liver disease [51 men and 34 women; mean age 47 years (range 26-67)] underwent liver biopsy and baseline ultrasound scans. Twenty-two of these patients were followed up longitudinally with 6-monthly ultrasound scans, whereas they were receiving anti-HCV eradication therapy with interferon and ribavirin. Perihepatic lymph nodes detected in the coeliac axis and peripancreatic region were noted, with the largest node size on maximal diameter recorded. The patients were subsequently assessed in the light of long-term virological response to treatment. **RESULTS**: Perihepatic lymph nodes were detected in 26 of the 85 patients. Of the 22 patients followed up longitudinally, 11 responded to antiviral treatment, nine failed to respond and two did not complete a course of treatment. No significant difference was found between patients with detectable lymphadenopathy and those without according to age, sex, disease severity and genotype. There was a general reduction in size of lymph nodes in both responders and nonresponders to treatment, although this reduction was only significant in the responder group (P=0.003). **CONCLUSION**: The presence of perihepatic lymphadenopathy when detected in patients with viral hepatitis can potentially serve as an indicator of response to treatment. However, as only 30-40% of patients have detectable lymphadenopathy, its clinical utility is limited.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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 Jan 16;81(3):459-466. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19152412?ordinalpos=2&itool=Email.EmailReport.Pubmed_ReportSelector.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.

Heat-shock protein 90 is essential for stabilization of the hepatitis C virus non-structural protein NS3.Ujino S, Yamaguchi S, Shimotohno K, Takaku H. J Biol Chem. 2009 Jan 16. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19150985?ordinalpos=7&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The hepatitis C virus (HCV) is a major cause of chronic liver disease. Here, we report a new and effective strategy for inhibiting HCV replication using 17-allylaminogeldanamycin (17-AAG), an inhibitor of heat-shock protein 90 (Hsp90). Hsp90 is a molecular chaperone with a key role in stabilizing the conformation of many oncogenic signalling proteins. We examined the inhibitory effects of 17-AAG on HCV replication in a HCV replicon cell-culture system. In HCV replicon cells treated with 17-AAG, we found that HCV RNA replication was suppressed in a dose-dependent manner and, interestingly, the only HCV protein degraded in these cells was nonstructural protein 3 (NS3). Immunoprecipitation experiments showed that NS3 directly interacted with Hsp90, as did proteins expressed from NS3 protease expression vectors. These **RESULTS** suggest that the suppression of HCV RNA replication is due to the destabilization of NS3 in disruption of the Hsp90 chaperone complex by 17-AAG.

Evolution and predictive factors of thyroid disorder due to interferon alpha in the treatment of hepatitis C. Gelu-Simeon M, Burlaud A, Young J, Pelletier G, Buffet C. World J Gastroenterol. 2009 Jan 21;15(3):328-33.
http://www.ncbi.nlm.nih.gov/pubmed/19140232?ordinalpos=22&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
AIM: To study predictive factors of thyroid dysfunction associated with interferon-alpha (IFNalpha) therapy in chronic hepatitis C (CHC) and to describe its long-term evolution in a large population without previous thyroid dysfunction. **METHODS**: We performed a follow-up of thyroid function and detection of thyroid antibodies in 301 patients treated for CHC with IFNalpha from 1999 to 2004. **RESULTS**: Thyroid disorder developed in 30/301 (10%) patients with a mean delay of 6 +/- 3.75 mo: 13 patients had hyperthyroidism, 11 had hypothyroidism, and 6 had biphasic evolution. During a mean follow-up of 41.59 +/- 15.39 mo, 9 patients with hyperthyroidism, 3 with hypothyroidism, and 4 with biphasic evolution normalized thyroid function in 7.88 +/- 5.46 mo. Recovery rate of dysthyroidism was not modified by treatment discontinuation, but was better for patients with negative thyroid antibodies before antiviral treatment (P = 0.02). Women had significantly more dysthyroidism (P = 0.05). Positive thyroid peroxidase and thyroglobulin antibodies were more frequent before antiviral treatment in patients who developed dysthyroidism (P < 0.0003 and P = 0.0003, respectively). In a multivariate model, low fibrosis was found to be a predictive factor of dysthyroidism (P = 0.039). **CONCLUSION**: In this monocentric population of CHC, dysthyroidism, especially hyperthyroidism, developed in 10% of patients. Low fibrosis was

found to be a predictive factor of dysthyroidism. Thyroid disorder recovered in 16/30 patients (53%) and recovery was better in the non-autoimmune form.

Transient and etiology-related transcription regulation in cirrhosis prior to hepatocellular carcinoma occurrence. Caillot F, Derambure C, Bioulac-Sage P, et al. World J Gastroenterol. 2009 Jan 21;15(3):300-9.
http://www.ncbi.nlm.nih.gov/pubmed/19140229?ordinalpos=23&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
AIM: To search for transcription dysregulation that could (1) differentiate hepatocellular carcinoma (HCC)-free from HCC-related cirrhosis (2) differentiate HCC-free cirrhosis related to HCV from that related to alcohol intake. **METHODS**: Using microarray analysis, we compared transcript levels in HCC-free cirrhosis (alcoholism: 7; hepatitis C: 7), HCC-associated cirrhosis (alcoholism: 10; hepatitis C: 10) and eight control livers. The identified transcripts were validated by qRT-PCR in an independent cohort of 45 samples (20 HCC-free cirrhosis; 15 HCC-associated cirrhosis and 10 control livers). We also confirmed our **RESULTS** by immunohistochemistry. **RESULTS**: In HCC-free livers, we identified 70 transcripts which differentiated between alcoholic-related cirrhosis, HCV-related cirrhosis and control livers. They mainly corresponded to down-regulation. Dysregulation of Signal Transduction and Activator of Transcription-3 (STAT-3) was found along with related changes in STAT-3 targets which occurred in an etiology-dependent fashion in HCC-free cirrhosis. In contrast, in HCC, such transcription dysregulations were not observed. **CONCLUSION**: We report that transcriptional dysregulations exist in HCC-free cirrhosis, are transiently observed prior to detectable HCC onset and may be appear like markers from cirrhosis to HCC transition.

Early gene expression profiles of patients with chronic hepatitis C treated with pegylated interferon-alfa and ribavirin. Younossi ZM, Baranova A, Afendy A, et al. Hepatology. 2009 Jan 12. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19140155?ordinalpos=25&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Responsiveness to hepatitis C virus (HCV) therapy depends on viral and host factors. Our **AIM** was to assess sustained virologic response (SVR)-associated early gene expression in patients with HCV receiving pegylated interferon-alpha2a (PEG-IFN-alpha2a) or PEG-IFN-alpha2b and ribavirin with the duration based on genotypes. Blood samples were collected into PAXgene tubes prior to treatment as well as 1, 7, 28, and 56 days after treatment. From the peripheral blood cells, total RNA was extracted, quantified, and used for one-step reverse transcription polymerase chain reaction to profile 154 messenger RNAs. Expression levels of messenger RNAs were normalized with six "housekeeping" genes and a reference RNA. Multiple regression and stepwise selection were performed to assess differences in gene expression at different time points, and predictive performance was evaluated for each model. A total of 68 patients were enrolled in the study and treated with combination therapy. The **RESULTS** of gene expression showed that SVR could be predicted by the gene expression of signal transducer and activator of transcription-6 (STAT-6) and suppressor of cytokine signaling-1 in the pretreatment samples. After 24 hours, SVR was predicted by the expression of interferon-dependent genes, and this dependence continued to be prominent throughout the treatment. **CONCLUSION**: Early gene expression during anti-HCV therapy may elucidate important molecular pathways that may be influencing the probability of achieving virologic response.

Proteomic analysis of HCV cirrhosis and HCV-induced HCC: identifying biomarkers for monitoring HCV-cirrhotic patients awaiting liver transplantation. Mas VR, Maluf DG, Archer KJ, et al. Transplantation. 2009 Jan 15;87(1):143-52.
http://www.ncbi.nlm.nih.gov/pubmed/19136905?ordinalpos=30&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND: Progression from chronic hepatitis C virus (HCV) infection to cirrhosis and hepatocellular carcinoma (HCC) **RESULTS** in protein changes in the peripheral blood. We evaluated global protein expression in plasma samples of HCV-cirrhotic and HCV-cirrhotic-HCC patients. **PATIENTS AND METHODS**: Plasma samples from 25 HCV-cirrhotic-HCC and 10 HCV-cirrhotic patients were quantitatively evaluated for protein expression. Tryptic peptides were analyzed using Thermo linear ion-trap mass spectrometer (LTQ) coupled with a Surveyor HPLC system (Thermo). SEQUEST and X!Tandem database search algorithms were used for peptide sequence identification. Protein relative quantification was performed using the area under the curve from the select ion chromatogram. A significant fold change between groups was based on controlling the false discovery rate (FDR) at less than 5%. **RESULTS**: We identified and quantified 2320 proteins from the analysis of the different protein pattern between HCV-cirrhosis and HCV-HCC samples. Gene ontology terms classified the more important biologic process related to these proteins as signal transduction, regulation of transcription DNA-dependent, protein amino acid phosphorylation, cell adhesion, transport, and immune response. Seven proteins showed significant expression changes with a FDR less than 5% between cirrhosis and tumor groups. Moreover, 18 proteins showed significant expression changes (FDR <5%) when plasma samples from HCV-cirrhosis were compared with early HCV-HCC. **CONCLUSIONS**: Differential protein expression was observed between samples from HCV patients with cirrhosis with and without HCC. Also, differences were observed between early and advanced HCV-HCC samples. This study provides important information for discovery of potential biomarkers for early HCC diagnosis in HCV cirrhotic patients.

Elevation of serum gamma-glutamyltranspeptidase activity is frequent in chronic hepatitis C, and is associated with insulin resistance. Benini F, Pigozzi MG, Pozzi A, et al. Dig Liver Dis. 2009 Jan 6. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19131283?ordinalpos=39&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND AND AIMS: Serum gamma-glutamyltranspeptidase level is often increased in patients with chronic hepatitis C, and we aimed to identify factors associated with this phenomenon in patients completely abstinent from alcohol (teetotal). **PATIENTS AND METHODS**: 71 teetotal patients have been identified by personal history, questioning of relatives, CAGE questionnaire administration and unscheduled alcoholemia measurements. **RESULTS**: 39 patients (55%) had elevated (>50IU/L) gamma-glutamyltranspeptidase level. Body mass index, insulin and C-peptide level, insulin resistance, piecemeal necrosis score >/=3, fibrosis score >/=2 and steatosis score >/=1 were significantly higher in these patients than in those (n=32) with normal gamma-glutamyltranspeptidase. At multiple linear regression analysis gamma-glutamyltranspeptidase level was associated with C-peptide level, insulin resistance and histopathologic grading. At multiple logistic regression analysis, C-peptide level (OR=2.13) and piecemeal necrosis score >/=3 (OR=4.59) were the only factors independently associated with elevated gamma-glutamyltranspeptidase. Sustained virological response during pegylated interferon plus ribavirine treatment was achieved by 97% and 49% patients with normal and elevated gamma-glutamyltranspeptidase, respectively (p=0.0001). **CONCLUSION**: Serum gamma-glutamyltranspeptidase level is often elevated in chronic hepatitis C and is associated with metabolic

and inflammatory factors; this phenomenon may contribute to explain and to predict resistance to treatment in this subgroup of patients.

Hepatitis C virus infection and the brain. Weissenborn K, Tryc AB, Heeren M, et al Metab Brain Dis. 2009 Jan 7. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19130196?ordinalpos=40&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
There is growing evidence that hepatitis C virus (HCV)-infection may affect the brain. About half of the HCV-infected patients complain of chronic fatigue irrespective of their stage of liver disease or virus replication rate. Even after successful antiviral therapy fatigue persists in about one third of the patients. Many patients, in addition, report of deficits in attention, concentration and memory, some also of depression. Psychometric testing revealed deficits in attention and verbal learning ability as characteristic for HCV-afflicted patients with normal liver function. Magnetic resonance spectroscopic studies showed alterations of the cerebral choline, N-acetyl-aspartate, and creatine content in the basal ganglia, white matter and frontal cortex, respectively. Recently, pathologic cerebral serotonin and dopamine transporter binding and regional alterations of the cerebral glucose utilisation compatible with alterations of the dopaminergic attentional system were observed. Several studies detected HCV in brain samples or cerebro-spinal fluid. Interestingly, viral sequences in the brain often differed from those in the liver, but were closely related to those found in lymphoid tissue. Therefore, the Trojan horse hypothesis emerged: HCV-infected mononuclear blood cells enter the brain, enabling the virus to reside within the brain (probably in microglia) and to infect brain cells, especially astrocytes.

Natural killer cell function is intact after direct exposure to infectious hepatitis C virions. Yoon JC, Shiina M, Ahlenstiel G, Rehermann B. Hepatology. 2009 Jan;49(1):12-21.
http://www.ncbi.nlm.nih.gov/pubmed/19085909?ordinalpos=83&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Although hepatitis C virus (HCV) has been shown to readily escape from virus-specific T and B cell responses, its effects on natural killer (NK) cells are less clear. Based on two previous reports that recombinant, truncated HCV E2 protein inhibits NK cell functions via crosslinking of CD81, it is now widely believed that HCV impairs NK cells as a means to establish persistence. However, the relevance of these findings has not been verified with HCV E2 expressed as part of intact virions. Here we employed a new cell culture system generating infectious HCV particles with genotype 1a and 2a structural proteins, and analyzed direct and indirect effects of HCV on human NK cells. Antibody-mediated crosslinking of CD16 stimulated and antibody-mediated crosslinking of CD81 inhibited NK cell activation and interferon gamma (IFN-gamma) production. However, infectious HCV itself had no effect even at titers that far exceeded HCV RNA and protein concentrations in the blood of infected patients. Consistent with these **RESULTS**, anti-CD81 but not HCV inhibited NK cell cytotoxicity. These **RESULTS** were independent of the presence or absence of HCV-binding antibodies and independent of the presence or absence of other peripheral blood mononuclear cell populations. **CONCLUSION**: HCV 1a or 2a envelope proteins do not modulate NK cell function when expressed as a part of infectious HCV particles. Without direct inhibition by HCV, NK cells may become activated by cytokines in acute HCV infection and contribute to infection outcome and disease pathogenesis.

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=88&itool=Email.EmailReport.Pubmed_ReportSelector.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 > or =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.

Screening of small-molecule compounds as inhibitors of HCV entry. Yang JP, Zhou D, Wong-Staal F. Methods Mol Biol. 2009;510:295-304.
http://www.ncbi.nlm.nih.gov/pubmed/19009270?ordinalpos=143&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The hepatitis C virus (HCV) has infected some 170 million people worldwide, and is expected to pose a significant medical problem for the foreseeable future. No vaccine is presently available, and the current antiviral therapies (pegylated interferon-alpha and ribavirin) are characterized by limited efficacy, high costs, and substantial side effects. Initiation of infection requires attachment of the HCV virus to the cell surface followed by viral entry and represents a critical determinant of tissue tropism and pathogenesis. Small molecules that inhibit the virus at the stage of viral entry, for example, by blocking the interactions between viral envelope glycoprotein and cellular receptor or coreceptor or by inhibiting the viral fusion process, would serve as attractive antiviral drugs. Recent development of HCV pseudoparticles (HCVpp), displaying unmodified and functional HCV glycoprotein on the surface of retroviral core particles, has greatly facilitated studies of HCV entry and provides an essential tool for the identification and characterization of molecules that block HCV entry. We have adapted the HCVpp infection assay with HCVpp harboring a luciferase reporter to a 96-well format and screened a small-molecule compound library to identify inhibitors of HCV entry. Such active viral entry inhibitors have the potential to be first-in-class antiviral drugs that can be incorporated into combinations of multiple drugs with different targets for the treatment of chronic HCV infection.

Toll-like receptor 4 mediates synergism between alcohol and HCV in hepatic oncogenesis involving stem cell marker Nanog. Machida K, Tsukamoto H, Mkrtchyan H, et al. Proc Natl Acad Sci U S A. 2009 Jan 26. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19171902?ordinalpos=8&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

Alcohol synergistically enhances the progression of liver disease and the risk for liver cancer caused by hepatitis C virus (HCV). However, the molecular mechanism of this synergy remains unclear. Here, we provide the first evidence that Toll-like receptor 4 (TLR4) is induced by hepatocyte-specific transgenic (Tg) expression of the HCV nonstructural protein NS5A, and this induction mediates synergistic liver damage and tumor formation by alcohol-induced endotoxemia. We also identify Nanog, the stem/progenitor cell marker, as a novel downstream gene up-regulated by TLR4 activation and the presence of CD133/Nanog-positive cells in liver tumors of alcohol-fed NS5A Tg mice. Transplantation of p53-deficient hepatic progenitor cells transduced with TLR4 **RESULTS** in liver tumor development in mice following repetitive LPS injection, but concomitant transduction of Nanog short-hairpin RNA abrogates this outcome. Taken together, our study demonstrates a TLR4-dependent mechanism of synergistic liver disease by HCV and alcohol and an obligatory role for Nanog, a TLR4 downstream gene, in HCV-induced liver oncogenesis enhanced by alcohol.

In vitro activity and pre-clinical profile of TMC435350, a potent HCV protease inhibitor. Lin TI, Lenz O, Fanning G, et al. Antimicrob Agents Chemother. 2009 Jan 26. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19171797?ordinalpos=9&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The hepatitis C virus (HCV) NS3/4A serine protease has been explored as a target for the inhibition of viral replication in pre-clinical models and in HCV-infected patients. TMC435350 is a highly specific and potent inhibitor of NS3/4A protease selected from a series of novel macrocyclic inhibitors. In biochemical assays using NS3/4A proteases of genotype 1a and 1b, inhibition constants (Ki) of 0.5 and 0.4 nM were determined respectively. TMC435350 inhibited HCV replication in a cellular assay (subgenomic 1b replicon) with a half maximal effective concentration (EC50) of 8 nM and a selectivity index of 5875. The compound was synergistic with interferon-alpha and an NS5B inhibitor in the replicon model, and additive with ribavirin. In rats, TMC435350 was extensively distributed to the liver and intestinal tract (tissue to plasma area under the curve (AUC) ratios > 35), and the absolute bioavailability was 44% after a single oral administration. Compound concentrations detected in both plasma and liver at 8 hours post dosing were above the EC99 value measured in the replicon. In **CONCLUSION**, given the selective and potent in vitro anti-HCV activity, the potential for combination with other anti-HCV agents and the favorable pharmacokinetic profile, TMC435350 has been selected for clinical development.

Clinical expression of insulin resistance in hepatitis C and B virus-related chronic hepatitis: Differences and similarities. Persico M, Masarone M, La Mura V, et al. World J Gastroenterol. 2009 Jan 28;15(4):462-6.
http://www.ncbi.nlm.nih.gov/pubmed/19152451?ordinalpos=24&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
AIM: To investigate the prevalence of the clinical parameters of insulin resistance and diabetes in patients affected by chronic hepatitis C (CHC) or chronic hepatitis B (CHB). **METHODS**: We retrospectively evaluated 852 consecutive patients (726 CHC and 126 CHB) who had undergone liver biopsy. We recorded age, sex, ALT, type 2 diabetes and/or metabolic syndrome (MS), body mass index (BMI), and apparent disease duration (ADD). **RESULTS**: Age, ADD, BMI, prevalence of MS and diabetes in patients with mild/moderate liver fibrosis were significantly higher in CHC. However, the degree of steatosis and liver fibrosis evaluated in liver biopsies did not differ between CHC and CHB patients. At multivariate analysis, age, sex, BMI, ALT and diabetes were independent risk factors for liver fibrosis in CHC, whereas only age was related to liver fibrosis in CHB. We also evaluated the association between significant steatosis (> 30%) and age, sex, BMI, diabetes, MS and liver fibrosis. Diabetes, BMI and liver fibrosis were associated with steatosis > 30% in CHC,

whereas only age and BMI were related to steatosis in CHB. **CONCLUSION**: These data may indicate that hepatitis C virus infection is a risk factor for insulin resistance.

HIV/HCV COINFECTION

Effects of HCV co-infection on apoptosis of CD4+ T cells in HIV-positive patients. Körner C, Krämer B, Schulte D, et al. Clin Sci (Lond). 2009 Jan 7. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19128241?ordinalpos=47&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND: Apoptosis importantly contributes to loss of CD4+ T cells in HIV infection, and modification of their apoptosis may explain why HIV/HCV-co-infected patients are more likely to die from liver-related causes, while effects of HCV on HIV infection remain unclear. **METHODS**: We studied in a cross-sectional and serial analysis spontaneous ex vivo CD4+ T cell apoptosis in HIV/HCV-co-infected and HIV-mono-infected patients before and after HAART. Apoptosis of peripheral blood CD4+ T cells was measured by both, a Poly (ADP-ribose) polymerase (PARP) and TdT-mediated dUTP-FITC nick end labelling (TUNEL) assay to detect cells with irreversible apoptosis. **RESULTS**: While hepatitis C alone did not increase CD4+ T cell apoptosis, HCV co-infection disproportionately increased elevated rates of apoptosis in CD4+ T cells from untreated HIV-positive patients. Increased CD4+ T cell apoptosis was closely correlated to HIV but not HCV viral loads. Under HAART increased rates of CD4+ T cell apoptosis rapidly decreased both in HIV-mono-infected and HIV/HCV-co-infected patients, without any significant difference in apoptosis rates between the two patients groups after 4 weeks of therapy. Nevertheless residual CD4+ T cell apoptosis did not reach the normal levels seen in healthy controls and remained higher in HIV patients receiving protease inhibitors than in patients with other antiretroviral regimens. **CONCLUSIONS**: Our **RESULTS** suggest that HCV co-infection sensitizes CD4+ T cells towards apoptosis in untreated HIV-positive patients. However, this effect is rapidly lost under effective antiretroviral therapy.

Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Laguno M, Cifuentes C, Murillas J, et al. Hepatology. 2009 Jan;49(1):22-31.
http://www.ncbi.nlm.nih.gov/pubmed/19085908?ordinalpos=84&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Although two pegylated interferons (Peg-IFN) are available to treat chronic hepatitis C virus (HCV) infection, no head-to-head comparative studies have been published. We **AIM** to compare the efficacy and safety of PEG IFN alfa-2b (PEG 2b) versus PEG IFN alfa-2a (PEG 2a), plus ribavirin (RBV). A prospective, randomized, multi-center, open-label clinical trial including 182 human immunodeficiency virus (HIV)-hepatitis C virus (HCV) patients naïve for HCV therapy was performed. Patients were assigned to PEG 2b (80-150 mug/week; n = 96) or PEG 2a (180 mug/week; n = 86), plus RBV (800-1200 mg/day) for 48 weeks. The primary endpoint was sustained virological response (SVR: negative HCV-RNA 24 weeks after completion of treatment). At baseline, both groups were well balanced: 73% male; 63% HCV genotype 1 through 4; 29% had fibrosis index of 3 or greater. The overall SVR was 44% (42% PEG 2b versus 46% PEG 2a, P = 0.65). Among genotypes 1 through 4, SVRs were 28% versus 32% (P = 0.67) and 62% versus 71% (P = 0.6) in genotypes 2 through 3 for PEG 2b and PEG 2a, respectively. Early virological response (EVR; >or=2 log reduction from baseline or negative HCV-RNA at week 12) was 70% in the PEG 2b group and 80% in the PEG 2a group (P = 0.13), reaching a positive predictive value of SVR of

64% and a negative predictive value of 100% in both arms. Side effects were present in 96% of patients but led to treatment discontinuation in 10% of patients (8% on PEG 2b and 13% on PEG 2a, P = 0.47). **CONCLUSION**: In patients with HIV, HCV therapy with PEG 2b or PEG 2a plus RBV had no significant differences in efficacy and safety.

Risks for HIV, HBV, and HCV infections among male injection drug users in northern Vietnam: a case-control study. Quan VM, Go VF, Nam le V, et al AIDS Care. 2009 Jan;21(1):7-16..
http://www.ncbi.nlm.nih.gov/pubmed/19085215?ordinalpos=85&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Injection drug use (IDU) and HIV infection are important public health problems in Vietnam. The IDU population increased 70% from 2000 to 2004 and is disproportionately affected by HIV and AIDS -- the country's second leading cause of death. Hepatitis B virus (HBV) and hepatitis C virus (HCV) share transmission routes with HIV and cause serious medical consequences. This study aimed to determine risk factors for acquisition of HIV, HBV, and HCV infections among IDUs in a northern province. We conducted a matched case-control study among active IDUs aged 18-45 who participated in a community-based survey (30-minute interview and serologic testing). Each HIV-infected IDU (case) was matched with one HIV-uninfected IDU (control) by age, sex (males only), and study site (128 pairs). Similar procedures were used for HBV infection (50 pairs) and HCV infection (65 pairs). Conditional logistic regression models were fit to identify risk factors for each infection. Among 309 surveyed IDUs, the HIV, HBV, and HCV prevalence was 42.4%, 80.9%, and 74.1%, respectively. Only 11.0% reported having been vaccinated against hepatitis B. While 13.3% of the IDUs reported sharing needles (past six months), 63.8% engaged in indirect sharing practices (past six months), including sharing drug solutions, containers, rinse water, and frontloading drugs. In multivariable models, sharing drugs through frontloading was significantly associated with HIV infection (odds ratio [OR]=2.8), HBV infection (OR=3.8), and HCV infection (OR=4.6). We report an unrecognized association between sharing drugs through frontloading and higher rates of HIV, HBV and HCV infections among male IDUs in Vietnam. This finding may have important implications for bloodborne viral prevention for IDUs in Vietnam.

Level, phenotype and activation status of CD4+FoxP3+ regulatory T cells in patients chronically infected with human immunodeficiency virus and/or hepatitis C virus. Rallón NI, López M, Soriano V, et al. Clin Exp Immunol. 2009 Jan;155(1):35-43.http://www.ncbi.nlm.nih.gov/pubmed/19076827?ordinalpos=89&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
CD4(+) regulatory T (T(reg)) cells have been involved in impaired immunity and persistence of viral infections. Herein, we report the level, phenotype and activation status of T(reg) cells in patients chronically infected with human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV). Expression of CD25, CD45RA, CD27, CD127 and CD38 was assessed on these cells using polychromatic flow cytometry in 20 healthy controls, 20 HIV-monoinfected, 20 HCV-monoinfected and 31 HIV/HCV-co-infected patients. T(reg) cells were defined as CD4(+)forkhead box P3 (FoxP3)(+). The percentage of T(reg) cells was increased significantly in HIV patients compared with controls. Moreover, there was a significant inverse correlation between CD4 counts and T(reg) cell levels. Fewer than 50% of T(reg) cells expressed CD25, with differences in terms of CD127 expression between CD25(+) and CD25((-)) T(reg) cells. CD4(+)Foxp3(+) T(reg) cells displayed predominantly a central memory phenotype (CD45RA(-)CD27(+)), without differences between patients and healthy controls. Activated T(reg) cells were increased in HIV patients, particularly considering the central memory subset. In summary, HIV infection, but not HCV, induces an up-

regulation of highly activated T(reg) cells, which increases in parallel with CD4 depletion. Hypothetically, this might contribute to the accelerated course of HCV-related liver disease in HIV-immunosuppressed patients.

Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. Thomson EC, Nastouli E, Main J, et al. AIDS. 2009 Jan 2;23(1):89-93.
http://www.ncbi.nlm.nih.gov/pubmed/19050390?ordinalpos=108&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
OBJECTIVE: An epidemic of acute hepatitis C virus (HCV) infection among HIV-positive men who have sex with men is occurring in urban centers in Western Europe and the United States. Early diagnosis and treatment of HCV **RESULTS** in improved sustained virological response rates. This study compared the sensitivity of reverse transcriptase PCR (RT-PCR) versus antibody screening for the diagnosis of early HCV infection in HIV-positive patients and estimated the length of time from HCV infection to the development of anti-HCV antibodies. DESIGN: Patients from the St Mary's Acute Hepatitis C Cohort (SMACC) were recruited retrospectively and prospectively between 2004 and 2008. **METHODS**: Archived plasma samples, obtained at 1-3 monthly intervals for routine monitoring of HIV viral load were assayed retrospectively for HCV in order to assess the sensitivity of RT-PCR and enzyme-linked immunosorbent assay (ELISA). **RESULTS**:: Forty-three HIV-positive patients with early HCV infection were identified. The median CD4 cell count was 570 cells/microl. The median alanine transaminase at the time of the first positive HCV PCR was 65 IU/ml. At this time, 75% of patients had a negative HCV antibody test. Three months later, 37% of patients still had a negative result. After 9 months, 10% of patients had a negative test and 5% remained negative after 1 year. **CONCLUSION**/DISCUSSION: Delayed seroconversion in HIV-positive individuals with acute HCV may result in delayed diagnosis and treatment. Where there is a clinical suspicion of recent HCV infection, for example, elevated alanine transaminase levels, HIV-infected patients should be screened for HCV RNA by RT-PCR.

Influence of liver fibrosis stage on plasma levels of efavirenz in HIV-infected patients with chronic hepatitis B or C. Meynard JL, Lacombe K, Poirier JM, et al. J Antimicrob Chemother. 2009 Jan 23. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19168543?ordinalpos=15&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
OBJECTIVES Liver function is a key component of efavirenz metabolism and might be altered in severe liver fibrosis induced by HIV/chronic hepatitis co-infection. However, data evaluating the impact of liver fibrosis stages on the plasma efavirenz level are lacking. **PATIENTS AND METHODS** In this study, conducted in 134 HIV-infected patients [77, 35 and 22 HIV mono-infected, HIV/hepatitis C virus (HCV) co-infected and HIV/hepatitis B virus (HBV) co-infected, respectively] treated with efavirenz 600 mg once a day in combination with other antiretroviral agents, plasma concentration was measured at least 8 h after the last drug intake using a validated HPLC method. The degree of liver fibrosis was determined by means of either liver biopsy or non-invasive biochemical markers (Fibrotest((R))). The proportions of patients above a threshold of 4000 ng/mL were compared by means of Pearson's chi(2) test or Fisher's exact test. **RESULTS** In HIV mono-infected and HIV/HCV and HIV/HBV co-infected patients, mean +/- SD efavirenz plasma concentrations were 3060 +/- 1928, 4108 +/- 3324 and 3163 +/- 2432 ng/mL, respectively. The proportion of patients with an efavirenz concentration above 4000 ng/mL differed significantly according to the presence of hepatitis and the fibrosis stage. A concentration above 4000 ng/mL was found in 14 patients (18.2%) mono-infected with HIV compared with 5 (22.7%, P = 0.01) and 9 (25.7%, P = 0.001) HIV/HBV or HIV/HCV co-infected patients, respectively. When the fibrosis

stage was considered in all patients with hepatitis, 3 cirrhotic patients (42.6%) had an efavirenz concentration above the 4000 ng/mL threshold [compared with 14 (18.2%) HIV mono-infected patients, P = 0.001]. **CONCLUSIONS** Therapeutic drug monitoring may be of interest in cirrhotic patients more at risk of side effects due to efavirenz overdosing.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Haemophilia, aging and sexuality. Gianotten WL, Heijnen L. Haemophilia. 2009 Jan;15(1):55-62.
http://www.ncbi.nlm.nih.gov/pubmed/19149847?ordinalpos=12&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
The older generation of patients with haemophilia still has musculoskeletal problems which limit activities and participation. One important aspect of male aging is the changes in sexuality. Sexual desire can be disturbed by fatigue, low testosterone or pain. Sexual excitement (erection) may be influenced by diabetes mellitus, arteriosclerosis, hypertension and side effects of antihypertensive and antiviral medication. Sexual response problems can be caused by antidepressant medication. In aging haemophiliacs arthropathy, iliopsoas muscle bleeding, chronic hepatitis C and HIV medications influence sexuality. The haemophilia care professionals should communicate proactively, give information on various practical aspects of sexuality (suggest suitable positions, recommend painkillers, reflect on prescribing erection-enhancing medication, refer to a sexology expert).

A new sensitive and automated chemiluminescent microparticle immunoassay for quantitative determination of hepatitis C virus core antigen. Morota K, Fujinami R, Kinukawa H, et al. J Virol Methods. 2009 Jan 19. [Epub ahead of print].
http://www.ncbi.nlm.nih.gov/pubmed/19135481?ordinalpos=33&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
A new sensitive and automated chemiluminescent assay was developed for the quantitative determination of hepatitis C virus (HCV) core antigen (Ag) in human sera or plasma: the Abbott ARCHITECT((R)) HCV Ag test. The assay sensitivity was determined by testing 10 commercial HCV seroconversion panels. Without exception, a positive result for HCV core Ag was observed before anti-HCV detection, resulting in an average reduction in the period between exposure and detection of 35.8 days. Both HCV core Ag and HCV RNA were detected in the panels at the same time, indicating equivalent sensitivity and detectability. A total of 197 HCV specimens comprising genotypes 1a, 1b, 2a, 2b, 3a, 3k, 4a, 5a and 6a were evaluated. Among these, 196 (99.5%), 191 (97%) and 193 (98%) were reactive using the HCV Ag, the immunoradiometric HCV Ag and the Amplicor HCV Monitor 2 assays, respectively. A comparison with the Amplicor HCV Monitor 2 showed a correlation coefficient (r) of 0.74. The specificity of the assay was established at 99.8% by testing 5403 specimens from US volunteer blood donors, hospitalized patients and individuals with medical conditions unrelated to HCV infection, in addition to specimens containing potentially interfering substances.

Nonhospital health care-associated hepatitis B and C virus transmission: United States, 1998-2008. Thompson ND, Perz JF, Moorman AC, Holmberg SD. Ann Intern Med. 2009 Jan 6;150(1):33-9.
http://www.ncbi.nlm.nih.gov/pubmed/19124818?ordinalpos=53&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

In the United States, transmission of hepatitis B virus (HBV) and hepatitis C virus (HCV) from health care exposures has been considered uncommon. However, a review of outbreak information revealed 33 outbreaks in nonhospital health care settings in the past decade: 12 in outpatient clinics, 6 in hemodialysis centers, and 15 in long-term care facilities, resulting in 448 persons acquiring HBV or HCV infection. In each setting, the putative mechanism of infection was patient-to-patient transmission through failure of health care personnel to adhere to fundamental principles of infection control and aseptic technique (for example, reuse of syringes or lancing devices). Difficult to detect and investigate, these recognized outbreaks indicate a wider and growing problem as health care is increasingly provided in outpatient settings in which infection control training and oversight may be inadequate. A comprehensive approach involving better viral hepatitis surveillance and case investigation, health care provider education and training, professional oversight, licensing, and public awareness is needed to ensure that patients are always afforded basic levels of protection against viral hepatitis transmission.

Predictors for non-compliance of notified hepatitis C virus-positive blood donors with recommendation to seek medical counseling. Kerzman H, Green MS, Shinar E. Vox Sang. 2009 Jan;96(1):20-8.
http://www.ncbi.nlm.nih.gov/pubmed/19121194?ordinalpos=57&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND Notification of blood donors represents the commonest method of informing asymptomatic individuals of abnormal test **RESULTS** indicating exposure to hepatitis C virus (HCV) infection. Such notification is therefore important from both health and economic perspectives. This study aimed to identify predictors for non-compliance of HCV-positive blood donors with the National Blood Services recommendation to seek medical counselling. Study Design and **METHODS** The current research is a cross-sectional study. Telephone interviews were conducted with 201 blood donors identified as HCV positive following blood donation during 2001-2002 (40% response rate). **RESULTS** About 25% of all the notified blood donors did not seek any counselling; 29% (44/150) of those who requested medical advice from their primary care physicians (general practitoner's) were not referred to specialists. Age, alcohol consumption and non-practice of health-promoting behaviour were independent predictors of non-compliance with the blood services' recommendation. In particular, smoking (odds ratio, 2.0; 95% confidence interval 1.0-4.2) and not undergoing professional teeth cleaning (odds ratio 2.8; 95% confidence interval 1.3-6.1) were found to be significant predictors of non-compliance. **CONCLUSION** The study provides essential data regarding the extent and risk factors for non-compliance of HCV-positive blood donors with recommendation to seek medical advice. Our **RESULTS** can assist in identifying blood donors who would not seek counselling, based on demographic factors and past exposure to risk factors for HCV. Improvements in the notification process and additional training of general practitoners regarding the management of HCV disease are needed.

Hepatitis B-hepatitis C seroprevalences and blunt-penetrating object injuries in housekeepers in Turkey: a survey study. Ozer ZC, Efe E, Oncel S, Taskinsoy H, Ulker M. J Clin Nurs. 2009 Jan;18(2):294-300.
http://www.ncbi.nlm.nih.gov/pubmed/19120756?ordinalpos=58&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
AIM: This study aims to identify housekeepers' use of protective measures, provide data about hepatitis B virus (HBV) and hepatitis C virus (HCV) seroprevalences and HBV immunisation, and investigate blunt-penetrating injuries in patient care services, routine cleaning services and orderly services. **BACKGROUND**: Hospitals have been described as hazardous work environments with

an increase in HBV-HCV seroprevalences and blunt-penetrating object injuries. This situation creates great risks and hazards for housekeepers in their jobs. DESIGN: Survey. **METHODS**: The study population was housekeepers who work in university hospitals. A total of 824 housekeepers were surveyed by using a 20-item questionnaire. The questionnaire included the sociodemographic characteristics of housekeepers and the risk level of the unit employed. Blood samples were taken from the housekeepers. **RESULTS**: Their mean age was 32.5 years. The majority of the housekeepers (52.5%) were women and graduates of primary school (51.1%). The mean length of employment was 2.6 years, 73% were working on medical/surgical units, 91.2% were working in routine cleaning and 70.9% had been injured with various blunt and penetrating objects while working in the hospital in the past six months. The obtained result for seroprevalence for HBV-HCV was 2.2%. Only 27.5% of the housekeepers had been immunised with Hepatitis B vaccine. A large percentage of housekeepers in this study had used universal precautions. **CONCLUSION**: This study showed high seroprevalence rates for HBV-HCV and blunt-penetrating object injuries in housekeepers. Therefore, more effort is necessary to increase the use of protective measures against HBV-HCV and blunt-penetrating object injuries in housekeepers. RELEVANCE TO CLINICAL PRACTICE: Hospitals need to take protective measures and implement innovative educational and support programmes organised for specific groups of housekeepers.

Insulin resistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. Cammà C, Petta S, Di Marco V, et al. Hepatology. 2009 Jan;49(1):195-203.http://www.ncbi.nlm.nih.gov/pubmed/19065558?ordinalpos=97&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
Indirect methods to predict the presence of esophageal varices (EV) in patients with cirrhosis are not sensitive enough to be used as a surrogate for endoscopy. We tested the effectiveness of liver stiffness measurement (LSM) by transient elastography and the presence of insulin resistance (IR), a marker associated with fibrosis progression, in the noninvasive prediction of portal hypertension. One hundred four consecutive patients with newly diagnosed Child A hepatitis C virus (HCV) cirrhosis underwent upper gastrointestinal endoscopy to search for EV. Clinical, anthropometric, biochemical, ultrasonographic, and metabolic features, including IR by the homeostasis model assessment (HOMA), and LSM by transient elastography, were recorded at the time of endoscopy. EVs were detected in 63 of 104 patients (60%). In 10 patients (16%), the EVs were medium-large (>or=F2). By multivariate analysis, the presence of EVs was independently associated with a low platelet count/spleen diameter ratio (OR, 0.998; 95% CI, 0.996-0.999) and a high HOMA-IR score (OR, 1.296; 95%CI, 1.018-1.649), not with LSM (OR, 1.009; 95%CI, 0.951-1.070). It is noteworthy that nine of ten patients with medium-large EVs had a platelet/spleen ratio of less than 792 or an HOMA-IR of greater than 3.5. The independent association between low platelet count/spleen diameter ratio (OR, 0.998; 95%CI, 0.996-1.000), high HOMA-IR score (OR, 1.373; 95%CI, 1.014-1.859) and presence of EV was confirmed in the subgroup of 77 nondiabetic subjects. **CONCLUSIONS**: In patients with Child A HCV cirrhosis, two simple, easy-to-get tests, namely the platelet/spleen ratio and insulin resistance measured by HOMA-IR, regardless of the presence of diabetes, significantly predict the presence of EV, outweighing the contribution given by transient elastography.

Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. Boursier J, Bacq Y, Halfon P, et al. Eur J Gastroenterol Hepatol. 2009 Jan;21(1):28-38. http://www.ncbi.nlm.nih.gov/pubmed/19060630?ordinalpos=102&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

OBJECTIVE: Blood tests are usually designed to identify significant fibrosis. We evaluated their diagnostic accuracy, and how to increase it, for the clinically important targets of severe fibrosis and cirrhosis. **METHODS**: The accuracy for severe fibrosis or cirrhosis of four blood tests was evaluated based on Metavir staging in 1056 patients with chronic hepatitis C recruited in five independent hospitals. **RESULTS**: Using original scores, an original diagnostic target (significant fibrosis) and best diagnostic cutoff, the correct classification rates in severe fibrosis and cirrhosis stages were, respectively: FibroMeter: 90.1, 100%, Fibrotest: 78.2, 95.1%, Hepascore: 73.8, 94.9%, aspartate aminotransferase to platelet ratio index (APRI): 71.4, 88.0% ($P<0.003$, $P=0.004$, respectively, between tests). The corresponding area under the receiver operating characteristics were FibroMeter: 0.885, 0.907, Fibrotest: 0.837, 0.882, Hepascore: 0.834, 0.896, APRI: 0.822, 0.841 ($P<0.003$, respectively). Observed 100% negative predictive values for severe fibrosis and cirrhosis were, respectively, FibroMeter: 15.4, 47.5%, Fibrotest: 3.6, 31.9%, Hepascore: 0.3, 24.6%, APRI: 1.4, 5.3% of patients ($P<0.003$, respectively, between tests). By calculating a specific test for cirrhosis, including the FibroMeter markers, the correct classification (93.0%) was significantly higher for the cirrhosis diagnosis compared with the original FibroMeter (90.9%, $P=0.005$). This specific test provided a 100% positive predictive value for cirrhosis diagnosis versus 88% for original FibroMeter. **CONCLUSION**: Using the most accurate original test, cirrhosis can be excluded in 47.5% of patients and is correctly diagnosed, as significant fibrosis, in 100% of patients. A specific test for cirrhosis provides a significant gain in diagnostic accuracy to 93% and in positive predictive value to 100% compared with the original test.

Reduction of hepatitis C virus using lectin affinity plasmapheresis in dialysis patients. Tullis RH, Duffin RP, Handley HH, et al. Blood Purif. 2009;27(1):64-9. Epub 2009 Jan 23.
http://www.ncbi.nlm.nih.gov/pubmed/19169020?ordinalpos=14&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
BACKGROUND/AIMS: To test the safety and efficacy of the Aethlon Hemopurifier, a lectin affinity cartridge, in clearing hepatitis C virus (HCV) from the blood of HCV-positive end-stage renal disease patients undergoing dialysis. Viral RNA was measured using real-time quantitative reverse transcriptase polymerase chain reaction. **RESULTS**: HCV clearance from plasma or blood was measured using either direct capture on immobilized Galanthus nivalis agglutinin (GNA) or using miniature plasmapheresis cartridges containing immobilized GNA. HCV in plasma samples was rapidly cleared by direct affinity capture (t(1/2) = approx. 20 min) and HCV in human blood was cleared using the Hemopurifier (t(1/2) = 2-3 h). Institutional-review-board-sanctioned clinical safety studies were conducted at the Apollo and Fortis Hospitals in India. At Apollo, 4 patients were treated 3 times/week for 2 weeks. HCV captured on the Hemopurifier averaged 8.9 x 10(8) viral copies/cartridge (n = 5), representing approximately 30% of the initial viral body burden. At Fortis, 3 patients treated 3 times/week for 1 week completed the viral load studies. Two patients showed measurable viral load reduction, while the third showed both increases and decreases in viral load. After Hemopurifier treatment, average HCV viral load was reduced by 57%. Surprisingly, average viral load was also 82% lower 7 days after treatment. Control samples also showed a marked transient reduction in HCV viral load as previously reported. **CONCLUSION**: The Hemopurifier rapidly cleared HCV from blood treated in vitro. In patients, the combination of the Hemopurifier plus dialysis decreased HCV viral load by 57% in 1 week. Moreover, viral load reduction continued up to 7 days after treatment.

HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. Muhlberger N, Schwarzer R, Lettmeier B, et al. BMC Public Health. 2009 Jan 22;9(1):34. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19161623?ordinalpos=20&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

ABSTRACT: BACKGROUND: Hepatitis C virus (HCV) is a leading cause of chronic liver disease, end-stage cirrhosis, and liver cancer, but little is known about the burden of disease caused by the virus. We summarised burden of disease data presently available for Europe, compared the data to current expert estimates, and identified areas in which better data are needed. **METHODS**: Literature and international health databases were systematically searched for HCV-specific burden of disease data, including incidence, prevalence, mortality, disability-adjusted life-years (DALYs), and liver transplantation. Data were collected for the WHO European region with emphasis on 22 countries. If HCV-specific data were unavailable, these were calculated via HCV-attributable fractions. **RESULTS**: HCV-specific burden of disease data for Europe are scarce. Incidence data provided by national surveillance are not fully comparable and need to be standardised. HCV prevalence data are often inconclusive. According to available data, an estimated 7.3-8.8 million people (1.1-1.3%) are infected in our 22 focus countries. HCV-specific mortality, DALY, and transplantation data are unavailable. Estimations via HCV-attributable fractions indicate that HCV caused more than 86 000 deaths and 1.2 million DALYs in the WHO European region in 2002. Most of the DALYs (95%) were accumulated by patients in preventable disease stages. About one-quarter of the liver transplants performed in 25 European countries in 2004 were attributable to HCV. **CONCLUSIONS**: Our **RESULTS** indicate that hepatitis C is a major health problem and highlight the importance of timely antiviral treatment. However, data on the burden of disease of hepatitis C in Europe are scarce, outdated or inconclusive, which indicates that hepatitis C is still a neglected disease in many countries. What is needed are public awareness, co-ordinated action plans, and better data. European physicians should be aware that many infections are still undetected, provide timely testing and antiviral treatment, and avoid iatrogenic transmission.

Liver cirrhosis and diabetes: Risk factors, pathophysiology, clinical implications and management. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. World J Gastroenterol. 2009 Jan 21;15(3):280-8.
http://www.ncbi.nlm.nih.gov/pubmed/19140227?ordinalpos=27&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum

About 30% of patients with cirrhosis have diabetes mellitus (DM). Nowadays, it is a matter for debate whether type 2 DM in the absence of obesity and hypertriglyceridemia may be a risk factor for chronic liver disease. DM, which develops as a complication of cirrhosis, is known as "hepatogenous diabetes". Insulin resistance in muscular and adipose tissues and hyperinsulinemia seem to be the pathophysiologic bases of diabetes in liver disease. An impaired response of the islet beta-cells of the pancreas and hepatic insulin resistance are also contributory factors. Non-alcoholic fatty liver disease, alcoholic cirrhosis, chronic hepatitis C (CHC) and hemochromatosis are more frequently associated with DM. Insulin resistance increases the failure of the response to treatment in patients with CHC and enhances progression of fibrosis. DM in cirrhotic patients may be subclinical. Hepatogenous diabetes is clinically different from that of type 2 DM, since it is less frequently associated with microangiopathy and patients more frequently suffer complications of cirrhosis. DM increases the mortality of cirrhotic patients. Treatment of the diabetes is complex due to liver damage and hepatotoxicity of oral hypoglycemic drugs. This manuscript will review evidence that exists in relation to: type 2 DM alone or as part of the metabolic syndrome in the development of liver disease; factors involved in the genesis of hepatogenous diabetes; the impact of DM on the clinical outcome of liver disease; the management of DM in cirrhotic patients and the role of DM as a risk factor for the occurrence and exacerbation of hepatocellular carcinoma.

Nomenclature and numbering of the hepatitis C virus. Kuiken C, Simmonds P. Methods Mol Biol. 2009;510:33-53.
http://www.ncbi.nlm.nih.gov/pubmed/19009252?ordinalpos=155&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum
International standardization and coordination of the nomenclature of variants of hepatitis C virus (HCV) is increasingly needed as more is discovered about the scale of HCV-related liver disease and important biological and antigenic differences that exist between variants. Consistency in numbering is also increasingly required for functional and clinical studies of HCV. For example, an unambiguous method for referring to amino acid substitutions at specific positions in NS3 and NS5B coding sequences associated with resistance to specific HCV inhibitors is essential in the investigation of antiviral treatment. Inconsistent and inaccurate numbering of locations in DNA and protein sequences is becoming a problem in the HCV scientific literature.A group of experts in the field of HCV genetic variability, and those involved in development of HCV sequence databases, the Hepatitis Virus Database (Japan), euHCVdb (France), and the Los Alamos National Laboratory (United States), convened to reexamine the status of HCV genotype nomenclature, resolve conflicting genotype or subtype names among described variants of HCV, and draw up revised criteria for the assignment of new genotypes as they are discovered in the future. They also discussed how HCV sequence databases could introduce and facilitate a standardized numbering system for HCV nucleotides, proteins, and epitopes.A comprehensive listing of all currently classified variants of HCV incorporates a number of agreed genotype and subtype name reassignments to create consistency in nomenclature. A consensus proposal was drawn up for the classification of new variants into genotypes and subtypes, which recognizes and incorporates new knowledge of HCV genetic diversity and epidemiology. The proposed numbering system was adapted from the Los Alamos HIV database, with elements from the hepatitis B virus numbering system. The system comprises both nucleotides and amino acid sequences and epitopes, and uses the full-length genome sequence of isolate H77 (accession number AF009606) as a reference. It includes a method for numbering insertions and deletions relative to this reference sequence.