



# Caring Ambassadors Hepatitis C Program Newsletter

April 2008

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## IN THE NEWS

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### **Caring Ambassadors Hepatitis C Program launches internet-based Hep C Discussion Point™ to assist people living with hepatitis C**

<http://www.marketwire.com/mw/release.do?id=831185>

The Caring Ambassadors Hepatitis C Program (CAP Hepatitis C), a national nonprofit organization, announces the Internet release of its new interactive medical management tool, Hep C Discussion Point™ at [www.HepCChallenge.org](http://www.HepCChallenge.org). Hep C Discussion Point™ takes the user through a guided series of questions about their hepatitis C experience. Custom-built software analyzes the user's responses and generates a report with information and topics specific to the user's inputs. The report is designed to be used as both a learning tool for the patient and as a guide to facilitate communication and enhance the health care partnership between people living with hepatitis C and their doctors.

Hep C Discussion Point™ was developed by CAP Hepatitis C in conjunction with leading experts in the field of hepatology to help facilitate, inform, and enhance the therapeutic decision-making process by providing discussion points on state-of-the-art hepatitis C management. Hep C Discussion Point™ is a groundbreaking effort, and is the only tool of its kind designed exclusively for hepatitis C clients and their health care providers. [truncated]

### **Researchers develop a process to disrupt hepatitis C virion production**

<http://www.sciencecentric.com/news/08032304.htm>

HCV is a significant human pathogen, infecting more than three percent of the world's population. The incidence of infection in the United States has been estimated to be as high as 4 million cases. In the March issue of the journal PLoS Pathogens, Timothy Tellinghuisen, an assistant professor in the Department of Infectology at Scripps Florida, and his colleagues describe how they used mutations of the viral NS5A phosphoprotein to disrupt virus particle production at an early stage of assembly. NS5A has long been proposed as a regulator of events in the HCV life cycle, but exactly how it orchestrates these events has been unclear.

'The interesting thing about this mutant is that while it triggers totally normal RNA replication, it causes severe defects in the output of infectious virus - in fact, it releases no infectious virus that we can detect,' says Tellinghuisen. 'And though this discovery isn't a cure for HCV, it is an important research tool that stops the assembly pathway.' Total disruption of the replication process would be a cure for the disease, he adds, and that's the team's long-term goal. [truncated]

### **Risk of hepatitis C from tattoo art not sharply defined, experts say**

[http://www.union-bulletin.com/articles/2008/03/23/local\\_news/local04.txt](http://www.union-bulletin.com/articles/2008/03/23/local_news/local04.txt)

While there is a dearth of strong evidence of a link between getting a tattoo and becoming infected with hepatitis C, the potential is there, said Wendy Dillon, coordinator for the state's adult viral hepatitis prevention program. "Here's what I say," she said at a recent meeting about safe tattooing. "If there is blood-to-blood contact, there is potential." While hepatitis A and B are vaccine preventable, no such treatment yet exists for hepatitis C. And no vaccine is likely to show up soon, Dillon said. "The virus mutates so quickly." [truncated]

### **Bexar County awaits AG opinion on needle-exchange program Project to prevent spread of disease legal only in Bexar, yet isn't**

<http://www.dallasnews.com/sharedcontent/dws/news/texasouthwest/stories/023408dnmetneedle.s.3aa9130.html>

SAN ANTONIO – Bill Day uses his shoe to brush aside a couple of used needles littering the ground near a concrete arroyo in a seedy west side neighborhood. The 73-year-old lay chaplain said he used to work with drug addicts at this spot all the time. He'd park the white minivan paid for in part by St. Mark's Episcopal Church and throw open the trunk. Sickly and desperate and dying, they'd swarm him as he directed them to places to get help and gave them clean needles in an effort to keep them from spreading HIV and hepatitis C.

Now, the red-haired retiree, himself living with AIDS for the last decade, is awaiting word on whether he'll land in jail for a year for administering a program that has been legalized in every state in the nation but Texas.

Here's the irony: Bexar County is the only place in Texas that has a law on the books intended to authorize a syringe-exchange program. It's also the only major metropolitan area, Dallas included, where churches or nonprofits aren't operating one anyway, with the tacit approval of law enforcement. But because prosecutors don't believe the 2007 law was written properly, it's now up to Texas Attorney General Greg Abbott to decide whether the law is valid. [truncated]

### **Indian clinics uncover high rate of hepatitis C**

<http://www.billingsgazette.net/articles/2008/03/22/news/state/23-hepc.txt>

An epidemiological study conducted at two Indian Health Service clinics in Montana uncovered a hepatitis C infection rate that is six times higher than is found in the general population. The finding surprised tribal and state health officials, who responded by creating an educational brochure that targets young American Indians.

The 2005-06 study, authored by IHS epidemiologist Christine Dubray, revealed a 6 percent hepatitis C infection rate among women who went to the clinics for prenatal care. Only about 1 percent of people in the U.S. population has hepatitis C, Dubray said.

"We have an unexpected number of young women with hepatitis C infection," she said. "In the general American population, the prevalence of hepatitis C is much lower in young women." [truncated]

### **15 hepatitis infections tied to ex-nurse**

<http://ap.google.com/article/ALeqM5hHvETNsob9ac-d7IYjpQ-aOLgm2AD8VHN82O0>

EL PASO, Texas— At least 15 military service members or their relatives are believed to have been infected with hepatitis by a nurse suspected of stealing their painkillers during surgery. The nurse, retired Army captain Jon Dale Jones, was arrested this month in Miami on federal charges of assaulting three of those patients and possession of a controlled substance by fraud.

Federal prosecutors said they believe Jones spread the disease in 2004 during surgeries at an El Paso military hospital by diverting fentanyl — a powerful painkiller often used for anesthesia — from patients to himself. The outbreak — and the nearly three-year-long criminal investigation that followed — apparently did not prevent Jones from continuing to work as nurse in Texas and at least two other states and Washington, D.C. [truncated]

### **XTL licenses hepatitis C program**

<http://www.globes.co.il/serveen/globes/DocView.asp?did=1000324589&fid=1725>

XTL Biopharmaceuticals Ltd has licensed its pre-clinical program in hepatitis C focused on the NS5A target to Presidio Pharmaceuticals Inc. Presidio will take over all further development and commercialization activities and costs relating to the hepatitis C program. XTL will receive an upfront payment of \$4 million, and up to an additional \$104 million upon reaching certain development and commercialization milestones. [truncated]

### **Inovio Biomedical reveals safety results of Tripep's ChronVac-C delivered using Inovio's Electroporation Delivery Systems**

<http://www.rttnews.com/sp/breakingnews.asp?date=03/17/2008&item=78&vid=0>

Monday morning, biomedical company Inovio Biomedical Corp. said that its partner Tripep AB of Sweden reported preliminary results from its Phase I/II clinical study of therapeutic hepatitis C virus, or HCV, vaccine, ChronVac-C, which was delivered using Inovio's electroporation-based DNA delivery system.

The primary objective of the study is to assess safety of ChronVac-C. It would also test whether the treatment boosts the immune response to HCV and its effect on virus replication in the liver. The study's intended enrollment is 12 patients divided into three dose groups with increasing doses of ChronVac-C. Each patient receives four ChronVac-C vaccinations one month apart. After the last vaccination, patients are followed for another six months. This first reported data was from the first patient in the lowest dose group. Five patients have been treated and no unexpected side effects have been observed.

Samples taken before, during and after treatment showed that before vaccination the patient did not have a detectable cell-mediated immune response against HCV but such an immune response became detectable after treatment was completed. Inovio's electroporation delivery technology is intended to enhance the potency of DNA-based immunotherapies, including DNA vaccines, against cancers and infectious diseases. [truncated]

### **Hepatitis C drug may offer potential treatment strategy for muscular dystrophy**

[http://www.thaindian.com/newsportal/world-news/hepatitis-c-drug-may-offer-potential-treatment-strategy-for-muscular-dystrophy\\_10028357.html](http://www.thaindian.com/newsportal/world-news/hepatitis-c-drug-may-offer-potential-treatment-strategy-for-muscular-dystrophy_10028357.html)

In a rodent study, researchers at Cincinnati Childrens Hospital Medical Centre have cited that an investigational antiviral drug, currently undergoing human trials in Europe for treating Hepatitis C infections, may act as a potential treatment strategy to reduce muscle cell damage in Duchenne and other forms of muscular dystrophy (MD). The drug, namely Debio-025, is a popular inhibitor of the protein cyclophilin D, regulates the swelling of mitochondria in response to cellular injury. [truncated]

### **Valeant Pharmaceuticals reports encouraging phase IIb results at treatment week 12 for Taribavirin**

[http://www.businesswire.com/portal/site/google/?ndmViewId=news\\_view&newsId=20080317005760&newsLang=en](http://www.businesswire.com/portal/site/google/?ndmViewId=news_view&newsId=20080317005760&newsLang=en)

Valeant Pharmaceuticals today reported results at the treatment week 12 analysis point for the Phase IIb clinical trial for its antiviral compound, taribavirin, a prodrug of ribavirin in development for the treatment of chronic hepatitis C in conjunction with a pegylated interferon.

The Phase IIb trial is a U.S. multi-center, randomized, parallel, open-label study in 278 treatment-naïve, genotype 1 patients evaluating taribavirin at 20 mg/kg, 25 mg/kg, and 30 mg/kg per day in combination with pegylated interferon alfa-2b. The control group is being administered weight-based dose ribavirin (800/1000/1200/1400mg daily) and pegylated interferon alfa-2b. Overall treatment duration is 48 weeks with a post-treatment follow-up period of 24 weeks. The primary endpoints for this study are viral load reduction at treatment week 12 and anemia rates throughout the study.

The 12-week early viral response (EVR) data from the Phase IIb study showed comparable reductions in viral load for weight-based doses of taribavirin and ribavirin. The anemia rate was statistically significantly lower for patients receiving taribavirin in the 20mg/kg and 25mg/kg arms versus the ribavirin control arm. [truncated]

### **Contest seeks to break silence; poster design competition aims to raise hep C awareness [Canada]**

<http://www.thesudburystar.com/ArticleDisplay.aspx?e=946053>

The way Ernie Zivny sees it, \$4,000 is a miniscule amount to spend if it can prevent even a handful of people from contracting a deadly, blood-borne liver disease. "That's why there is a \$500 first prize," explained the Greater Sudbury man, about the Circle C Support Group's "Break the Silence and Win" Contest. "If they are going to do their own research, we are going to get good involvement in finding out about hep C and by putting it in their entry - 'how can I get it, how can I prevent it?' They are going to keep that with them for the rest of their life." Zivny, who contracted hepatitis C through a tainted blood transfusion a 1978 operation and only learned he had the disease in 2001, is providing the \$4,000 total prize money for the contest, which is open to all ages, but focuses on students. [truncated]

### **Oncolys and Tacere partner in hepatitis C drug development**

[http://www.pharmaceutical-business-review.com/article\\_news.asp?guid=E7001310-C6F2-47FE-88EB-E41FA17CC53A](http://www.pharmaceutical-business-review.com/article_news.asp?guid=E7001310-C6F2-47FE-88EB-E41FA17CC53A)

Oncolys BioPharma and Tacere Therapeutics have entered into a strategic alliance and license agreement to develop and commercialize throughout Asia, Tacere's RNA interference-based hepatitis C virus compound, TT-033.

This agreement resulted from the strategic alliance entered into by Tacere and Oncolys in June 2007, whereby Oncolys was granted an option to acquire the Asian rights for TT-033. Under the terms of the agreement, Oncolys and Tacere will form a joint steering committee that will work with the Tacere and Pfizer steering committee to oversee preclinical R&D efforts for TT-033 (code-named by Oncolys as OBP-701). [truncated]

### **Blood donations down after Las Vegas hepatitis C scare**

<http://www.signonsandiego.com/news/state/20080315-1214-nv-blood donations.html>

Blood donations have dropped since a hepatitis scare triggered a massive health alert in southern Nevada. Officials say donations at the United Blood Services five fixed sites have dropped 25 percent since early March. That's when 40,000 former patients at the Endoscopy Center of Southern Nevada were told to be tested for potentially fatal viruses hepatitis B and C and HIV. The clinic was found to be practicing unsafe injection procedures.

Blood bank recruiter Amy Hutch says many potential donors have expressed concerns about the safety of giving blood. She says she assures people that blood banks never reuse needle and dispose of needles immediately after their use. Hutch and others said the drop off in donation had not yet caused a serious shortage.

### **Hepatitis C may reduce EPO requirements**

<http://www.renalandurologynews.com/Hepatitis-C-May-Reduce-EPO-Requirements/article/107948/>

Hemodialysis patients infected with hepatitis C virus (HCV) have a significantly decreased requirement for erythropoietin (EPO) compared with hemodialysis patients with no history of HCV infection, according to researchers.

A team at Texas A & M University in Temple, led by Anand Khurana, MD, studied 66 hemodialysis patients: 22 with HCV infection and 44 age-, gender-, and race-matched controls without HCV. The mean EPO requirement for the HCV-infected group was 17,307 U/month compared with 49,134 U/month for controls, the investigators reported in *Hemodialysis International* (2008;12:94-99). The HCV-infected patients also tended to have higher hemoglobin levels at baseline.

“The possible explanation for these findings may be the release of hepatic EPO because of chronic hepatic inflammation secondary to HCV,” the authors wrote. The mean dose of IV iron was higher for the HCV group than controls (120 vs. 163 mg/month), but the difference was not statistically significant.

The researchers noted that hemodialysis patients who not need EPO or have very low requirements usually prompts investigation for acquired renal cystic disease, renal cell carcinoma, or polycythemia vera. “We suggest that it should be a reason to look for occult HCV infection, given the higher risk of acquiring this infection on hemodialysis and having normal ALT levels.”

### **DA raids office of Dix Hills doc in hep C probe**

<http://www.newsday.com/news/local/suffolk/ny-lifink125610558mar12,0,7008996.story>

The Nassau County district attorney's office raided Dr. Harvey Finkelstein's office yesterday as part of a probe into whether the Dix Hills physician caused two cases of hepatitis C and not one as state health authorities previously believed, according to court records, medical documents and interviews.

Investigators seized medical records and a computer hard drive from Finkelstein's Plainview medical office on Old Country Road yesterday morning. Prosecutors are considering whether they can bring felony charges. They could include second-degree assault, apparently for causing the infections, and falsifying business records and offering a false instrument, for changing or withholding records from the state Department of Health, according to an affidavit for the search warrant. [truncated]

### **HIV-positive gay men being infected with HCV soon after HIV; cases of HCV superinfection reported**

<http://www.aidsmap.com/en/news/B42AA0AE-389C-4B9A-842D-3A21E07737C4.asp>

Many gay men are being infected with hepatitis C virus soon after they contract HIV, according to a study conducted in London and published in the March 12th edition of AIDS. The study, conducted at St Mary's Hospital, found that 7% of gay men diagnosed with HIV at the hospital between 1999 and 2006 went on to become infected with hepatitis C virus through sex.

[truncated]

### **AANA condemns unsafe injection practices** <http://www.earthtimes.org/articles/show/aana-condemns-unsafe-injection-practices,306128.shtml>

In a decisive response to recent incidents in Nevada and New York in which patients were infected with hepatitis C allegedly through the reuse of needles and syringes, the American Association of Nurse Anesthetists (AANA) today called on healthcare professionals across the nation to exercise the utmost care and vigilance when performing or observing injections on patients.

"It is astounding that in this day and age there are nurse anesthetists, anesthesiologists, and other healthcare professionals who still risk using needles and syringes on more than one patient, or know of such activities and don't report them," said Wanda Wilson, CRNA, PhD, president of the 37,000 member AANA. "Published standards and guidelines dictate that single-use and disposal of these products is the best way to ensure patient safety. Patient safety is our primary focus --- not cost savings, time savings, or any other factor." Wilson added that while the AANA believes the vast majority of Certified Registered Nurse Anesthetists (CRNAs), anesthesiologists, and other healthcare professionals who give injections practice in a safe manner according to established drug-handling and administration guidelines, recent hepatitis C outbreaks at an endoscopy center in Las Vegas, Nev., and a pain management facility in Long Island, N.Y., leave no doubt that unsafe practices are still occurring and can cause great harm to patients. [truncated]

### **Egypt: Poor hygiene, ignorance blamed for prevalence of hepatitis C**

***HCV has a higher prevalence among older Egyptians, but is still spreading among the younger generation***

<http://www.irinnews.org/Report.aspx?ReportId=77141>

The results of an ongoing national survey on the prevalence of the hepatitis C virus (HCV) in Egypt, to be released later this year, will tell how much of a problem the disease still is in the country, said specialists. The survey is being conducted by the National Committee for the Control and Prevention of Viral Hepatitis, a government body formed last year to tackle the disease. A similar survey in 1996 showed that 10-12 percent of the population had HCV, with 70,000-140,000 new infections each year, according to Manal Hamdy al-Sayed, Professor of Paediatrics at Cairo's Ain Shams University and a member of the Committee. Al-Sayed was part of a team which formulated an action plan to fight the disease and combat rising mortality. Egypt has one of the highest HCV prevalence rates in the world. About one in every 10 persons has the virus, said al-Sayed. [truncated]

**Outreach offers hepatitis C test kits**

<http://www.kmbc.com/newslinks/15507017/detail.html>

A local nonprofit organization is offering free kits to test for Hepatitis C. The Hepatitis C Multicultural Outreach in Kansas City is asking for donations of about \$10 for the kit. Anyone interested in picking up a kit can call 816-442-8089. Hepatitis C Multicultural Outreach is located at 10515 Blue Ridge Blvd. Suite 207 in Kansas City.

**In memory of an assemblyman, NY legislature creates hepatitis council**

<http://www.pressconnects.com/apps/pbcs.dll/article?AID=/20080305/NEWS01/803050358>

There were some tears and some people got choked up as they spoke, but the goal was unwavering: fighting hepatitis C, what they called "a silent epidemic." In the wake of the death last year of state Assemblyman Kenneth Zebrowski, D-New City, Rockland County, to hepatitis C, state officials and lawmakers announced Wednesday the creation of a hepatitis C Advisory Council to improve prevention, detection and treatment of the disease. Gov. Eliot Spitzer put \$1.6 million in his 2008-09 budget proposal to form the council and fund research and programs. [truncated]

**Hepatitis C investigation creating doctor shortage**

<http://www.ktnv.com/Global/story.asp?S=8081269>

Health experts estimate the Hepatitis C scare is taking a toll on gastroenterologists in the Valley. Officials found staff at the Endoscopy Center of Southern Nevada reused syringes on patients, putting thousands of people who visited the Shadow Lane office at risk for various viruses. Before the health scare, there were about 46 GI doctors practicing in Southern Nevada. Now, there may only be about 18 practicing.

Action News reporter Tania Reyes explains how it is affecting patient care. The Clark County Medical Society says there is a possibility many of the doctors involved in the Hepatitis scare may not be practicing since some of the clinics closed their doors.

Action News talked to one local gastroenterologist who says within the last month or so his work load has increased significantly.

"This event has been a terrible disruption of health care and a terrible ordeal for patients," explained Dr. Frank Nemec. Doctor Nemec is a gastroenterologist along with five other doctors in practice at the Southern Hills hospital. He says lately there has been a change in the amount of patients coming in. "The volume has gone up considerably," explained Dr. Nemec.

### **50 Riverside patients scheduled for hepatitis C screenings**

[http://www.dailypress.com/news/dp-local\\_hepc\\_0328mar28,0,6873160.story](http://www.dailypress.com/news/dp-local_hepc_0328mar28,0,6873160.story)

NEWPORT NEWS - Riverside nurses have scheduled about 50 appointments for hepatitis C screenings. The screenings are being offered to 310 patients who came in contact with a nurse anesthetist who worked there and is accused of infecting up to 15 patients with hepatitis C in Texas in 2004. Jon Dale Jones, 45, a retired Army captain, worked for an independent contractor at Riverside Regional Medical Center from July 9 to Dec. 22.

There's no indication Riverside patients were exposed to the infection, but the health system is offering screenings for those 310 patients as a precaution, said Chris Stolle, vice president of medical affairs. [truncated]

### **U.S. hepatitis C soars in those over 45**

[http://www.upi.com/NewsTrack/Health/2008/03/25/us\\_hepatitis\\_c\\_soars\\_in\\_those\\_over\\_45/3542/](http://www.upi.com/NewsTrack/Health/2008/03/25/us_hepatitis_c_soars_in_those_over_45/3542/)

U.S. mortality rates for hepatitis C in people ages 45 to 54 rose 375 percent from 1995 to 2004, researchers said. The findings, published in Hepatology, found hepatitis C rose in those ages 55 to 64 rose by 188 percent during the same period. "Substantial increases in overall hepatitis-C-related mortality rates have occurred since 1995," the study authors said in a statement. "The relatively young age of persons dying from hepatitis C-related liver disease has made hepatitis C-related disease a leading infectious cause of years of potential life lost as well as an important cause of premature mortality overall." [truncated]

### **Vertex Pharmaceuticals announces acceptance of late-breaker abstract on Telaprevir, investigational HCV protease inhibitor, for presentation at EASL annual meeting**

[http://www.businesswire.com/portal/site/google/?ndmViewId=news\\_view&newsId=20080331005774&newsLang=en](http://www.businesswire.com/portal/site/google/?ndmViewId=news_view&newsId=20080331005774&newsLang=en)

Vertex Pharmaceuticals Incorporated today announced that data related to its investigational hepatitis C protease inhibitor telaprevir will be featured in a late-breaker poster presentation during the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL) in Milan, April 23-27, 2008.

The title of the abstract is "A Study of Telaprevir (TVR) with Peginterferon alfa-2A (P) and Ribavirin (R) in Subjects with Well-documented Prior P/R Null Response, Non-Response or Relapse: Preliminary Results" and will be presented at EASL starting on Thursday, April 24. Accepted late-breaker abstracts for the EASL meeting are now available on the EASL website. Information contained in the late-breaker poster abstract has also been filed by Vertex with the U.S. Securities and Exchange Commission on a Form 8-K. [truncated]

### **Allman Brothers Band says Gregg Allman has hepatitis C; cancels several concerts**

<http://www.iht.com/articles/ap/2008/03/28/arts/People-Allman-Brothers-Band.php>

An Allman Brothers Band member says Gregg Allman is unable to play several upcoming concerts because of his treatments for hepatitis C. Drummer Butch Trucks says the band has canceled appearances in Florida next month and bowed out of its annual run of shows at Manhattan's Beacon Theatre in May. Trucks says Allman began undergoing treatment last year. The Allman Brothers Band was founded in Florida in the late 1960s, but gained fame while living in Macon, Ga. The band was inducted into the Rock and Roll Hall of Fame in 1995.

### **Government of Canada funds research to address hepatitis C virus in Central Alberta [Canada]**

<http://www.marketwire.com/mw/release.do?id=837573>

MP Bob Mills, Member of Parliament for Red Deer, today announced on behalf of Health Minister Tony Clement, a \$10,000 contribution to the Central Alberta AIDS Network Society (CAANS) to fund a project that aims to reduce the incidence of hepatitis C virus (HCV) in Central Alberta by assessing the health needs of those most at-risk of becoming infected.

The project, entitled Street Smarts Outreach: Rural Needs Assessment in Central Alberta, will determine the health needs of drug users in the region and the capacity of rural communities to increase HCV awareness and prevention initiatives. [truncated]

### **Doctors link 'heroin days' to hepatitis C**

<http://www.guampdn.com/apps/pbcs.dll/article?AID=/20080331/NEWS01/803310302/1002>

The heroin problem on Guam between the late 1970s and early 1980s still haunts some island families today. Needle-sharing associated with the use of heroin helped spread Hepatitis C on island, and complications of the disease have led to "the premature deaths of too many Guamanians," according to fliers that some Guam doctors are circulating to try to raise awareness of the problem. "If you shared a needle 30 or 40 years ago, you could be infected with a deadly disease and not even know it," according to the fliers, which are being circulated islandwide.

Complications from Hepatitis C can lead to cancer of the liver and other liver-related health problems, said Dr. Chris Perez, one of the doctors participating in the awareness campaign. "All you need (to get infected) is one needle," Perez said. "You may have (Hepatitis C) for years and not know," he added. Part of the information drive's goal, Perez said, is to encourage those with a heroin past, no matter how briefly it might have happened, to bring up that piece of history with their doctors. [truncated]

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### **CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

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**Association between hepatitis B/C viral infection, chronic kidney disease and insulin resistance in individuals undergoing general health screening.** Ishizaka N, et al. Hepatol Res. 2008 Mar 25 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18371161?ordinalpos=4&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18371161?ordinalpos=4&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**AIM:** Previous studies have shown that hepatitis B virus (HBV) and hepatitis C virus (HCV) infection may be associated with glomerulonephritis. **METHODS:** In the current study, we investigated the possible association between HBV/HCV infection, estimated GFR (eGFR) and

albuminuria by analyzing cross-sectional data from individuals undergoing general health screening. **RESULTS:** Of 12 535 individuals enrolled, 130 (1.0%) and 72 (0.6%) tested positive for HBV surface antigen and HCV core antigen, respectively. In comparison with hepatitis-negative individuals, the prevalence of low eGFR and albuminuria was significantly greater in individuals with HCV infection, but not in those with HBV infection. Logistic regression analysis adjusted for age, sex, systolic blood pressure and fasting plasma glucose showed that HCV infection was positively associated with low eGFR (odds ratio 1.63 [95% CI 0.95-2.80, P = 0.077] ) and with albuminuria (odds ratio 2.00 [95% CI 1.06-3.76, P = 0.003] ). By contrast, prevalence of neither low eGFR nor albuminuria was greater in individuals with HBV infection than in hepatitis-negative subjects. Further adjustment for either HOMA-IR or serum alanine aminotransferase levels abolished the statistical significance in the association between HCV infection and albuminuria. **CONCLUSION:** Our data suggest that although both HCV and HBV infection are associated with increased insulin resistance, the different viruses may have different impacts on chronic kidney disease among Japanese individuals undergoing general health screening.

**Racial differences in liver transplantation outcomes in the MELD era.** Ananthakrishnan AN, Saeian K. Am J Gastroenterol. 2008 Mar 26 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18371131?ordinalpos=6&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18371131?ordinalpos=6&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVES:** Beginning February 28, 2002, the Model for End-Stage Liver Disease (MELD) score was introduced to better allocate donor livers. Racial differences in orthotopic liver transplantation (OLT) outcomes prior to this time have been attributed to late listing of some racial groups. Racial differences in post-transplant survival in the MELD era have not been previously examined. **METHODS:** We performed a retrospective observational cohort study using the United Network for Organ Sharing database for adult liver transplants performed between 2002 and 2006. We examined patient and graft survival at 2 yr and compared disease-specific survival rates among the different races. **RESULTS:** A total of 10,409 whites, 1,133 blacks, 1,548 Hispanics, and 765 transplant recipients belonging to other races were included in the study. On multivariate analysis, blacks had lower overall (hazard ratio for death [HR] 1.29, 95% confidence interval [95% CI] 1.10-1.52) and graft (HR 1.38, 95% CI 1.20-1.58) survival at 2 yr compared to whites, while Hispanics had better overall (HR 0.78) and graft (HR 0.82) survival. Compared to whites, blacks transplanted for hepatitis C or HCC had lower survival at 2 yr. **CONCLUSION:** In the MELD era, black patients have significantly lower overall and graft survival at 2 yr compared to whites.

**Scientific rationale and study design of the individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial: determining optimal dosing in patients with genotype 1 chronic hepatitis C.** McHutchison J, Sulkowski M. J Viral Hepat. 2008 Mar 24 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18363672?ordinalpos=12&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18363672?ordinalpos=12&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Current standard-of-care antiviral treatment for patients with chronic hepatitis C is combination therapy with pegylated interferon (PEG-IFN) alfa plus ribavirin. Two large clinical trials determined that each PEG-IFN alfa compound, when given in combination with ribavirin, results in overall sustained virological response (SVR) rates of approximately 50%; SVR rates in patients infected with hepatitis C virus (HCV) genotype 1 are typically lower (42-46%).

Differences in study design, treatment regimens, and patient populations preclude comparison of the data across trials; therefore, the most effective use of PEG-IFN alfa in combination with ribavirin is unclear. The Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study is a phase 3b, randomized, parallel-group, US multicentre trial in treatment-naïve genotype 1 patients with chronic hepatitis C. Initially, this study was undertaken to evaluate the efficacy and safety of weight-based ribavirin dosing (800-1400 mg / day) and PEG-IFN alfa-2b dosing (arm 1: PEG-IFN alfa-2b 1.5 mug / kg / week; arm 2: PEG-IFN alfa-2b 1.0 mug / kg / week). However, because a clinical trial directly comparing the efficacy and safety of PEG-IFN alfa-2a and alfa-2b in combination with weight-based ribavirin dosing has not been performed, an additional arm (arm 3: PEG-IFN alfa-2a 180 mug / week plus ribavirin 1000-1200 mg / day) was included to address this important issue. IDEAL is fully enrolled (>3000 patients) and complete study data, including SVR rates, are expected in early 2008. Herein, we present the scientific rationale and study design, discuss key data from other trials, and summarize our expectations of this study.

**Hepatitis B virus DNA in liver tissue and risk for hepatocarcinogenesis in patients with hepatitis C virus-related chronic liver disease. A prospective study.** Obika M, et al.

Intervirology. 2008 Mar 18;51(1):59-68 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18349544?ordinalpos=45&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18349544?ordinalpos=45&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**AIMS:** To prospectively study whether occult hepatitis B virus (HBV) infection can promote the development of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV)-related chronic liver disease. In addition, to evaluate the difference among HBV DNA-negative patients and patients with high and low HBV copy numbers. **METHODS:** A total of 167 patients with HCV-related chronic liver disease without HBV surface antigen (HBsAg) were studied. HBV DNA in liver tissue was determined using polymerase chain reaction (PCR). **RESULTS:** HBV DNA was detected in 9 of 167 patients (5.4%) by single PCR and in 25 patients (15.0%) by nested PCR. HCC developed in 12 of 167 patients (7.2%). Ten of 142 HBV DNA-negative patients (7.0%) and 2 of 9 patients with a high HBV copy number (22.2%) developed HCC, whereas none of 16 patients with a low HBV copy number developed HCC. The incidence rate of HCC in patients with a high HBV copy number was significantly higher than in HBV DNA-negative patients and patients with low HBV copy number. **CONCLUSION:** A high amount of HBV DNA in liver tissue of HBsAg-negative patients with HCV-related liver disease might be associated with HCC development.

**The efficacy of short-term interferon-beta therapy for chronic hepatitis C patients with low virus load.** Kawamura Y, et al. Intern Med. 2008;47(5):355-60. Epub 2008 Mar 3

[http://www.ncbi.nlm.nih.gov/pubmed/18310963?ordinalpos=17&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18310963?ordinalpos=17&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVE:** The aim of this study was to elucidate the efficacy of short-term interferon (IFN) therapy for chronic hepatitis C patients with low virus load. **METHODS:** The present study was a retrospective cohort study. Inclusion criteria were biopsy-proven chronic hepatitis, the serum hepatitis C virus (HCV) RNA level of less than 100 KIU/ml, IFN period of 8 weeks or less. One hundred and eleven consecutive patients satisfied above criteria were treated with IFN-beta (dose: 6 MU, daily for 4, 6, or 8 weeks). **RESULTS:** Background of clinical profiles were as follows: median (range) age=56 (20-73) years, male/female=64/47, genotype 1b/2a/2b=40/68/3,

and median (range) HCV-RNA=34 (4.5-81) KIU/ml. Out of 111, 64 patients (57.7%) had sustained viral response (SVR). Based on the difference of HCV genotype, the SVR rate was 47.5% (19/40) in genotype 1 and 63.3% (45/71) in genotype 2. In genotype 1, the SVR rate in patients treated with the 8-week-regimen was significantly higher than that in patients treated with the 4- or 6-week regimen. In contrast, in genotype 2, the SVR in patients treated with the 8-week regimen was not significantly different from that in patients treated with the 6-week regimen. None of the patients had severe IFN-related side effects. **CONCLUSIONS:** The 6 or 8-week regiment of IFN-beta therapy is one selection of therapy for chronic hepatitis C patients who have tended to have a SVR and who show IFN-related adverse events.

**Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients.** Imazeki F, et al. Liver Int. 2008 Mar;28(3):355-62.

[http://www.ncbi.nlm.nih.gov/pubmed/18290778?ordinalpos=37&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18290778?ordinalpos=37&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND/AIMS:** Our aim was to evaluate the relationship between hepatitis C virus (HCV) infection and development of diabetes mellitus (DM) or insulin resistance (IR) in comparison with hepatitis B virus (HBV) infection and eradication of HCV infection by interferon treatment. **METHODS:** This study consisted of 952 outpatients, including 544 HCV-infected (HCV+chronic), 286 HBV-infected (HBV+chronic) and 122 patients whose HCV was cleared by interferon treatment (HCV+cleared) (diabetes study). Among 849 without overt DM, IR was assessed in 423 patients, including 232 HCV-infected (HCV+chronic), 135 HBV-infected (HBV+chronic) and 56 HCV-eradicated patients (HCV+cleared) (IR substudy).

**RESULTS:** The prevalence of DM in the HBV+chronic, HCV+chronic and HCV+cleared groups was 6.3, 13.6 and 9.0%, respectively (HBV+chronic vs HCV+chronic,  $P<0.005$ ), in the diabetes study, and the prevalence of IR in the HCV+chronic group (54.3%) was also higher than that in the HBV+chronic (36.3%) ( $P<0.005$ ) and HCV+cleared groups (35.7%) ( $P<0.05$ ) in the IR substudy. However, HCV infection was not shown to be independently associated with DM development [odds ratio (OR) 1.669;  $P=0.0936$ ] and with IR (OR 1.531;  $P=0.2154$ ) by multivariate analysis in comparison with HBV infection as control. **CONCLUSIONS:** HCV-infected patients showed a higher prevalence of DM and IR than those with HBV infection. However, in Japan, other confounding factors appeared to be more important risk factors for the development of disturbance in glucose metabolism.

**Clinical significance of elevated alpha-fetoprotein in Alaskan Native patients with chronic hepatitis C.** Bruce MG, et al. J Viral Hepat. 2008 Mar;15(3):179-87

[http://www.ncbi.nlm.nih.gov/pubmed/18233991?ordinalpos=10&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18233991?ordinalpos=10&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

The clinical significance of elevated serum alpha-fetoprotein (AFP) in patients with chronic hepatitis C virus (HCV) infection is not well defined. We analysed data from a population-based cohort of patients with HCV infection to assess the prevalence of elevated serum AFP, to determine its association with clinical and virologic parameters and with clinical outcomes. We defined a slightly elevated serum AFP level as 8 to  $<15$  and a high-AFP level as  $>$  or  $=15$  microg/L. Among 541 HCV-RNA-positive persons, 61 (11%) had a slightly elevated or high AFP at the time of consent. AFP  $>$  or  $=8$  microg/L was associated with the older age, aspartate aminotransferase/alanine aminotransferase ratio  $>1$ , and higher alkaline phosphatase levels, but

not with heavy alcohol use, IV drug use, genotype, viral load or duration of HCV infection. Among 192 persons with an AFP at liver biopsy, 17% had an AFP  $\geq$  8 microg/L. The sensitivity/specificity of an AFP level  $\geq$  8 in detecting Ishak 3-6 fibrosis was 39%/95%. Among 372 persons with a minimum of four AFP measurements over 6 years, 5% had persistently elevated AFP  $\geq$  8 microg/L, 19% had both elevated and normal AFP measurements, and 76% had persistently normal AFP. Elevated AFP at consent was associated with hepatocellular carcinoma (HCC) and end-stage liver disease. Over 6 years of follow-up, persistently elevated AFP was associated with the development of HCC; no person with AFP persistently  $<$  8 microg/mL developed HCC. Serial AFP measurements appear to be useful in identifying persons with advanced fibrosis and help to determine who needs periodic screening with liver ultrasound to detect HCC.

### **Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial.**

Hepatology. 2008 Mar;47(3):836-43. Goodman ZD, et al.

[http://www.ncbi.nlm.nih.gov/pubmed/18167062?ordinalpos=47&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18167062?ordinalpos=47&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

There is relatively little information in the literature on the histopathology of chronic hepatitis C in children. The Peds-C Trial, designed to test the efficacy and safety of peginterferon alfa-2a and ribavirin in children, provided an opportunity to examine liver biopsies from 121 treatment-naïve children, ages 2 to 16 (mean, 9.8 years) infected with the hepatitis C virus (HCV) and with no other identifiable cause for liver disease, signs of hepatic decompensation, or another significant nonhepatic disease. Liver biopsies were scored for inflammation, fibrosis, steatosis, and other histological features. Inflammation in the biopsy was minimal in 42%, mild in 17%, moderate in 38%, and severe in only 3%. Five had bridging fibrosis, and 2 had cirrhosis. Steatosis was absent in 56%, minimal in 34%, and mild in 10%. Inflammation scores correlated with fibrosis scores, serum alanine aminotransferase levels, and duration of infection, but not with age, body mass index z score, or HCV genotype. Fibrosis scores correlated with inflammation but not with age, HCV genotype, body mass index z score, or steatosis parameters. Steatosis correlated with serum alanine aminotransferase levels and body mass index z scores; overweight children had more fibrosis than the non-overweight. In conclusion, in this cohort of HCV-infected children, inflammation, fibrosis, and steatosis were milder than reported for treatment-naïve adults with chronic hepatitis C, but there were several with bridging fibrosis or cirrhosis. The positive correlation of inflammation with duration of infection and fibrosis and of obesity with fibrosis suggest that children with chronic hepatitis C will be at risk for progressive liver disease as they age and possibly acquire other comorbid risk factors.

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## **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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### **Steatosis correlates with hepatic expression of death receptors and activation of nuclear factor-kappaB in chronic hepatitis C.** Hung CH, et al. Liver Int. 2008 Mar;28(3):339-46.

[http://www.ncbi.nlm.nih.gov/pubmed/18290776?ordinalpos=39&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18290776?ordinalpos=39&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** Steatosis is recognized as a predictor of the severity as well as the progression of fibrosis in chronic hepatitis C. The mechanisms that cause increased hepatocellular injury associated with steatosis remain largely unknown. **METHODS:** We studied the correlation of hepatic expression of death receptors: Fas and tumour necrosis factor-

alpha receptor 1 (TNF-R1), and downstream caspase (caspase-3) with hepatic steatosis by immunohistochemical study in chronic hepatitis C and determined the role of nuclear factor-kappaB (NF-kappaB). **RESULTS:** Ninety patients (49 males and 41 females, mean age of 50.5 +/- 10.4 years, genotype 1 or 2) with chronic hepatitis C virus infection were recruited. The factors associated with steatosis grade were body mass index (P=0.004) and fibrosis stage (P=0.034). Moderate/severe steatosis was an independent variable associated with advanced fibrosis stage by stepwise logistic regression analysis. The expression of immunoreactivity for Fas, TNF-R1 and active caspases-3 in liver tissues was significantly correlated with the steatosis grade (P<0.001, P<0.001 and P<0.001 respectively). The extent of active caspases-3 correlated significantly with the expression of Fas (r=0.659, P<0.001) and TNF-R1 (r=0.617, P<0.001). NF-kappaB p65 expression correlated significantly with the extent of Fas (r=0.405, P<0.001), TNF-R1 (r=0.448, P=0.002) and active caspase-3 (r=0.313, P=0.003), and correlated with steatosis grade (P<0.001) but not with inflammatory and fibrosis scores. **CONCLUSION:** Our observations suggest a mechanism whereby steatosis contributes to the progression of liver injury in chronic hepatitis C through upregulation of death receptors and activation of NF-kappaB.

**Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C.** Fontana RJ, Hepatology. 2008 Mar;47(3):789-98. [http://www.ncbi.nlm.nih.gov/pubmed/18175357?ordinalpos=44&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18175357?ordinalpos=44&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

This study determined the utility of a panel of serum fibrosis markers along with routine laboratory tests in estimating the likelihood of histological cirrhosis in a cohort of prior nonresponders with chronic hepatitis C. The relationship between serum markers and quantitative hepatic collagen content was also determined. Liver biopsy samples from 513 subjects enrolled in the HALT-C trial were assigned Ishak fibrosis scores. The collagen content of 386 sirius-red stained, nonfragmented biopsy samples was quantified using computerized morphometry. Serum tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), amino-terminal peptide of type III procollagen (PIIINP), hyaluronic acid (HA), and YKL-40 levels were determined using commercially available assays. Sixty-two percent of patients had noncirrhotic fibrosis (Ishak stage 2-4) whereas 38% had cirrhosis (Ishak stage 5,6). Multivariate analysis identified a 3-variable model (HA, TIMP-1, and platelet count) that had an area under the receiver operating curve (AUROC) of 0.81 for estimating the presence of cirrhosis. This model was significantly better than that derived from the cirrhosis discriminant score (AUROC 0.70), the AST-to-platelet ratio (AUROC 0.73), and a prior model developed in HALT-C patients (AUROC 0.79). Multivariate analysis demonstrated that the serum fibrosis markers correlated substantially better with Ishak fibrosis scores than with the log hepatic collagen content (AUROC 0.84 versus 0.72). **CONCLUSION:** A 3-variable model consisting of serum HA, TIMP-1, and platelet count was better than other published models in identifying cirrhosis in HALT-C Trial subjects. The stronger correlation of the serum markers with Ishak scores suggests that serum fibrosis markers.

**Interferon and ribavirin therapy does not select for resistance mutations in hepatitis C virus polymerase.** Ward CL, et al. J Viral Hepat. 2008 Mar 24 [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/18363671?ordinalpos=13&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18363671?ordinalpos=13&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Ribavirin has a minor and transient effect on hepatitis C virus (HCV) replication and has been suggested to select a novel mutation, F415Y, in the RNA-dependent RNA polymerase of subtype 1a viruses. Twenty-nine patients with chronic hepatitis C (subtyped by INNO LiPA as 1a, 17; 1b, 11; 1a/1b, 1) who were nonresponders to interferon-based therapies were identified retrospectively and screened at Baseline, week 24 of treatment, and 24 weeks post-treatment. Selection of resistance mutations, including at amino acid position 415 of the polymerase, was investigated. Using clonal sequencing and pyrosequencing of the NS5B gene, we screened for the F415Y resistance mutation among patients who received combination therapy with ribavirin and interferon alpha. Of the 15 subtype 1a patients treated with interferon plus ribavirin, only one had the F415Y change at week 24, and an F/Y mixture was still present 24 weeks after therapy. Four additional patients in this group had the F415Y change 24 weeks post-therapy. The NS5B genes were sequenced in order to identify amino acid changes associated with ribavirin therapy, but no evidence was found that ribavirin selects for particular amino acids in the RNA-dependent RNA polymerase. Ribavirin, a weak inhibitor of HCV replication, does not select for resistance mutations in the sequence of the HCV RNA polymerase.

**Toll-like receptor-stimulated non-parenchymal liver cells can regulate hepatitis C virus replication.** Broering R, et al. J Hepatol. 2008 Mar 3 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18362039?ordinalpos=16&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18362039?ordinalpos=16&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND/AIMS:** The aim of this study was to further elucidate the role of the IFN and the Toll-like receptor (TLR) system in the control of HCV replication by non-parenchymal liver cells (NPC). **METHODS:** Murine HCV replicon bearing MH1 cells were incubated with supernatants from TLR1-9-stimulated murine NPC (Kupffer cells (KC), liver sinusoidal endothelial cells (LSEC)) and bone marrow-derived myeloid dendritic cells (mDC). HCV replication and expression of IFN-stimulated genes (ISGs) as well as TLR1-9 mRNA were determined by real-time rtPCR. **RESULTS:** IFNs (-alpha, -beta, -gamma) and TLR3 ligands only (despite the expression of TLR1-7 and TLR9 mRNA) achieved direct suppression of HCV replication by about 80-90% or 60%, respectively. Supernatants from TLR3- and 4-stimulated NPC only, however, led to potent suppression of HCV replication through IFN-beta and induction of ISGs. By contrast, mDCs could be stimulated by TLR2, -3, -4, -7 and -9 to produce antiviral cytokines. **CONCLUSIONS:** TLR3- and TLR4-stimulated NPC are able to regulate HCV replication through production of IFN-beta. This can also, at least partly explain the high level of ISG expression in HCV infected livers. These novel findings are of particular relevance for the control of HCV replication by the innate immune system of the liver.

**Essential role of domain III of nonstructural protein 5A for hepatitis C virus infectious particle assembly.** Appel N, et al. . PLoS Pathog. 2008 Mar 28;4(3):e1000035.

[http://www.ncbi.nlm.nih.gov/pubmed/18369481?ordinalpos=8&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18369481?ordinalpos=8&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Persistent infection with the hepatitis C virus (HCV) is a major risk factor for the development of liver cirrhosis and hepatocellular carcinoma. With an estimated about 3% of the world population infected with this virus, the lack of a prophylactic vaccine and a selective therapy, chronic hepatitis C currently is a main indication for liver transplantation. The establishment of cell-based replication and virus production systems has led to first insights into the functions of HCV proteins. However, the role of nonstructural protein 5A (NS5A) in the viral replication

cycle is so far not known. NS5A is a membrane-associated RNA-binding protein assumed to be involved in HCV RNA replication. Its numerous interactions with the host cell suggest that NS5A is also an important determinant for pathogenesis and persistence. In this study we show that NS5A is a key factor for the assembly of infectious HCV particles. We specifically identify the C-terminal domain III as the primary determinant in NS5A for particle formation. We show that both core and NS5A colocalize on the surface of lipid droplets, a proposed site for HCV particle assembly. Deletions in domain III of NS5A disrupting this colocalization abrogate infectious particle formation and lead to an enhanced accumulation of core protein on the surface of lipid droplets. Finally, we show that mutations in NS5A causing an assembly defect can be rescued by trans-complementation. These data provide novel insights into the production of infectious HCV and identify NS5A as a major determinant for HCV assembly. Since domain III of NS5A is one of the most variable regions in the HCV genome, the results suggest that viral isolates may differ in their level of virion production and thus in their level of fitness and pathogenesis.

**Altered natural killer cell subset distributions in resolved and persistent hepatitis C virus infection following single source exposure.** Golden-Mason L, et al. Gut. 2008 Mar 27 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18372499?ordinalpos=1&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18372499?ordinalpos=1&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** Natural killer (NK) cells may be impaired in patients with persistent hepatitis C virus (HCV) infection, but studies to date have yielded inconsistent findings due to patient and virus heterogeneity and difficulties obtaining appropriate controls. **AIMS:** To overcome these variables, we have examined numbers, phenotypes, cytotoxic activities and cytokine profiles of circulating NK cells from Irish females who acquired infection through administration of HCV genotype 1b-contaminated anti-D immunoglobulin from a single source and matched controls. **RESULTS:** Comparing 29 women who developed persistent infection with 21 who spontaneously resolved infection and 26 controls, we found that NK cell numbers were consistently lower in the persistently-infected group ( $p=0.02$  and  $0.002$ ). This decrease was due to depletions of NK cells expressing low levels of CD56 (CD56dim NK cells;  $p=0.004$  and  $0.0001$ ), whilst CD56bright NK cells were expanded ( $p=0.004$  and  $0.0001$ ). Compared to HCV resolvers, CD56dim NK cells from persistently-infected patients less frequently expressed CD16 and more frequently expressed NKG2A/C/E. These phenotypic changes did not significantly affect natural or interleukin-2-induced cytotoxicity by peripheral blood mononuclear cells against K562 and Daudi targets. Greater frequencies of CD56bright NK cells from chronic HCV patients produced interferon-gamma compared to HCV responders ( $p=0.05$ ) and controls ( $p=0.0001$ ) after phorbol ester stimulation in vitro. **CONCLUSIONS:** Alterations in NK subset distributions in chronic HCV infection may explain why previous reports of impaired NK cell functions were difficult to confirm. Altered NK cell functions may contribute to impaired cellular immune responses and chronicity of disease following HCV infection.

**A critical role of virion-associated cholesterol and sphingolipid in hepatitis C virus infection.** Aizaki H, et al. J Virol. 2008 Mar 26 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18367533?ordinalpos=10&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18367533?ordinalpos=10&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

In this study, we establish that cholesterol and sphingolipid associated with hepatitis C virus (HCV) particles are important for virion maturation and infectivity. In a recently-developed culture system enabling study of the complete life cycle of HCV, mature virions were enriched with cholesterol as assessed by the cholesterol/phospholipids molar ratio of virion and cell membranes. Depletion of cholesterol from the virus or hydrolysis of virion-associated sphingomyelin almost completely abolished HCV infectivity. Supplementation of cholesterol-depleted virus with exogenous cholesterol enhanced infectivity to untreated control values. Cholesterol-depleted or sphingomyelin-hydrolyzed virus had markedly defective internalization but no influence on cell attachment. Significant portions of HCV structural proteins partitioned into cellular detergent-resistant, lipid raft-like, membranes. Combined with the observation that inhibitors of the sphingolipid biosynthetic pathway block virion production, but not RNA accumulation, of a JFH-1 isolate, **our findings suggest** that altering the lipid composition of HCV particles might be a useful approach when designing anti-HCV therapy.

**Expansion of hepatitis C-specific CD4(+)CD25(+) regulatory T cells after viral clearance: A mechanism to limit collateral damage?** Godkin A, et al. J Allergy Clin Immunol. 2008 Mar 18 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18355912?ordinalpos=28&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18355912?ordinalpos=28&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** Data from rodent models suggest that a subpopulation of CD4(+) T cells, characterized by the constitutive expression of CD25, play a key role in regulating many immune responses. Human CD4(+)CD25(+) T cells also appear to possess a regulatory function, but their role in infections is not fully defined. **OBJECTIVES:** We sought to explore the possibility of a role for CD4(+)CD25(+) T cells in controlling immunity to hepatitis C virus (HCV). We hypothesized that CD4(+)CD25(+) T cells might account for the paucity of immune responses measurable in chronically viremic patients by suppressing the immune responses to HCV antigens. **METHODS:** We compared the responses of PBMCs to 3 different recombinant HCV antigens before and after depletion of CD25(+) cells in 15 chronically viremic patients, 14 nonviremic HCV antibody-positive subjects, and 14 healthy control subjects. We also tested the ability of CD4(+)CD25(+) T cells purified from HLA-matched viremic or nonviremic blood to suppress the responses of HCV epitope-specific T-cell clones. **RESULTS:** To our surprise, depletion of peripheral blood CD25(+) cells led to a pronounced increase in proliferation of and IFN-gamma production by PBMCs only in nonviremic patients. Furthermore, the CD4(+)CD25(+) T cells purified from HLA-matched nonviremic blood (in contrast to CD4(+)CD25(+) T cells isolated from chronically viremic blood) inhibited the responses of HCV epitope-specific T-cell clones. **CONCLUSION:** HCV-specific CD4(+)CD25(+) regulatory T cells appear to accompany successful viral clearance.

**Existence of hepatitis C virus NS5B variants naturally resistant to non-nucleoside, but not to nucleoside, polymerase inhibitors among untreated patients.** Le Pogam S, et al. J Antimicrob Chemother. 2008 Mar 20 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18343801?ordinalpos=7&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18343801?ordinalpos=7&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVES** To characterize the effect of hepatitis C virus (HCV) polymerase intrinsic genetic heterogeneity on the inhibitory activity of nucleoside and non-nucleoside HCV polymerase inhibitors. **METHODS** The sensitivity of genotype (GT) 1 HCV NS5B clinical

isolates from treatment-naive patients to nucleoside and non-nucleoside polymerase inhibitors was assessed. The genetic diversity at the population level, as well as that of their quasispecies, was correlated with the observed reduced sensitivity to inhibitors. **RESULTS** R1479 and NM107 (nucleoside analogues that have entered Phase 2 clinical trials as prodrugs R1626 and NM283, respectively) were similarly active across the tested clinical isolates. Resistance mutations to nucleoside analogues were not observed in any of the isolates. However, the activity of the non-nucleoside thumb II inhibitor NNI-1, palm I inhibitors NNI-2 and NNI-3, and palm II inhibitor HCV-796 was reduced across different isolates. This reduction in inhibitory activity for non-nucleoside inhibitors (NNIs) was, in most cases, correlated with the existence of known NNI resistance mutations in the NS5B polymerase population of the clinical isolates, as detected by population sequencing. Resistance mutations to NNIs were also observed at a low frequency within the clinical isolates' viral quasispecies that allowed for their rapid selection upon drug selective pressure. **CONCLUSIONS** The higher frequency of known NNI resistance mutations or polymorphisms known to affect their antiviral potency when compared with the lack of detection of resistance mutations to the nucleoside analogues suggests a potential for primary reduced responsiveness as well as faster development of clinically significant resistance.

### **Comparison of hepatic oxidative DNA damage in patients with chronic hepatitis B and C.**

Fujita N, et al. J Viral Hepat. 2008 Mar 6 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18331251?ordinalpos=31&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18331251?ordinalpos=31&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

8-Hydroxydeoxyguanosine (8-OHdG) is a promutagenic DNA lesion produced by hydroxyl radicals and is recognized as a useful marker in estimating DNA damage induced by oxidative stress. **The aim** of this study was to clarify the clinical significance of hepatic 8-OHdG levels in patients with chronic viral hepatitis. Hepatic 8-OHdG accumulation was investigated in patients with chronic hepatitis C (CH-C) (n = 77) and chronic hepatitis B (CH-B) (n = 34) by immunohistochemical staining of liver biopsy samples. 8-OHdG positive hepatocytes were significantly higher in patients with CH-C compared to CH-B (median 55.0 vs 18.8 cells/10(5)  $\mu\text{m}^2$ ,  $P < 0.0001$ ). The number of positive hepatocytes significantly increased with the elevation of serum aminotransferase levels, especially in CH-C patients (8-OHdG vs alanine aminotransferase (ALT)/aspartate aminotransferase (AST) were  $r = 0.738/0.720$  in CH-C and  $0.506/0.515$  in CH-B). 8-OHdG reactivity was strongly correlated with body and hepatic iron storage markers in CH-C (vs serum ferritin,  $r = 0.615$ ; vs hepatic total iron score,  $r = 0.520$ ; vs hepatic hepcidin mRNA levels,  $r = 0.571$ ), although it was related to serum HBV-DNA titers ( $r = 0.540$ ) and age of patients ( $r = -0.559$ ) in CH-B. **These results** indicate that hepatic oxidative DNA damage is common in chronic viral hepatitis, in particular chronic HCV-infected patients, suggesting a possible link between chronic hepatic inflammation and hepatocarcinogenesis. The strong positive correlation between hepatic DNA damage and iron overload suggests that iron content is one of the most likely mediators of hepatic oxidative stress and iron reduction may be beneficial to reduce the incidence of hepatic cancer in CH-C patients.

### **Cutting edge: programmed death-1 expression is increased on immunocytes in chronic hepatitis C virus and predicts failure of response to antiviral therapy: race-dependent differences.**

Golden-Mason L, et al. J Immunol. 2008 Mar 15;180(6):3637-41.

[http://www.ncbi.nlm.nih.gov/pubmed/18322167?ordinalpos=2&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18322167?ordinalpos=2&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Up-regulation of programmed death-1 (PD-1) identifies exhausted T cells in various mouse and human viral models including chronic hepatitis C virus (HCV) infection, which is characterized by impaired CTL function. A large proportion of patients fail to eradicate HCV with current IFN-based antiviral therapy; in particular, African Americans are less likely to respond, but the mechanisms for these differences are not fully elucidated. **In this study**, in 72 treatment-naive patients with persistent HCV we found that PD-1 was significantly up-regulated on CD4(+) and CD8(+) T cells, HCV-specific CTLs, and NK cells. Increased PD-1 on HCV-specific CTLs was significantly associated with failed early and sustained virologic response to therapy in African American but not Caucasian American patients. Patients with sustained virologic response showed decreases in PD-1 on total CD4(+) T cells, HCV-specific CTLs, and the CD56(bright) NK subset after therapy completion. **Collectively, these data indicate** that PD-1 is critical in persistent HCV and successful therapy results in global down-regulation of its expression.

**Iminosugars in combination with interferon and ribavirin permanently eradicate non-cytopathic bovine viral diarrhoea virus from persistently infected cells.** Woodhouse SD, et al. Antimicrob Agents Chemother. 2008 Mar 3 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18316522?ordinalpos=13&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18316522?ordinalpos=13&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

We evaluated interferon (IFN) and ribavirin (RBV) as dual therapy and as part of triple combination therapies with the iminosugars N-butyl deoxynojirimycin (NB-DNJ), N-nonyl-DNJ (NN-DNJ) and N7-oxanonyl-6-deoxy-methyl-galactonojirimycin (N7-DGJ). The ability of these compounds to clear bovine viral diarrhoea virus (BVDV), a surrogate model for hepatitis C virus (HCV), from a persistently infected MDBK cell line was determined by monitoring secretion of viral RNA and the infectivity of secreted virions. In the BVDV system, after treatment with IFN/RBV alone, viral rebound is observed immediately after removal of the drugs. In contrast, we demonstrate that a triple drug combination of IFN, RBV and an iminosugar eradicates the BVDV infection in a time- and dose-dependent manner, leading to a sustained viral clearance. Importantly, in the case of NB-DNJ, the sustained viral clearance is achieved using physiologically relevant and tolerated drug concentrations. Therefore triple combination therapy including an iminosugar may prove to be of greater therapeutic value for the treatment of HCV infection than IFN/RBV alone.

**HCV infection in haemodialysed patients: A role for serum IL-10 and TGF-beta(1) in liver damage?** Burra P, et al. Dig Liver Dis. 2008 Mar 25 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18372225?ordinalpos=2&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18372225?ordinalpos=2&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** Hepatitis C virus (HCV) infection is often clinically silent in haemodialysed (HD) patients and their immune response may modulate liver damage in HCV infection. IL-10 and TGF-beta(1) could play a role in this setting as, IL-10 down-regulates hepatic fibrosis, while TGF-beta(1) is a pro-fibrotic cytokine. **AIM:** To evaluate the role of IL-10 and TGF-beta(1) in HD/HCV+ patients. **PATIENTS:** 71 HD/HCV+ patients (58 with normal [HD/HCV-N] and 13 with high serum transaminases [HD/HCV-H]), 40 non-uremic patients with chronic hepatitis C (HCV+), 56 HD anti-HCV- patients and 20 healthy volunteers (H). **METHODS:** IL-10 and TGF-beta(1) serum levels were assessed using ELISA tests. Liver histology was assessed by Ishak's score. **RESULTS:** IL-10 serum levels were significantly higher in HD patients, both HCV+ (3.7+/-0.4pg/ml; p<0.01) and HCV- (3.8+/-0.8pg/ml; p<0.05) than in non-uremic HCV

patients (2.3±0.4pg/ml). Among the HD/HCV+ patients, IL-10 serum levels were similar in HD/HCV-N and in HD/HCV-H patients. Among the HD/HCV+ patients, IL-10 serum levels were similar in those with moderate histological damage compared to those with mild damage. TGF-beta(1) serum levels were significantly lower in HD patients, both HCV+ (4.6±0.9ng/ml) and HCV- (6.0±0.9ng/ml) than in non-uremic HCV+ patients (8.1±1.1ng/ml; p<0.001 and p<0.01, respectively), but similar to the values found in H (5.3±0.9ng/ml; p=n.s.). No correlation was seen between IL-10 and TGF-beta(1) serum levels in any of the groups considered. **CONCLUSIONS:** Patients on haemodialysis treatment to have high levels of IL-10, which remain high even when patients are anti-HCV+, whereas the opposite is true of TGF-beta(1). The cytokine pattern observed in HD patients is compatible with the hypothesis explaining the relatively benign evolution of HCV-related liver disease in HD patients, and has a pathophysiological role.

**HCV selection and HVR1 evolution in a chimpanzee chronically infected with HCV-1 over 12 years.** Lu L, et al. Hepatol Res. 2008 Mar 4 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18328069?ordinalpos=39&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18328069?ordinalpos=39&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**AIM:** To study hepatitis C virus (HCV) selection and hypervariable region-1 (HVR1) evolution in a chimpanzee chronically infected with HCV-1 over 12 years after inoculation with a human factor VIII concentrate contaminated with HCV. **METHODS:** From the inoculum, the earliest chimpanzee plasma and 12 annual plasma samples, HCV fragments including HVR1 were amplified followed by cloning and sequencing. **RESULTS:** Five HCV subtypes - 1a, 1b, 2a, 2b, 3a - and multiple 1a strains were identified in the inoculum. Two 1a strains were found in the earliest chimpanzee sample, while a single HCV-1 strain was detected in the 12 annual samples. None of the chimpanzee sequences were identical to those found in the inoculum. Over 12 years, HVR1 patterns changed irregularly, but a few patterns showed identical nucleotide or amino acid sequences. In the last three years, the variety of HVR1 patterns decreased, while the proportion of major patterns increased. These corresponded to a higher virus load and a lower number of amino acid substitutions. Simultaneously, the HVR1 sequences became more similar to the consensus sequence of the 1a subtype. **CONCLUSION:** HCV selection was observed from the inoculum to the inoculated chimpanzee and from the early acute hepatitis to the persistent chronic infection. The selection occurred at three levels: among subtypes after transmission, among isolates during acute hepatitis and among quasispecies in chronic infection.

**Genetic variability in hepatitis C virus and its role in antiviral treatment response.** Torres-Puente M, et al. J Viral Hepat. 2008 Mar;15(3):188-99.

[http://www.ncbi.nlm.nih.gov/pubmed/18233992?ordinalpos=9&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18233992?ordinalpos=9&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Hepatitis C virus (HCV) is a major health problem worldwide, infecting an estimated 170 million people. The high genetic variability of HCV contributes to the chronicity of hepatitis C. Here, we report results from a large-scale sequence analysis of 67 patients infected with HCV genotype 1, 23 with subtype 1a and 44 with subtype 1b. Two regions of the HCV genome were analysed in samples prior to combined therapy with alpha interferon plus ribavirin, one compressing the hypervariable regions (HVR1, HVR2 and HVR3) of the E2 glycoprotein and another one including the interferon-sensitive determining region (ISDR) and the V3 domain of the NS5A protein. Genetic diversity measures showed a clear tendency to higher genetic

variability levels in nonresponder patients to antiviral treatment than in responder patients, although highly disperse values were present within each response group for both subtypes. A more detailed analysis of amino acid composition revealed the presence of several subtype-specific variants in a few positions, but no discriminating positions between responder and nonresponder patients were detected. Our results also revealed that most amino acid positions were highly conserved, especially for subtype 1a. **We conclude** that the outcome of the antiviral treatment might depend not only on the nature of one or a few independent positions, but more likely on the combination of several positions along the HCV genome. Moreover, the own host's ability to generate an appropriate systemic response, in combination with the action of antivirals, is also likely to be essential for treatment outcome.

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## HIV/HCV COINFECTION

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**Association of HIV infection and HIV/HCV coinfection with C-reactive protein levels: the fat redistribution and metabolic change in HIV infection (FRAM) study.** Reingold JS, et al. J Acquir Immune Defic Syndr. 2008 Mar 13 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18344877?ordinalpos=4&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18344877?ordinalpos=4&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVE:** Inflammation is a potential mechanism to explain the accelerated atherosclerosis observed in HIV-and hepatitis C virus (HCV)-infected persons. We evaluated C-reactive protein (CRP) in HIV-infected and HIV/HCV-coinfected individuals in the era of effective antiretroviral (ARV) therapy. **DESIGN:** Cross-sectional study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) cohort and controls from the Coronary Artery Risk Development in Young Adults (CARDIA) study. **METHODS:** CRP levels were measured in 1135 HIV-infected participants from the FRAM cohort and 281 controls from the CARDIA study. The associations of HIV and HIV/HCV infection with CRP levels were estimated by multivariable linear regression. **RESULTS:** Compared with controls, HIV mono-infection was associated with an 88% higher CRP level in men ( $P < 0.0001$ ) but with no difference in women (5%;  $P = 0.80$ ) in multivariate analysis. CRP levels were not associated with ARV therapy, HIV RNA level, or CD4 cell count. Compared with controls, HIV/HCV coinfection was associated with a 41% lower CRP level in women ( $P = 0.012$ ) but with no difference in men (+4%;  $P = 0.90$ ). Among HIV-infected participants, HCV coinfection was associated with 50% lower CRP levels after multivariable analysis ( $P < 0.0001$ ) in men and women. Greater visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were strongly associated with CRP levels. Among HIV-infected participants, CRP levels were 17% ( $P < 0.001$ ) and 21% ( $P = 0.002$ ) higher per doubling of VAT and SAT; among controls, CRP levels were 34% ( $P < 0.001$ ) and 61% ( $P = 0.009$ ) higher, respectively. **CONCLUSIONS:** In the absence of HCV coinfection, HIV infection is associated with higher CRP levels in men. HCV coinfection is associated with lower CRP levels in men and women.

**The cyclophilin inhibitor Debio-025 shows potent anti-hepatitis C effect in patients coinfecting with hepatitis C and human immunodeficiency virus.** Flisiak R, et al. Hepatology. 2008 Mar;47(3):817-26.

[http://www.ncbi.nlm.nih.gov/pubmed/18302285?ordinalpos=28&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18302285?ordinalpos=28&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Debio-025 is an oral cyclophilin (Cyp) inhibitor with potent anti-hepatitis C virus activity in vitro. Its effect on viral load as well as its influence on intracellular Cyp levels was investigated in a randomized, double-blind, placebo-controlled study. Mean hepatitis C viral load decreased significantly by 3.6 log(10) after a 14-day oral treatment with 1200 mg twice daily ( $P < 0.0001$ ) with an effect against the 3 genotypes (1, 3, and 4) represented in the study. In addition, the absence of viral rebound during treatment indicates that Debio-025 has a high barrier for the selection of resistance. In Debio-025-treated patients, cyclophilin B (CypB) levels in peripheral blood mononuclear cells decreased from 67 +/- 6 (standard error) ng/mg protein (baseline) to 5 +/- 1 ng/mg protein at day 15 ( $P < 0.01$ ). **CONCLUSION:** Debio-025 induced a strong drop in CypB levels, coinciding with the decrease in hepatitis C viral load. These are the first preliminary human data supporting the hypothesis that CypB may play an important role in hepatitis C virus replication and that Cyp inhibition is a valid target for the development of anti-hepatitis C drugs.

**Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors.** Bani-Sadr F, et al. Clin Infect Dis. 2008 Mar 1;46(5):768-74.

[http://www.ncbi.nlm.nih.gov/pubmed/18248298?ordinalpos=4&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18248298?ordinalpos=4&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** We determined the prevalence and determinants of worsening fibrosis in patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) who were receiving anti-HCV therapy. **METHODS:** Among 383 HIV-HCV-coinfected patients who received at least 1 dose of anti-HCV treatment (weekly subcutaneous injections of 1.5 mg/kg pegylated interferon-alpha-2b plus daily ribavirin or thrice-weekly subcutaneous injections of 3 MU of interferon-alpha-2b plus daily ribavirin for 48 weeks), paired pretreatment and posttreatment liver biopsy specimens were available and interpretable for 198 cases. Hepatic necroinflammation and fibrosis were graded with Ishak's classification. Histological worsening of fibrosis was defined as a score increase of  $>$  or  $=2$  points in patients with fibrosis stage of  $<4$  and as a score increase of 1 point in patients with stage-5 fibrosis. **RESULTS:** The mean interval +/- standard deviation between the 2 biopsies was 109 +/- 34 weeks. Fibrosis worsened in 34 patients (17.1%). In univariate analysis, ongoing antiretroviral therapy, failure to achieve a sustained viral response, nucleoside reverse-transcriptase inhibitor therapy, didanosine therapy, and stavudine therapy were significantly associated with worsening of fibrosis. Didanosine (odds ratio, 3.34; 95% confidence interval, 1.39-7.96;  $P = .007$ ) and failure to have a sustained viral response (odds ratio, 9.05; 95% confidence interval, 2.06-39.66;  $P = .003$ ) remained significantly associated with worsening of fibrosis. **CONCLUSION:** The mitochondrial toxicity of antiretrovirals, such as didanosine, seems to play a major role in worsening of fibrosis during HCV therapy. Therefore, anti-HCV therapy should ideally be administered before antiretroviral treatment initiation. If anti-HCV and anti-HIV treatments have to be administered concomitantly, then nucleoside reverse-transcriptase inhibitors with the lowest mitochondrial toxicity should be preferred.

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#### COMPLEMENTARY & ALTERNATIVE THERAPY

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**Acetyl-L- -Carnitine treatment in minimal hepatic encephalopathy.** Malaguarnera M, et al. Dig Dis Sci. 2008 Mar 21 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18357530?ordinalpos=26&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18357530?ordinalpos=26&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Minimal hepatic encephalopathy (MHE) is characterized by disturbance of mental state and neuromuscular function. To assess the clinical efficacy of acetyl-L: -carnitine (ALC) in the treatment of MHE, we performed a randomized, double-blind, placebo-controlled study administering ALC in cirrhotic patients with this disease and evaluating their cognitive functions. One hundred and twenty-five cirrhotic patients, of whom 21 were infected by hepatitis B virus, 75 by hepatitis C virus and 29 with cryptogenic cirrhosis, were enrolled in our study. Patients were randomly divided into two groups, and using double-blind administration, group A was treated with ALC and group B with placebo for 90 days. The two groups were similar in demographic characteristics, aetiology of cirrhosis, duration and Child-Pugh grade. Minimal hepatic encephalopathy was diagnosed with the Trail Making Test (TMT), Symbol Digit Modalities Test (SDMT) and Auditory Verbal Learning Test (AVL) and cognitive function with the Mini Mental State Examination (MMSE). After 90 days in group A treated with ALC, we observed a significant decrease in prothrombin time ( $P < 0.001$ ), bilirubin serum levels ( $P < 0.01$ ), AST ( $P < 0.001$ ), fasting NH(4) serum levels ( $P < 0.001$ ), Trail Making Test-A ( $P < 0.001$ ) and Trail Making Test-B ( $P < 0.001$ ), and a significant increase in albumin serum levels ( $P < 0.005$ ), MMSE test ( $P < 0.001$ ), Symbol Digit Modalities Test ( $P < 0.001$ ), BDT ( $P < 0.001$ ), AVL long-term test ( $P < 0.001$ ) and AVL total test ( $P < 0.001$ ). No significant differences were observed in EEG in either group of patients treated with ALC or placebo. The benefits of ALC in comparison with placebo are demonstrated in greater reductions in serum ammonia levels, as well as in improvements of neuropsychological functioning.

**Suppressive effect of oral administration of branched-chain amino acid granules on oxidative stress and inflammation in HCV-positive patients with liver cirrhosis.** Ohno T, et al. . Hepatol Res. 2008 Mar 4 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18328070?ordinalpos=38&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18328070?ordinalpos=38&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**AIM:** In chronic hepatitis C virus (HCV) infection, it is thought that both chronic persistent inflammation and oxidative stress contribute to the development of hepatocellular carcinoma (HCC), and it has been reported that long-term oral supplementation with branched-chain amino acid (BCAA) granules could inhibit liver carcinogenesis. However, the extent of the involvement of these factors remains obscure. **METHODS:** To clarify the involvement of inflammation and oxidative stress in the inhibition of liver carcinogenesis, we evaluated the effect of oral administration of BCAA granules on oxidative stress and inflammation in HCV-positive patients with liver cirrhosis. **RESULTS:** Twenty-seven patients were enrolled in the study: 18 of the patients were treated with BCAA granules (administered group) and nine were observed without BCAA granules (non-administered group). In the non-administered group, the production of oxidative stress, as indicated by urine 8-hydroxydeoxyguanosine (8-OHdG) and 15-F2t-Isoprostane (8-IsoPs), significantly increased with time, while in the administered group the levels of ferritin and 8-OHdG decreased significantly. Comparison of the two groups demonstrated that highly sensitive CRP, ferritin, 8-OHdG and 8-IsoPs were significantly reduced by taking BCAA granules. The time-course analysis showed that ferritin and highly sensitive CRP seemed to decrease first, followed by a decrease of 8-OHdG and 8-IsoPs. **CONCLUSION:** These findings indicated that the administration of BCAA granules influenced microinflammation and the metabolism of iron in HCV-positive patients with liver cirrhosis, and

subsequently seemed to reduce the production of oxidative stress, possibly leading to a decrease in the occurrence of HCC.

**Eicosapentaenoic acid supplementation for chronic hepatitis C patients during combination therapy of pegylated interferon alpha-2b and ribavirin.** Kawashima A, et al. *Lipids*. 2008 Mar 5 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18320252?ordinalpos=9&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18320252?ordinalpos=9&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Eicosapentaenoic acid (EPA) (1.8 g/day) was administered to 12 chronic hepatitis C patients receiving combination therapy of pegylated interferon (PEG-IFN) alpha-2b and ribavirin for 48 weeks (EPA group). Twelve patients were not administered EPA (control group). All patients also received vitamin E and C (300, 600 mg/day, respectively) during the therapy. Serum alanine aminotransferase improved to a normal level in 8 of 12 patients from the EPA group and 6 of 12 patients from the control group after 12 weeks. Lymphocyte counts decreased significantly after 8 weeks in the control group, but not the EPA group. T-helper (Th) 1 decreased after 4 weeks in the control group, but not in the EPA group (two-way ANOVA;  $P < 0.05$ ). Th1/Th2 ratios were elevated in 9 of 12 patients in the EPA group, and 3 out of 12 in the control group ( $P < 0.05$ ) after 8 weeks. After 12 weeks, the arachidonic acid/EPA molar ratio of erythrocyte membrane phospholipid correlated negatively with the leukocyte count ( $n = 24$ ,  $r = -0.439$ ,  $P < 0.05$ ) and the neutrophil count ( $n = 24$ ,  $r = -0.671$ ,  $P < 0.02$ ). The hemoglobin level improved after 48 weeks compared with 24 weeks in only the EPA group. **These findings suggest** that EPA supplementation may be useful in therapy for chronic hepatitis C.

**Circulating beliefs, resilient metaphors and faith in biomedicine: hepatitis C patients and interferon combination therapy.** Jenner A, Scott A. *Sociol Health Illn*. 2008 Mar;30(2):197-216.

[http://www.ncbi.nlm.nih.gov/pubmed/18290932?ordinalpos=35&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18290932?ordinalpos=35&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

In this paper, we argue that circulating metaphors and beliefs can create an environment in which particular biomedical treatments make cultural sense, even if they seem to be ineffective or are associated with unpleasant side effects. We develop this argument in relation to interferon combined therapy. An innovative methodology combining the collection and deconstructive analysis of visual and narrative texts produced by people with hepatitis C is used to demonstrate links between a predisposition towards Western biomedical practice, discomfort with uncertainty, a desire to reassert control, and adoption of conflict metaphors associated with the tropes of invasion and eradication.

**All-trans retinoic acid for treatment of chronic hepatitis C.** Böcher WO, et al. *Liver Int*. 2008 Mar;28(3):347-54.

[http://www.ncbi.nlm.nih.gov/pubmed/18290777?ordinalpos=38&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18290777?ordinalpos=38&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND/AIMS:** In vitro studies in the subgenomic hepatitis C virus (HCV) replicon system have identified all-trans retinoic acid (ATRA) as a potential therapeutic against hepatitis C. Thus, the antiviral potential of this drug should be assessed in vivo. **METHODS:** Twenty highly treatment experienced serotype 1 patients with non-response to conventional or pegylated interferon-alpha (Peg-/IFN-alpha) and ribavirin were randomly assigned to 12 weeks of

monotherapy with ATRA (group A) or a combination of ATRA and PegIFN-alpha2a (group B). HCV RNA was assessed by bDNA assay and if negative by highly sensitive polymerase chain reaction. **RESULTS:** During treatment, five of 10 patients in group A had a drop of viraemia >1log, while in group B after 8 weeks five of 10 dropped >2log, and three of 10 cleared HCV RNA from serum. Viraemia relapsed after treatment cessation. ATRA was rather well tolerated, with transient headache, dry skin and mucosa representing the most common side effects. **CONCLUSIONS:** The viral load reduction under ATRA monotherapy, although limited and transient, supports the antiviral activity of ATRA. However, the rapid loss of HCV RNA in three of 10 previous non-responders under ATRA and PegIFN-alpha2a treatment demonstrates a strong additive or synergistic ATRA effect and calls for a controlled trial to assess the therapeutic potential of this drug.

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#### EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Screening for hepatitis C in sexual health clinic attendees.** Mapagu MC, et al. Sex Health. 2008 Mar;5(1):73-6.

[http://www.ncbi.nlm.nih.gov/pubmed/18361858?ordinalpos=18&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18361858?ordinalpos=18&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**INTRODUCTION:** Hepatitis C virus (HCV) prevalence has been shown to be higher in some sexual health clinic attendees than the general population. Screening for HCV in sexual health clinics may be based on risk assessment or universal screening. The aim of this audit was to explore the value of routine HCV screening in a sexual health centre population. **METHODS:** Medical records and pathology data concerning all patients tested for HCV between 2000 and 2002 at Canberra Sexual Health Centre were audited to determine whether the diagnosis of HCV was already known and which, if any, risk factors were identified at the time of testing.

**RESULTS:** A total of 3845 tests were conducted on 3156 individuals over the 3-year period. HCV seropositivity was confirmed in 95 patients (3.0%; 95% CI 2.4-3.7), of which 29 (30.5%) were new diagnoses. A total of 85.3% of all patients with confirmed HCV infection reported a history of injecting drug use. Tattoos and body piercings were the most common risk factor in those who denied ever injecting. Risk factor assessment correctly identified all but one positive patient. **CONCLUSIONS:** HCV testing based on clinician-led risk assessment is an effective approach to HCV screening.

**Occult hepatitis C virus infection during an outbreak in a hemodialysis unit in Thailand.**

Thongsawat S, J Med Virol. 2008 Mar 21;80(5):808-815 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18360894?ordinalpos=20&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18360894?ordinalpos=20&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Control of hepatitis C virus (HCV) in hemodialysis populations is a major public health priority, but the preferred methods to prevent and rapidly detect HCV outbreaks in these populations remains subject to debate. We enrolled 231 hemodialysis patients at three dialysis centers in Chiang Mai, Thailand. Patients were followed every 6 months for 3 years and tested for the presence of serum HCV antibody and HCV RNA at each visit. We additionally isolated and tested peripheral blood mononuclear cells (PBMCs) for HCV RNA collected at the 30-month follow-up visit. Fifty-one study participants negative for anti-HCV at the baseline enrollment visit seroconverted over the course of the 3-year follow-up period. Of 11 individuals who transiently lost detectable serum HCV viremia, we were able to detect HCV RNA from the

PBMCs of two individuals. Our results suggest that occult HCV infection may be common among hemodialysis patients, and serum HCV RNA testing may be supplemented with PBMC testing to maximize diagnostic sensitivity and aid in outbreak containment. Further work on the diagnostic implications of HCV compartmentalization in hemodialysis and other settings is urgently needed.

**Pain, substance use disorders and opioid analgesic prescription patterns in veterans with hepatitis C.** Whitehead AJ, et al. *J Pain Symptom Manage.* 2008 Mar 19 [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/18358690?ordinalpos=24&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18358690?ordinalpos=24&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

To examine the prevalence of pain, substance use disorder (SUD) diagnoses, and opioid analgesic prescription patterns among veterans infected with the hepatitis C virus (HCV), a retrospective review of the medical records of 8,224 HCV-positive (HCV+) veterans was performed. Twenty-nine percent and 46% of HCV+ patients were prescribed opioids in the prior one and three years, respectively. Sixty-seven percent of HCV+ patients had documented pain diagnoses and 56% had SUD diagnoses. Patients with co-occurring pain and SUD were less likely to be prescribed opioids than patients with pain only (prior year: 36% vs. 43%,  $P<0.001$ ; three years: 56% vs. 60%,  $P<0.01$ ). There were no differences in numbers of early opioid prescription fills or numbers of opioid prescribers when comparing patients with co-occurring pain and SUD to patients with pain only. Veterans with co-occurring pain and opioid use disorder had fewer early opioid fills than veterans with pain only (prior year: 2.6 vs. 5.3 days,  $P<0.01$ ; three years: 6.1 vs. 13.4 days,  $P<0.001$ ). These data demonstrate that pain and SUD diagnoses were common among HCV+ patients, and that opioids were frequently prescribed. Co-occurring SUD was not associated with indicators of prescription opioid misuse.

**Prevalence and determinants of hepatitis C virus infection among female drug injecting sex workers in Glasgow.** Taylor A, et al. *Harm Reduct J.* 2008 Mar 20;5(1):11 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18355407?ordinalpos=30&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18355407?ordinalpos=30&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**ABSTRACT: BACKGROUND:** Few studies of the prevalence of hepatitis C virus (HCV) infection have focussed on women who work as street sex workers to finance their drug use. **METHODS:** The investigators report the survey findings of such a population in Glasgow. All women attending the health and social care drop-in centre, situated in Glasgow's "Red Light Area", during a four-week period in 1999 were invited to participate in a survey involving the provision of a saliva sample for anonymous HCV testing and the self-completion of a questionnaire seeking demographic, sexual and injecting practice data. **RESULTS:** Of the 223 women who attended, 51% agreed to participate. Of the 98 women who provided a sufficient saliva sample, 64% (95% CI: 54%-74%) tested HCV antibody positive; 98% of those who tested positive had ever injected drugs. Adjusting for the 85% sensitivity of the saliva test, the HCV antibody prevalence among IDU sex workers sampled was 81%; a rate which is considerably higher than those recorded, contemporaneously, among Glasgow IDUs generally. Two factors were independently associated with HCV antibody positivity in saliva: ever shared needles and syringes (adjusted OR 5.7, 95% CI 2-16) and number of times imprisoned (adjusted OR 7.3, 95% CI 1.4-39, for more than five times compared to zero times). **CONCLUSIONS:** Women who engage in street sex work to finance their drug habit are a particularly desperate, chaotic and

vulnerable population. This study demonstrates that their HCV infection risk may be greater than that for other IDUs. Those responsible for designing interventions to prevent HCV infection among IDUs should consider the special needs of this group.

**Surveillance for acute viral hepatitis--United States, 2006.** Wasley A, Grytdal S, Gallagher K. MMWR Surveill Summ. 2008 Mar 21;57(2):1-24.

[http://www.ncbi.nlm.nih.gov/pubmed/18354374?ordinalpos=35&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18354374?ordinalpos=35&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**PROBLEM/CONDITION:** In the United States, acute viral hepatitis most frequently is caused by infection with three viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). These unrelated viruses are transmitted through different routes and have different epidemiologic profiles. Safe and effective vaccines have been available for hepatitis B since 1981 and for hepatitis A since 1995. No vaccine exists against hepatitis C. **REPORTING**

**PERIOD COVERED:** Cases in 2006, the most recent year for which data are available, are compared with those from previous years. **DESCRIPTION OF SYSTEM:** Cases of acute viral hepatitis are reported voluntarily to CDC by state and territorial epidemiologists via CDC's National Notifiable Disease Surveillance System (NNDSS). Reports are received electronically via CDC's National Electronic Telecommunications System for Surveillance (NETSS).

**RESULTS:** During 1995-2006, hepatitis A incidence declined 90% to the lowest rate ever recorded (1.2 cases per 100,000 population). Declines were greatest among children and in those states where routine vaccination of children was recommended beginning in 1999. An increasing proportion of cases occurred in adults. During 1990-2006, acute hepatitis B incidence declined 81% to the lowest rate ever recorded (1.6 cases per 100,000 population). Declines occurred among all age groups but were greatest among children aged <15 years. Following a peak in the late 1980s, incidence of acute hepatitis C declined through the 1990s; however, since 2003, rates have plateaued, with a slight increase in reported cases in 2006. In 2006, as in previous years, the majority of these cases occurred among adults, and injection-drug use was the most common risk factor. **INTERPRETATION:** The results documented in this report suggest that implementation of the 1999 recommendations for routine childhood hepatitis A vaccination in the United States has reduced rates of infection and that universal vaccination of children against hepatitis B has reduced disease incidence substantially among younger age groups. Higher rates of hepatitis B continue among adults, particularly males aged 25-44 years, reflecting the need to vaccinate adults at risk for HBV infection. The decline in hepatitis C incidence that occurred in the 1990s was attributable primarily to a decrease in incidence among injection-drug users. The reasons for this decrease were unknown but likely reflected changes in behavior and practices among injection-drug users. **PUBLIC HEALTH ACTIONS:** The expansion in 2006 of recommendations for routine hepatitis A vaccination to include all children in the United States aged 12-23 months is expected to reduce hepatitis A rates further. Ongoing hepatitis B vaccination programs ultimately will eliminate domestic HBV transmission, and increased vaccination of adults with risk factors will accelerate progress toward elimination. Prevention of hepatitis C relies on identifying and counseling uninfected persons at risk for hepatitis C (e.g., injection-drug users) regarding ways to protect themselves from infection and on identifying and preventing transmission of HCV in health-care settings.

**Gastroenterologists' perceptions of need and availability of psychiatric services for patients with hepatitis C.** Gleason O, Fucci J, Yates W. Psychosomatics. 2008 Mar-Apr;49(2):132-6

[http://www.ncbi.nlm.nih.gov/pubmed/18354066?ordinalpos=36&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18354066?ordinalpos=36&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

The authors examined gastroenterologists' perceptions of psychiatric comorbidity in hepatitis C, access to, and use of psychiatric services. An eight-item survey was mailed to gastroenterologists, with a total of 75 participating. Fifty-eight (77.3%) agreed with the statement "My patients with hepatitis C have significant rates of psychiatric and substance-abuse comorbidity." Less than half (41%) agreed or strongly agreed that "My patients with hepatitis C have adequate access to psychiatric consultation." However, only eight (11%) referred to a mental health provider. Gastroenterologists are aware of the need for psychiatric services for their hepatitis C patients, but few refer for it, and access may be limited.

### **Quality-of-life tradeoffs for hepatitis C treatment: do patients and providers agree?**

Schackman BR, et al. *Med Decis Making*. 2008 Mar-Apr;28(2):233-42. Epub 2008 Mar 18.

[http://www.ncbi.nlm.nih.gov/pubmed/18349430?ordinalpos=46&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18349430?ordinalpos=46&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** The authors investigated differences between how patients and providers evaluate the quality-of-life tradeoffs associated with HCV treatment in computer-assisted interviews. They interviewed 92 treatment-naive HCV patients at gastroenterology, methadone maintenance, and HIV clinics at 3 hospitals in New York City and 23 physicians or nurses experienced in treating HCV at other hospitals in New York City. Subjects completed rating scale and standard gamble evaluations of current health and hypothetical descriptions of HCV symptoms and treatment side effects on a scale from 0 (death or worse than death) to 1 (best possible health). **RESULTS:** Treatment side effects were rated worse by patients than providers using the rating scale (moderate side effects 0.42 v. 0.62; severe side effects 0.24 v. 0.40) and standard gamble (moderate side effects 0.61 v. 0.91; severe side effects 0.52 v. 0.75) (all  $P \leq 0.01$ ). A year of severe side effects was equivalent to 4.1 years of mild HCV symptoms avoided for patients if they returned to their current health after treatment compared with 2.0 years avoided if they achieved average population health. For patients with depression symptoms, HCV treatment with severe side effects had lower value unless it would also improve their current health. **CONCLUSIONS:** Patients have more concerns about treatment side effects than providers. Further research is warranted to develop HCV decision aids that elicit patient preferences and to evaluate how improved communication of the risks and benefits of HCV treatment and more effective treatment of depression may alter these preferences.

### **Identified cases of acute hepatitis C from computerized laboratory database: A hospital-based epidemiological and clinical study.** Hung CH, et al. *J Infect*. 2008 Mar 15 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18346790?ordinalpos=50&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18346790?ordinalpos=50&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVE:** Diagnosis of acute hepatitis C (AHC) relies on documented positive-seroconversion of antibody to hepatitis C virus (anti-HCV) that is infrequently encountered. To clarify the epidemiology and clinical course of AHC, we tried to find more AHC patients from a computerized laboratory database by using a supplemental criterion of rising anti-HCV titer. **METHODS:** All the computerized laboratory databases of anti-HCV and alanine aminotransferase (ALT) were reviewed. Candidates for AHC were identified by either anti-HCV positive seroconversion, rise of anti-HCV titer (signal to cut-off ratio (S/CO) ratio  $<40$  to  $\geq 40$ ),

or spontaneous HCV RNA clearance. AHC cases and their matched chronic hepatitis C controls were interviewed by a case-control study concerning risk factors. **RESULTS:** AHC was identified in 123 patients (68 men and 55 women; median age: 48.4+/-13.9years), who had higher rates of recent surgery (p=0.037) and frequent injection therapy (p=0.036) compared to controls. Self-limited AHC was observed in 18 (19.1%, 95% confidence interval: 12.3-25.9%) of 94 AHC patients who had been followed for 6months, with a higher bilirubin level ( $\geq 2$  vs.  $< 2$ , p=0.007) compared to those evolved to chronic infection. **CONCLUSIONS:** Screening of a laboratory database for anti-HCV and ALT might uncover more AHC candidates to disclose the epidemiology and clinical course of AHC.

**Hepatitis C virus reinfection in liver transplant patients: Evaluation of liver damage progression with echo-color doppler.** Bolognesi M, et al. Liver Transpl. 2008 Mar 6 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18324620?ordinalpos=48&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18324620?ordinalpos=48&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Liver transplant recipients are a model of rapid progression of hepatitis C virus (HCV)-related liver disease, from normal to cirrhosis. The aim of the study was the analysis of the relationship between portohepatic hemodynamics and modification in liver histology during the progression of HCV liver disease after transplant. Patients transplanted for HCV cirrhosis were considered for the study. At least every 6-12 months, the portal blood flow velocity, hepatic and splenic pulsatility indices, and a portal hypertensive index (obtained from the combination of the portal blood velocity and splenic pulsatility index) were measured with echo-Doppler. Liver biopsy was performed whenever necessary. The time course of echo-Doppler parameters during the histological progression of the liver disease was analyzed. Posttransplant patients without HCV were included as controls. Forty-nine patients with histology-proven relapse of HCV hepatitis were included in the study. At the onset of recurrent hepatitis, the portal blood flow velocity significantly decreased ( $P < 0.001$ ), and the splenic pulsatility index increased ( $P = 0.020$ ), whereas the hepatic pulsatility index remained unchanged. In the following years, in addition to a further slight decrease in the portal blood velocity ( $P = 0.027$ ), a progressive increase in the hepatic and splenic pulsatility indices was also detected ( $P = 0.009$  and  $P < 0.0001$ , respectively). The portal hypertensive index steadily increased with the progression of the disease and was related to the degree of liver fibrosis. **In conclusion**, the information obtainable from splanchnic Doppler parameters can be used to monitor the progression of liver fibrosis in transplant patients with HCV reinfection.

**Can urban methadone patients complete health utility assessments?** Teixeira PA, Schackman BR. Patient Educ Couns. 2008 Mar 1 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18314295?ordinalpos=14&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18314295?ordinalpos=14&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVE:** To assess the ability of methadone maintenance treatment (MMT) patients to use two standardized health assessment tools to value health states related to chronic hepatitis C virus (HCV) infection and HCV treatment-associated side effects. An estimated 65-90% of MMT patients are chronically infected with HCV. **METHODS:** We employed qualitative methods to explore how patients completed computerized rating scale assessments and standard gamble utility assessments by (1) having them discuss their responses in a think-aloud interview immediately after each health state assessment, and (2) allowing them the opportunity to

recalibrate prior responses after considering subsequent health states. **RESULTS:** MMT patients used the rating scale boundaries appropriately and used the standard gamble to rank the health states in an a priori logical order. A guided assessment approach that allowed recalibration provided additional insight into values assigned to the health states presented. **CONCLUSION:** MMT patients are able to perform the tasks associated with rating scale assessments and standard gamble utility assessments of HCV health states. **PRACTICE IMPLICATIONS:** These assessment methods should be considered as a means to elicit MMT patients' values for HCV treatment, since the treatment outcome is uncertain but it is likely that side effects will adversely affect current health.

**Impact of chronic liver disease and cirrhosis on health utilities using SF-6D and the health utility index.** Dan AA, et al. Liver Transpl. 2008 Mar;14(3):321-6.

[http://www.ncbi.nlm.nih.gov/pubmed/18306356?ordinalpos=21&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18306356?ordinalpos=21&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Assessment of health-related quality of life (HRQL) and health utilities have become important aspects of clinical research. Patient-derived utility adjustments are frequently used in economic analysis. Although HRQL has been frequently studied among patients with liver disease, extensive data on the health utilities of patients with liver disease are not available. Recently, SF-6D has been developed to obtain utility scores from the widely used Short Form 36 questionnaire. To assess health utilities of patients with chronic liver disease using 2 utility assessments [SF-6D and Health Utility Index 2 (HUI-2)], a total of 140 patients were identified from our Liver Disease Quality of Life Database with HRQL data available, as well as clinical and demographic data. Of the 140 patients, 42% were female, had a mean age of 49.4 years (standard deviation = +/-11.2) 36% had hepatitis B virus (HBV), 29% had hepatitis C (HCV), 24% had cholestatic liver disease, and 11% had another liver disease (for example, nonalcoholic steatohepatitis). Bivariate analyses indicated that HBV patients had the highest health status as measured by all of SF-6D and HUI-2 subscales and the overall SF-6D and HUI-2 utility measures, whereas patients with HCV and cholestatic liver disease had similar scores, and those with other liver diseases had the poorest quality of life. When controlling for the effects of gender, age, and cirrhosis, impact of chronic liver disease diagnosis on utility scores persisted only for the SF-6D, with HCV patients having significantly poorer health than HBV patients. **In conclusion,** SF-6D provides not only a generic assessment of HRQL but also a utility score that can be used for economic analysis of patients with chronic liver disease.

**Outcome of an exercise to notify patients treated by a general surgeon infected with the hepatitis C virus.** Ross RS, et al. J Clin Virol. 2008 Apr;41(4):314-7. Epub 2008 Mar 4.

[http://www.ncbi.nlm.nih.gov/pubmed/18304865?ordinalpos=26&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18304865?ordinalpos=26&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** Health-care workers infected with the hepatitis C virus (HCV) and performing exposure-prone procedures may expose their patients to the risk of nosocomial HCV infection. **OBJECTIVE:** To assess the number of provider-to-patient transmissions of HCV among former patients of an HCV-infected general surgeon. **RESULTS:** The notification exercise covered 1461 individuals, on whom the surgeon performed 1683 operations. Eighty-two percent of these patients were tested for markers of HCV infection, and all but six subjects turned out to be not infected with the virus. Two of the anti-HCV positive patients were already infected before their operations, one individual was not available for further molecular analyses,

and three subjects harboured HCV isolates that belonged to a different subtype (i.e. 1b) than the variant detected in the surgeon's serum. **CONCLUSION:** In this retrospective survey, no provider-to-patient transmission of HCV was detected among 1192 former patients of an infected general surgeon. This finding, one more time, suggests that such nosocomial transmission events are probably very rare. Consequently, recommendations for the management and guidance of HCV-infected health-care workers should carefully balance the workers' rights against justified patients' interests.

**Hepatitis C testing and infection rates in bipolar patients with and without comorbid substance use disorders.** Matthews AM, et al. *Bipolar Disord.* 2008 Mar;10(2):266-70.  
[http://www.ncbi.nlm.nih.gov/pubmed/18271905?ordinalpos=48&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18271905?ordinalpos=48&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVES:** To determine and compare hepatitis C (HCV) screening and testing rates among four groups: those with (i) bipolar disorder [BD group (history of BD but no substance use disorder)]; (ii) substance use disorders [SUD group (history of SUD but no BD)]; (iii) co-occurring disorders [DD group (history of both BD and an SUD)]; and (iv) a control group (no history of either bipolar disorder or substance use disorder). Our hypothesis was that HCV antibody testing rates and HCV prevalence would be higher in the BD, SUD, and DD groups than the control group. **METHODS:** Data were retrospectively collected on 325,410 patients seen between 1998 and 2004 within facilities and clinics of the Veterans Integrated Service Network (VISN) 20 Northwest Veterans Health Care Administration from electronic medical records. HCV screening and prevalence rates were compared between the BD, SUD, DD, and control groups. Odds ratios and relative risks were determined and compared between groups. Results: Patients in the BD, SUD, and DD groups had been tested at a higher rate than controls and were at increased risk for HCV infection compared with controls. These high-risk groups had a 1.31-fold, 4.86-fold, and 5.46-fold increase in the relative risk of HCV infection, respectively. Overall, compared to the control group, the relative risk of a patient having HCV if he or she had BD (with or without an SUD) was 3.6. **CONCLUSIONS:** Patients with BD and comorbid SUD had an over fourfold increase in relative risk for HCV than our control group and a similar risk as patients in our SUD group. Furthermore, even if bipolar patients did not have a comorbid SUD (the BD group), their relative risk of HCV was significantly higher than that of the control group. This suggests that patients with BD, particularly those with a comorbid SUD, should be screened and tested for HCV

**The effect of early virological response in health-related quality of life in HCV-infected patients.** Quarantini LC, et al. *J Med Virol.* 2008 Mar;80(3):419-23.  
[http://www.ncbi.nlm.nih.gov/pubmed/18205211?ordinalpos=26&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18205211?ordinalpos=26&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Twenty-nine HCV-infected patients were treated with pegylated interferon alpha. Diagnosis was based on serum HCV RNA-PCR positive results and liver biopsy. All patients had elevated serum levels of alanine aminotransferase at the time of the study, but liver disease was compensated. Patients were evaluated at baseline treatment and after 4 and 12 weeks of antiviral treatment with the Medical Outcomes Study 36-item Short-Form Health Survey. The Mini-International Neuropsychiatric Interview was used to exclude previous or current psychiatric diagnoses. Both patients and psychiatrists were blind to the HCV RNA status, and serum HCV RNA test results only became available after the visit at week 12. After antiviral treatment, 16

patients (55.2%) were classified as nonresponders and 13 (44.8%) were classified as responders. When compared to nonresponders, responders had a greater improvement in the HRQOL scores for the mental health domain ( $P < .019$ ). Differences in other domains were not significant. The present study confirms that active viral infection is one possible reason for the poor Health-Related Quality of Life in this population.

**Optical analysis of computed tomography images of the liver predicts fibrosis stage and distribution in chronic hepatitis C.** Romero-Gómez M, et al. *Hepatology*. 2008 Mar;47(3):810-6.

[http://www.ncbi.nlm.nih.gov/pubmed/18098299?ordinalpos=10&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18098299?ordinalpos=10&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

This study was undertaken to evaluate an image processing method for assessing liver fibrosis in conventional computed tomography (CT) scans in patients with chronic hepatitis C. Two cohorts (designated "estimation,"  $n = 34$ ; and "validation,"  $n = 107$ ) of chronic hepatitis C patients were assessed using digitized conventional helical CT. Weighted CT mean fibrosis (Fibro-CT) was calculated as a nonlinear weighted mean F-score for each sample. Fibrosis was defined according to Scheuer on the F0 to F4 scale by 2 pathologists blinded regarding the Fibro-CT data. Fibrosis according to Fibro-CT correlated with histology-determined fibrosis ( $r = 0.69$ ;  $P < 0.001$ ) and with increasing F-stage: F0 =  $0.23 \pm 0.39$ ; F1 =  $0.90 \pm 0.99$ ; F2 =  $1.41 \pm 0.94$ ; F3 =  $2.79 \pm 0.55$ ; F4 =  $3.15 \pm 0.35$  [analysis of variance:  $P < 0.0001$ ]. The receiver operating characteristics curve to diagnose significant fibrosis ( $\geq F2$ ) was 0.83; 95% confidence interval (95%CI), 0.75 to 0.91; and, to diagnose advanced fibrosis ( $\geq F3$ ), was 0.86, 95%CI: 0.80 to 0.93. The correlation between Fibro-CT and fibrosis was higher in patients with homogeneous distribution of fibrosis than in patients with heterogeneous distribution ( $r = 0.77$  versus  $r = 0.43$ ;  $P < 0.05$ ). **CONCLUSION:** Optical digital analysis of CT images of the liver is effective in determining the stage and distribution of liver fibrosis in chronic hepatitis C. In patients with homogeneous fibrosis distribution, the correlation between Fibro-CT and histology was better than in patients with heterogeneous distribution. Fibro-CT is a simple to use, readily available, and useful method for the diagnosis of fibrosis in patients with chronic hepatitis C.

**Diagnostic Accuracy of Serum Hyaluronic Acid, FIBROSpect II, and YKL-40 for Discriminating Fibrosis Stages in Chronic Hepatitis C.** Mehta P, et al. *Am J Gastroenterol*. 2008 Mar 25 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/18371145?ordinalpos=5&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18371145?ordinalpos=5&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**OBJECTIVES:** Noninvasive serum markers of liver fibrosis are being used as an alternative to liver biopsy. Currently available tests distinguish, with accuracy, only absent/minimal fibrosis (Ishak stages 0-1) and advanced fibrosis/cirrhosis (Ishak stages 4-6), but not intermediate fibrosis (Ishak stages 2-3). Our aim was to evaluate the diagnostic accuracy of hyaluronic acid (HA), FIBROSpect II (FS-II), and YKL-40 (chondrex, human cartilage glycoprotein-39) in various clinically important categories of fibrosis, and further correlate these serum markers with digital quantification of fibrosis (DQF) and Ishak stages. **METHODS:** Serum HA, YKL-40, and FS-II were retrospectively assessed and correlated with Ishak stages and DQF scores in 75 patients with chronic hepatitis C (HCV). Spearman's rho statistics assessed relationships among all parameters, and receiver operator characteristic curves evaluated accuracy of each parameter when compared to the Ishak stages. **RESULTS:** All three serum markers and DQF correlated

highly with one another ( $P \leq 0.01$ ) and with Ishak stages of fibrosis. Among the serum markers, HA was effective in discriminating between Ishak stages 0-1 and Ishak stages 2-3 compared with FS-II, with an area under the curve of 0.76 versus 0.66 and a false-positive rate of 0.33 versus 0.67, respectively. All three serum markers predicted advanced fibrosis and cirrhosis. YKL-40 had the highest false-positive rates in all categories of fibrosis. **CONCLUSIONS:** HA can be utilized as a reliable surrogate marker in distinguishing three clinically relevant stages of fibrosis: absent/minimal, intermediate, and advanced/cirrhosis. HA should be considered as a cost-effective alternative to other serum markers for staging fibrosis and for determining the timing and selection of HCV treatment.

**Rapid viral response and treatment outcome in genotype 2 and 3 chronic hepatitis C: comparison between two HCV RNA quantitation methods.** Carlsson T, Quist A, Weiland O. J Med Virol. 2008 Mar 21;80(5):803-807 [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/18360893?ordinalpos=21&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18360893?ordinalpos=21&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

Fifty consecutive patients with genotype 2 or 3 chronic hepatitis C were treated with peg-IFN alfa-2a 135 microg weekly and ribavirin (11 mg/kg body weight) daily during 24 weeks. Rapid viral response treatment week 4, end-of-treatment response, and sustained viral response were analyzed by two different HCV RNA quantitation methods, the Cobas Amplicor Monitor test and the TaqMan test with a sensitivity of 600 and 15 IU/ml, respectively. The TaqMan test differentiated patients with rapid viral response finally achieving sustained viral response better. Hence, patients with and without rapid viral response as tested by the TaqMan test finally achieved sustained viral response in 97% (32/33) versus in 75% (12/16),  $P < 0.017$ . The corresponding figures for the Cobas Amplicor test was 91% (41/45) versus (80%) 4/5 a non-significant difference. In conclusion, the more sensitive TaqMan test yielded a lower number of patients with rapid viral response than the less sensitive Amplicor Monitor test, but predicted sustained viral response in a higher percentage of patients with rapid viral response than the Amplicor Monitor test. A rapid viral response meaning HCV RNA levels  $<15$  IU/ml predicted a sustained viral response in 97% of patients with genotype 2 or 3.

**(13)C-methacetin-breath test compared to also noninvasive biochemical blood tests in predicting hepatic fibrosis and cirrhosis in chronic hepatitis C.** Dinesen L, et al. Dig Liver Dis. 2008 Mar 11 [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/18339592?ordinalpos=16&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_HVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18339592?ordinalpos=16&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_HVDocSum)

**BACKGROUND:** The (13)C-methacetin-breath test and also several noninvasive blood tests comprising routine laboratory parameters have been proposed to predict fibrosis and cirrhosis in chronic hepatitis C. The aim of the study was to compare the diagnostic accuracy between these tests referring to hepatic histology as gold standard. **METHODS:** 96 patients with chronic hepatitis C virus infection underwent percutaneous liver biopsy and the (13)C-methacetin-breath test. The Fibroindex, the aspartate aminotransferase to platelet ratio index, and the aspartate aminotransferase to alanine aminotransferase ratio were used as parameters for the staging of fibrosis. The main endpoint was the area under the characteristic curves for the diagnosis of advanced fibrosis (F3-F4) and cirrhosis (F4) according to the Batts Ludwig criteria. **RESULTS:** ROC analysis revealed a cut-off  $<14.6$  per thousand best with 92.6% sensitivity and 84.1% specificity for the (13)C-methacetin-breath test, for the Fibroindex  $>1.82$  70.4% sensitivity and

91.3% specificity, for the aspartate aminotransferase to platelet ratio  $>1.0$  a 66.7% sensitivity and 75.4% specificity, and for the aspartate aminotransferase to alanine aminotransferase ratio  $>1.0$  63.0% sensitivity and 59.4% specificity in predicting liver cirrhosis. The areas under the curve for the breath test, the Fibroindex, aspartate aminotransferase to platelet ratio and the aspartate aminotransferase to alanine aminotransferase ratio were 0.958, 0.845, 0.799, and 0.688, respectively, when predicting cirrhosis. For identifying patients with advanced fibrosis, the areas under the curve were 0.827, 0.804, 0.779, and 0.561, respectively. Discordances between Fibroindex (21%), aspartate aminotransferase to platelet ratio (29%) or aspartate aminotransferase to alanine aminotransferase ratio (37.6%) and liver biopsy were significantly more frequent than between (13)C-breath test (11.6%) and liver biopsy ( $P<0.05$ ).

**CONCLUSION:** The (13)C-methacetin-breath test is more reliable in predicting advanced fibrosis and cirrhosis than simple biochemical parameters (aspartate aminotransferase to platelet ratio; aspartate aminotransferase to alanine aminotransferase ratio).