



Caring Ambassadors Hepatitis C Program Newsletter
www.HepCChallenge.org
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IN THE NEWS	1- 8
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	8-15
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	15-17
HIV/HCV COINFECTION	17-19
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS	19-22

IN THE NEWS

New Weapon Fights Hepatitis C

Experimental drug clears hurdle on its way to joining standard drug combinations

http://www.sciencenews.org/view/generic/id/43337/title/New_weapon_fights_hepatitis_C

“Ten years ago, John McHutchison never used the word “cure” when discussing hepatitis C with his patients. But the results seen from drugs cleared for use since then — and particularly a new drug now in the final stages of testing — are changing that, says the gastroenterologist from Duke University in Durham, N.C. “As far as these patients are concerned, they’re pretty much cured,” McHutchison says. “We don’t need to see them anymore.”

The new drug, called telaprevir, works with a standard hepatitis C drug combination to clear the virus from patients’ blood substantially better than the standard treatment alone, according to a study coauthored by McHutchison and another study, both in the April 30 *New England Journal of Medicine*. The new findings, in people getting their first course of drugs for the disease caused by the virus, also indicate that typically lengthy hepatitis C treatment could be halved with telaprevir’s addition.” [truncated]

Debiopharm Starts Phase IIb Study After Record Time Patient Randomisation

<http://news.prnewswire.com/DisplayReleaseContent.aspx?ACCT=104&STORY=/www/story/04-30-2009/0005016166&EDATE=>

“Debiopharm Group a global biopharmaceutical development specialist that focuses on serious medical conditions, particularly in the field of oncology, announced that on April 7, 2009 the last patient was randomised to take part in a phase IIb clinical study with Debio 025, a selective cyclophilin (Cyp) inhibitor with a potent anti-hepatitis C (HCV) effect. In a record time of three months, a total of 290 patients were randomised in seven countries, including Poland, Germany, Belgium, France, Spain, Italy and Romania. This double-blind, placebo-controlled, parallel-group study will investigate the efficacy and safety of three different treatment regimens combining Debio 025 with Peg interferon alpha 2a (peg-IFN-alpha-2a) and ribavirin in treatment naive chronic HCV genotype 1 patients.

“We are proud to have randomised our patients in such a short period, this demonstrates the investigator's confidence in our product,” said Rolland-Yves Mauvernay, President and Founder of Debiopharm Group. “The efficiency of the recruitment is very motivating for us in our development of Debio 025, as we are eager to provide HCV patients with a more effective treatment.”” [truncated]

First Evidence For DNA-based Vaccination Against Chronic Hepatitis C

<http://www.sciencedaily.com/releases/2009/04/090423082642.htm>

“The first-proof-of-concept for a DNA-based therapeutic vaccination against chronic hepatitis C was announced April 23 at EASL 2009, the Annual Meeting of the European Association for the Study of the Liver in Copenhagen, Denmark. In the first clinical trial of a therapeutic vaccination using naked DNA delivered by in vivo electroporation (EP), antiviral effects were shown in patients with hepatitis C (HCV). Researchers hope that this will encourage further clinical development. The data also provide further evidence for the antiviral role of the HCV-specific T cell response. It is estimated that some 3% of the world's population is infected with HCV. In industrialised countries, hepatitis C accounts for 70% of chronic hepatitis cases. One of the main concerns is that HCV infection remains asymptomatic until advanced stages of the disease.

Clearance of HCV infection correlates with activation of the host T cell response. Therefore, in this study, researchers developed a T cell vaccine based on a codon-optimised HCV non-structural (NS) 3/4A DNA-gene expressed under the control of the cytomegalovirus immediate-early promoter (ChronVac-C®) delivered by in vivo electroporation (EP). A first phase I/IIa clinical trial in HCV infected patients is currently ongoing.” [truncated]

UPDATE 2-Schering hepatitis C Drug Shines, but Anemia Seen

<http://news.alibaba.com/article/detail/chemical/100090468-1-update-2-schering-hepatitis-c-drug.html>

“A Schering-Plough Corp drug knocked the hepatitis C virus down to undetectable levels in three-fourths of patients in a mid-stage study, twice the effectiveness seen with standard treatments, researchers said on Thursday. But half the patients taking the boceprevir experimental medicine developed anemia -- a potential commercial disadvantage to a similar pill called telaprevir that Vertex Pharmaceutical Inc is developing.

Both drugs work through a new mechanism -- by blocking a protein called protease that the virus needs to replicate -- and are considered potential big-selling products. As many as 4 million Americans are believed to be infected with the virus, the leading reason for liver transplants. Results of the Phase II boceprevir trial, involving 595 patients who were infected with the virus but had not previously been treated, were presented in Copenhagen at the annual meeting of the European Association for the Study of the Liver. Patients had genotype 1, the most common form of the virus.” [truncated]

Scynexis Sees Positive Results in Trial of Hepatitis C Drug

http://www.techjournalouth.com/news/article.html?item_id=7331

“Scynexis Inc. says it saw positive results in its Phase 1b clinical trial of its lead oral antiviral drug in patients with hepatitis C infections. The drug, SCY-635, represents a new pharmacological class of inhibitors of hepatitis C virus (HCV) replication.

In this 15-day study, SCY-635 was well-tolerated with no serious adverse events, no discontinuations and no dose-limiting toxicities. At the highest dose tested in the study (900 milligrams/day) SCY-635 exhibited clinically relevant antiviral activity. “In this single-agent study SCY-635 demonstrated highly potent antiviral activity that was sustained throughout treatment with the nadir occurring on the last day of the study, suggesting that with a longer treatment period we may see even greater

reductions in viral load,” said Dr. Sam Hopkins, SCYNEXIS’ Chief Scientific Officer. The drug may eventually be used in combination with other treatments for even greater effect, the company says.”

Amarillo Biosciences Supplies Oral Interferon for Taiwanese Hepatitis C Study

<http://startups.ultizer.com/node/934619>

“Amarillo Biosciences, Inc. today announced that clinical supplies were shipped to AMAR's partner in Taiwan, CytoPharm, Inc., to be used in a study of 165 patients with chronic hepatitis C virus infection. The aim of the trial is to reduce the virologic relapse rate for those patients who have completed the standard combination therapy, which consists of high dose injectable interferon alpha and Ribavirin. Although most patients respond to the standard therapy, up to 50% of those with certain viral genotypes relapse after treatment. The trial is expected to start in the second quarter of 2009 and to be completed in 2010. The patients will receive one of two different dosages of oral human interferon alpha or placebo daily for 24 weeks, followed by untreated observation for 24 weeks to check for relapse.” [truncated]

Hepatitis at A.C. hospital probed

Fifteen dialysis patients at the facility have contracted hepatitis C since 2005.

http://www.philly.com/inquirer/local/20090425_Hepatitis_at_A_C_hospital_probed.html

“New Jersey health officials are trying to unravel how 15 dialysis patients at an Atlantic City hospital have contracted hepatitis C, a serious liver disease, since 2005. Hospital administrators at AtlantiCare Regional Medical Center City Campus contacted the state this month after discovering five new hepatitis C cases during federally required annual hepatitis C testing of all dialysis patients.

The testing, in late March and early April, showed the five patients had become positive for the disease since starting dialysis treatment at the hospital. It is unclear if the cases are linked to the hospital, state Health Department officials said yesterday. All new patients are tested for hepatitis C, according to a hospital policy. Mohammed Mourad, who heads the hospital's division of nephrology, said it was unknown when or how those patients contracted the disease.

After seeing the test results, the hospital contacted the state, which asked the hospital to review four years of patient records. Those records showed that 10 others had also been found to have hepatitis C. The hospital said yesterday that those 15 testing positive since 2005 had come from a total group of 245 patients. All 15 cases now been officially reported to the state, as required by law.”

[truncated]

HIV No Barrier to Liver Transplant

<http://www.medpagetoday.com/Gastroenterology/LiverTransplantation/13895>

“People with HIV do just as well as others after a liver transplant -- as long as they don't have hepatitis C as well, researchers said in Copenhagen. In one of the few studies with data on long-term outcomes, those with HIV had one- and five-year survival rates of 86.5% and 74% respectively, according to John O'Grady, M.D., of Kings College Hospital in London.

By comparison, HIV-negative liver transplant patients in the prospective UK Transplant Database had rates of 87.1% and 78%, which were not significantly different, Dr. O'Grady reported at the annual meeting of the European Association for the Study of the Liver. "In terms of HIV, the clinical guidance is that these patients do very well, (and) they should be considered for transplant in the normal way," he said. "They don't present any particular different clinical problem than the general liver transplant population." On the other hand, he said, patients with both HIV and hepatitis C are a significantly greater challenge.” [truncated]

Anadys Hepatitis C Drug Shows Potent Effect in Small Study

<http://www.xconomy.com/san-diego/2009/04/23/anadys-hepatitis-c-drug-shows-potent-effect-in-small-study/>

“San Diego-based Anadys Pharmaceuticals generated a ton of buzz almost four months ago when it offered an early peek at data suggesting its hepatitis C drug might be working, and now a presentation of the full data appears to reinforce the first impression. Anadys’ lead drug candidate, ANA598, was able to wipe out more than 99 percent of the hepatitis C virus at all three doses tested in a trial of 35 patients, according to data presented today at the European Association for the Study of the Liver meeting in Copenhagen, Denmark. No patients had any serious side effects, and none showed signs of developing resistance to the drug or having their virus bounce back while taking the pill twice-daily over three days.

“The potent antiviral activity demonstrated at all three doses in this study is very encouraging for the prospects of ANA598 when used in combination with other HCV agents,” said Anadys CEO Steve Worland, in a statement. Hepatitis C is an infection of the liver caused by virus.” [truncated]

More than 12,000 Patients are Being Offered HIV and Hepatitis C Tests After a Healthcare Worker was Found to Have Both Diseases. (England)

<http://www.telegraph.co.uk/health/healthnews/5215389/More-than-12000-patients-being-offered-HIV-and-Hepatitis-C-tests.html>

“All patients treated by the worker, who had not been named, are to be contacted by NHS Lewisham and offered the blood tests. The healthcare trust said that it understood how concerned patients would be but emphasised that there was a small chance that they would have contracted either disease.

Patients at the centre of the scare include an 11-year-old boy whose father has talked of their family's anxiety. The man, from Downham, south-east London, said that he had received a letter from on Tuesday alerting him that his son was at risk and should have a blood test. He said: "I was shocked to receive a letter like this and my first thought was how something like this could be allowed to happen. "He is due to start secondary school in September and we don't want anything to upset him so we've had to lie to him about why he needs a blood test. "Even though we know the chances of him having anything are slim, we are very worried."” [truncated]

Zymo Drug Kills Hep C Virus

http://www.seattlepi.com/xconomy/405494_xconomy21660.html

“ZymoGenetics a Seattle biotech company, and partner Bristol-Myers Squibb said today that a drug they are co-developing for hepatitis C was able to kill the virus with minimal side effects in a small four-week study. The trial looked at pegylated interferon lambda on its own, or in combination with a standard ribavirin treatment. The full data was presented at the European Association for the Study of the Liver meeting in Copenhagen, Denmark.” [truncated]

Metabolic Syndrome Hikes Mortality in Hepatitis C

<http://www.medpagetoday.com/Gastroenterology/Hepatitis/13878>

“Patients with hepatitis C infection appear more likely to die from the condition if they also suffer from one or more components of metabolic syndrome, a researcher said. Excess body weight and hypertension both significantly heightened the risk of liver-related mortality in hepatitis C patients, according to data from the third National Health and Nutrition Examination Survey (NHANES)

series, reported Zobair Younossi, M.D., of Inova Health System in Falls Church, Va.

Those two factors as well as the third component of metabolic syndrome -- type 2 diabetes -- also made death from all causes more likely during the study period, said Dr. Younossi.” [truncated]

UPDATE 1-Roche Has Promising Results From Hep C Trial

<http://www.reuters.com/article/rbssPharmaceuticals%20-%20Diversified/idUSLR7218020090427>

Hepatitis C combination study shows "significant" potency

“Roche Holding AG has announced promising results from a study of a combination therapy for patients chronically infected with hepatitis C. Roche announced the results along with InterMune) and Pharmasset which they presented on Saturday at the annual meeting of the European Association for the Study of the Liver in Copenhagen. They said the study, which combined two oral direct-acting antivirals, R7227 and R7128, showed no serious adverse effects during 14 days of dosing and showed "significant" potency in reducing the viral load of hepatitis C patients. Roche is developing R7227, a protease inhibitor, with InterMune, and R7128, a nucleoside polymerase inhibitor, with Pharmasset.” [truncated]

Avila Therapeutics May Have Found “Achilles’ Heel” of Hepatitis C Virus

<http://www.xconomy.com/boston/2009/04/27/avila-therapeutics-may-have-found-achilles-heel-of-hepatitis-c-virus/>

“Avila Therapeutics emerged from stealth mode in December and told Xconomy about its secret sauce to systematically create permanent, covalent bonds with protein disease targets. Now the Waltham, MA-based biotech (pronounced AH-vill-uh) reports that its experimental drug for hepatitis C virus may be able to wipe out multiple variations and mutated forms of the virus. The firm’s drug, dubbed AVL-181, is a small molecule protease inhibitor intended to silence a key protein for the survival and replication of the virus. The drug targets a region of the protein that the company believes is common among many known forms of the virus, even those that are resistant to standard treatments, meaning that the firm may have found an “Achilles’ heel” of the protein, says Nagesh Mahanthappa, vice president of business development and operations at the biotech. Over the weekend, the company presented results of a study, in which infected mice were treated with the drug, at the European Association for the Study of the Liver meeting in Copenhagen, Denmark.

“When we look across all known published genetic sequences of the hepatitis C protease, from a variety of mutants, we find that the particular site where we get bond formation with our drug is constant,” Mahanthappa says. “It remains possible that that site is somehow critical for the protease’s normal function, or the general fitness of the virus.”” [truncated]

70 Percent of Hepatitis C Cases Curable With Early Treatment

http://www.thaindian.com/newsportal/sci-tech/70-percent-of-hepatitis-c-cases-curable-with-early-treatment_100185065.html

“Up to 70 percent of hepatitis C cases are curable if early treatment is sought, according to a new international study. The study by National Centre for HIV Epidemiology and Clinical Research (NCHECR) also found that a standard combination drug treatment was as effective as a stronger regimen of therapy associated with serious side-effects.

Advocacy group Hepatitis Australia estimates that more than 300,000 people in the country alone are infected with chronic hepatitis C, yet fewer than two percent receive treatment. Most common

routes of infection include contact with infected needles and sexual transmission. The findings were part of a trial involving 702 patients from Australia, and 194 from New Zealand, Canada, Thailand, Argentina and Mexico. All had hepatitis C genotype 1 - the most difficult to treat. Study co-author Greg Dore, professor at NCHECR, said early treatment was vital to prevent the onset of serious liver conditions. Hepatitis C is the principal reason for liver transplants in Australia, said an NCHECR release.” [truncated]

Human Genome Sciences Releases Final Test Results for Hepatitis C Drug

<http://www.bizjournals.com/washington/stories/2009/04/27/daily11.html>

“Human Genome Sciences Inc. released final results from the last stage of clinical trials of its hepatitis C drug, Albuferon, in a formal presentation at a scientific conference in Copenhagen. While they didn’t differ from past announcements of study results of the Albuferon trials, which finished one set of phase III trials in December and a second set in March, Human Genome Sciences officials said these latest presentations gave them a chance to look more broadly at the results. “It talks about the results across the program,” said Jerry Parrott, spokesman for Human Genome Sciences. “You’re looking at the phase III results in an overall sense.”

Human Genome Sciences and Swiss giant Novartis AG are developing Albuferon together, and they plan to request federal authorization this fall to start selling the drug as early as next year.” [truncated]

Ironwood Hosts Hepatitis C Conference

<http://www.blythecanews.com/main.asp?SectionID=1&subsectionID=1&articleID=11246>

“BLYTHE - In conjunction with the University of California at San Francisco, Ironwood State Prison welcomed Joanne Imperial, MD, Director, Hepatitis C Program at UCSF, Patricia Nachin, Registered Nurse, Hepatitis Specialty Nurse and Tonia Woodson, Clinical Services Filed Manager on March 18. The purpose of the visit was to give continuing education and consultations regarding Hepatitis C, a disease that harms the liver and is more prevalent in the prison system than in the general population. The audience was made up of the staff from ISP and other California state prisons, which included doctors, nurses, educators, custody, and administrators. Dr. Imperial is the Director of the Hepatitis C Program at UCSF, and is responsible for guidelines throughout the entire state, especially in regard to the prison population.

Hepatitis C is a chronic disease that could eventually lead to cirrhosis, liver cancer, and possibly death. Dr. Imperial is also available to ISP and other prisons, via Telemedicine and Warm-Line Consultations. Telemedicine involves an interactive, real-time consultation whereby the doctor and patient are televised to teach other.” [truncated]

Hospital Heads Axed After Hep C Infections

http://www.chinadaily.com.cn/china/2009-04/01/content_7637551.htm

“Twenty patients were infected with Hepatitis C during hemodialysis treatment at two hospitals in Shanxi province, the Ministry of Health said on Monday. The infected patients are among 47 people who received hemodialysis at the Taiyuan Public Transportation Company's hospital and the Shanxi Coalmine Central Hospital, between December and January. The heads of the two hospitals were held under investigation and those directly responsible for the incident were removed from their posts, Xinhua News Agency quoted the ministry's circular as saying.” [truncated]

STDs Increase in Amsterdam Alarms Health Workers

<http://www.radionetherlands.nl/news/zijlijn/6243468/VD-increase-in-Amsterdam-alarms-health-workers>

“Figures released by Amsterdam's health service show the number of local people who became infected with sexually transmitted diseases in 2008 was dramatically up on the year before. Infections, including HIV, chlamydia, syphilis, and Hepatitis C are all on the increase. Health workers are alarmed by the steady and steep rise, fearing they may soon face a peak in infections comparable to that of the mid-1980s.

There were 178 new diagnoses of HIV in the capital in 2008, the largest number of new cases ever and nearly half of all the new infections registered nationwide. This is partially explained by the fact that more people than ever before are being tested for the HIV virus, which can cause AIDS. The rise in cases of syphilis and Hepatitis C was most marked in homosexual men, while the number of chlamydia infections in people under 20 showed an explosive increase. Hepatitis C is being seen increasingly often in gay men who are HIV positive and only about 60 percent of such cases respond to treatment. Left untreated, Hepatitis C can lead to major problems such as liver cancer.”
[truncated]

Doctor's License Suspension Sought After Infections

<http://www.app.com/article/20090403/NEWS02/904030327/1070/NEWS02>

“TOMS RIVER — Patients can have their blood tested with their health care provider or at one of Community Medical Center's outpatient laboratories, for which an appointment is not required. Patients are asked to bring a copy of the health department's letter, an insurance card and identification. For more information about locations or hepatitis B, call the Ocean County Health Department at (732) 341-9700, ext. 7502. The state is seeking to temporarily suspend the license of a Toms River doctor who is being investigated by health officials after five patients were infected with hepatitis B. Dr. Parvez Dara, who has offices in Toms River and the Whiting section of Manchester, has been ordered to appear today before the state Board of Medical Examiners in Newark.”
[truncated]

VA Continues Notification Process for Veterans Affected by Reprocessing Issues

<http://news.prnewswire.com/DisplayReleaseContent.aspx?ACCT=104&STORY=/www/story/04-03-2009/0005000731&EDATE=>

“The Department of Veterans Affairs (VA) has announced 3,174 Veterans have already been notified of the results of testing they underwent recently; that testing was conducted because of improperly reprocessed endoscopy equipment that may have been used in their care. These Veterans, in the Tennessee, Georgia and South Florida areas were among 10,555 Veterans sent letters offering free testing.

VA patients, who believe that they may have been exposed to cross contamination, were patients that received endoscopic procedures at the VA's Murfreesboro, Tenn., facility from April 2003 to December 2008 and the VA's Augusta, Ga., hospital from January 2008 to November 2008 and the VA's Miami hospital from May 2004 to March 2009.” [truncated]

Schering-Plough Highlights Hepatitis C Clinical Data Presentations at the European Association for the Study of the Liver (EASL) Annual Meeting

Final results from three large PEGINTRON(TM) clinical studies address key questions in the treatment of hepatitis C

<http://news.prnewswire.com/DisplayReleaseContent.aspx?ACCT=104&STORY=/www/story/04-27-2009/0005013115&EDATE=>

“Schering-Plough Corporation today reported that final results of three large PEGINTRON(TM) (peginterferon alfa-2b) clinical studies address longstanding questions in the hepatitis C research community and provide important insights. The results of the studies, involving a total of more than 2,700 patients, were presented at the 44th European Association for the Study of the Liver (EASL) 2009 Annual Meeting.

"Physicians are constantly looking for ways to improve hepatitis C treatment outcomes by increasing response rates or reducing side effects and making treatment more tolerable for their patients," said Robert J. Spiegel, M.D., chief medical officer and senior vice president, Schering-Plough Research Institute. "We undertook these large PEGINTRON studies to help investigators address these important clinical issues. Conducting these studies demonstrates Schering-Plough's longstanding commitment to investigating potential new treatment strategies for patients with hepatitis C."

Combination therapy with peginterferon and ribavirin is a recognized standard of care worldwide for treating chronic hepatitis C virus (HCV) infection. Patients with HCV genotype 1, the most common and hardest to treat form of hepatitis C, are typically treated for 48 weeks, while patients with HCV genotypes 2 or 3 are treated for 24 weeks. The aim of the three PEGINTRON studies was to evaluate investigational regimens in these patient populations compared to current standard practice.” [truncated]

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

HALT-C in the final analysis: A molehill out of a mountain. Almasio PL. J Hepatol. 2009 Mar 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19398229?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: In patients with chronic hepatitis C who do not have a response to antiviral treatment, the disease may progress to cirrhosis, liver failure, hepatocellular carcinoma, and death. Whether long-term antiviral therapy can prevent progressive liver disease in such patients remains uncertain. **METHODS:** We conducted a randomized, controlled trial of peginterferon alfa-2a at a dosage of 90µg per week for 3.5 years, as compared with no treatment, in 1050 patients with chronic hepatitis C and advanced fibrosis who had not had a response to previous therapy with peginterferon and ribavirin. The patients, who were stratified according to stage of fibrosis (622 with noncirrhotic fibrosis and 428 with cirrhosis), were seen at 3-month intervals and underwent liver biopsy at 1.5 and 3.5 years after randomization. The primary end point was progression of liver disease, as indicated by death, hepatocellular carcinoma, hepatic decompensation, or, for those with bridging fibrosis at baseline, an increase in the Ishak fibrosis score of 2 or more points. **RESULTS:** We randomly assigned the patients to receive peginterferon (517 patients) or no therapy (533 patients) for 3.5 years. The level of serum aminotransferases, the level of serum hepatitis C virus RNA, and histologic necroinflammatory scores all decreased significantly ($P < 0.001$) with treatment,

but there was no significant difference between the groups in the rate of any primary outcome (34.1% in the treatment group and 33.8% in the control group; hazard ratio, 1.01; 95% confidence interval, 0.81-1.27; P=0.90). The percentage of patients with at least one serious adverse event was 38.6% in the treatment group and 31.8% in the control group (P=0.07). **CONCLUSIONS:** Long-term therapy with peginterferon did not reduce the rate of disease progression in patients with chronic hepatitis C and advanced fibrosis, with or without cirrhosis, who had not had a response to initial treatment with peginterferon and ribavirin.

High sustained virological response rate to combination therapy in genotype 1 patients with histologically mild hepatitis C. Gheorghe L, Iacob S, Grigorescu M, et al. J Gastrointestin Liver Dis. 2009 Mar;18(1):51-56.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Gheorghe%20L%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Patients with mild hepatitis C have a significant risk of disease progression at medium- and long-term follow-up and should be considered for antiviral therapy. **AIM:** To evaluate the rate of sustained viral response (SVR) and predictive factors of SVR in HCV genotype 1 patients with mild hepatitis C (fibrosis stage F0/F1) treated with combination antiviral therapy.

METHODS: 260 naïve patients were followed-up during 72 weeks in three referral hepatology centers between 2004 and 2006. Univariate and multivariate logistic regression analysis was conducted. **RESULTS:** Early virological response was 88.1% and SVR was 74.2%. In the univariate analysis, SVR was associated with young age (p=0.001), very low (<400,000 IU/mL) baseline viremia (p=0.03) and high aminotransferase levels (p=0.04) and was not associated with gender, body mass index, inflammatory activity, steatosis, ribavirin and peginterferon dose changes, premature cessation of therapy. Multivariate analysis identified the following independent predictors of SVR: age <50 years (p=0.0009), viral load <400,000 IU/mL (p=0.03) and aminotransferase level >2 times normal value (p=0.02). **CONCLUSIONS:** Genotype 1 HCV patients with mild hepatitis have a high rate of SVR, similar to genotype non-1. Young age, very low viremia and significant hepatocytolysis are independent predictors of SVR in patients with mild hepatitis.

HCV genotype 1 is almost exclusively present in Romanian patients with chronic hepatitis C. Grigorescu M. J Gastrointestin Liver Dis. 2009 Mar;18(1):45-50.

http://www.ncbi.nlm.nih.gov/pubmed/19337633?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIM: To investigate the HCV genotype distribution in Romania in the first national study, to establish the correlations with epidemiological, biochemical, virological and histological features and to compare our results with those from neighboring countries. **PATIENTS AND METHODS:**

Two distinct groups of patients and two methods were used: 153 patients in the frame of ACHIEVE study with genotyping and subtypes determination (Versant HCV genotype 2.0 assay) and 461 patients in the frame of an Epidemiological National Multicenter Study having only genotype determination with a commercial kit (Roche Molecular System). Epidemiological, biochemical, virological and histological features were investigated only in the ENMS group.

RESULTS: Genotype 1b was found in 93.46% (ACHIEVE study) and genotype 1 (without subtype identification) in 99.13% of patients (ENMS study). Percutaneous routes of transmission were found in 85.9% of cases. The prevalence of HCV infection increased with age. A high viral load (> 600,000 IU/ml) was found in 67.9% of patients, especially those older than 40 years. Significant fibrosis >= F2 was present in patients older than 40 years (70.9%). There were no correlations between HCV-RNA levels and histological features or between ALT levels and METAVIR activity or fibrosis scores. A similar homogeneity of HCV genotype distribution has

been reported for Moldavia (96%) and Hungary (94.5%). **CONCLUSIONS:** Type 1 HCV genotype was found almost exclusively in Romanian patients with chronic hepatitis C by two different methods of investigation. The pattern showed by this distribution in Romania and some neighboring countries suggests an epidemic profile of HCV infection.

Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. Jensen DM, Marcellin P, Freilich B, et al. *Ann Intern Med.* 2009 Apr 21;150(8):528-40.

http://www.ncbi.nlm.nih.gov/pubmed/19380853?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Many patients with chronic hepatitis C have not responded to therapy with pegylated interferon plus ribavirin. **OBJECTIVE:** To evaluate use of peginterferon-alpha2a plus ribavirin to re-treat nonresponders to peginterferon-alpha2b plus ribavirin. **DESIGN:** Randomized, parallel-group trial conducted between September 2003 and February 2007. Patients and researchers were not blinded to intervention assignment. Random assignment was centralized, computer-generated, and stratified by geographic region, hepatitis C virus (HCV) genotype, and histologic diagnosis. **SETTING:** 106 international centers. **PATIENTS:** 950 nonresponders to 12 or more weeks of therapy with peginterferon-alpha2b plus ribavirin. **INTERVENTION:** Peginterferon-alpha2a, 360 microg/wk, for 12 weeks, then 180 microg/wk to complete 72 weeks (group A) or 48 weeks (group B), or peginterferon-alpha2a, 180 microg/wk for 72 weeks (group C) or 48 weeks (group D). All patients received ribavirin, 1000 or 1200 mg/d. **MEASUREMENTS:** Sustained virologic response (SVR), defined as undetectable (<50 IU/mL) HCV RNA levels 24 weeks after the end of treatment. **RESULTS:** The SVR rates in groups A (n = 317), B (n = 156), C (n = 156), and D (n = 313) were 16%, 7%, 14%, and 9%, respectively (relative risk [RR] for group A vs. group D [the primary comparison], 1.80 [95% CI, 1.17 to 2.77]; P = 0.006). Extended treatment duration increased SVR rates (16% for 72 weeks [groups A and C] vs. 8% for 48 weeks [groups B and D]; RR, 2.00 [CI, 1.32 to 3.02]; P < 0.001). Complete viral suppression (HCV RNA level <50 IU/mL) at week 12 was achieved in 21% of patients in groups A and B and 13% of those in groups C and D. Rates of SVR were 49% (77 of 157 patients) and 4% (32 of 719 patients) among those with and without complete viral suppression at week 12, respectively. **LIMITATION:** Nonresponders to peginterferon-alpha2a plus ribavirin were not evaluated. **CONCLUSION:** Re-treating nonresponders to therapy with peginterferon-alpha2b plus ribavirin for 72 weeks significantly increases SVR rates compared with re-treating them for 48 weeks. The overall SVR rate was low, but patients who are most likely to respond to re-treatment can be identified at week 12.

Mutations in the hepatitis C virus core gene are associated with advanced liver disease and hepatocellular carcinoma. Fishman SL, Factor SH, Balestrieri C, et al. *Clin Cancer Res.* 2009 Apr 21. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Fishman%20SL%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

PURPOSE: Hepatitis C virus (HCV) infection can promote the development of hepatocellular carcinoma (HCC). Published data implicate the HCV core gene in oncogenesis. We tested the hypothesis that core gene sequences from HCC patients differ from those of patients without cirrhosis/HCC. **EXPERIMENTAL DESIGN:** Full-length HCV sequences from HCC patients and controls were obtained from the investigators and GenBank and compared with each other. A logistic regression model was developed to predict the HCC risk of individual point mutations and other sequence features. Mutations in partial sequences (bases 36-288) from HCC patients and controls were also analyzed. The first base of the AUG start codon was designated position 1.

RESULTS: A logistic regression model developed through analysis of full-length core gene sequences identified seven polymorphisms significantly associated with increased HCC risk (36G/C, 209A, 271U/C, 309A/C, 435A/C, 481A, and 546A/C) and an interaction term (for 209A-271U/C) that had an odds ratio <1.0. Three of these polymorphisms could be analyzed in the partial sequences. Two of them, 36G/C and 209A, were again associated with increased HCC risk, but 271U/C was not. The odds ratio of 209A-271U/C was not significant. **CONCLUSIONS:** HCV core genes from patients with and without HCC differ at several positions. Of interest, 209A has been associated with IFN resistance and HCC in previous studies. Our findings suggest that HCV core gene sequence data might provide useful information about HCC risk. Prospective investigation is needed to establish the temporal relationship between appearance of the viral mutations and development of HCC.

An open pilot study exploring the efficacy of fluvastatin, pegylated interferon and ribavirin in patients with hepatitis C virus genotype 1b in high viral loads. Sezaki H, Suzuki F, Akuta N, et al. *Intervirology*. 2009 Apr 17;52(1):43-48. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19372703?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: Response to pegylated (PEG) interferon (IFN) and ribavirin is achieved only in 40-50% of patients infected with hepatitis C virus (HCV) of genotype 1 in high viral loads, which needs to be improved. **METHODS:** In an open-label pilot study, fluvastatin (HMG-CoA reductase inhibitor), 20 mg daily, was given along with PEG-IFN/ribavirin to 21 patients with chronic hepatitis C. They were followed for HCV RNA in serum. **RESULTS:** During treatment for 48 weeks, HCV RNA was lost from serum in 93% of the patients. In the 15 patients who received 48-week therapy, a sustained virological response (SVR) with loss of HCV RNA 24 weeks after completion was achieved in 10 (67%), including 7 of the 9 (78%) male and 3 of the 6 (50%) female patients. In the remaining 6 patients who received 72-week therapy, SVR was gained in 4 (67%), including 1 of the 2 male and 3 of the 4 female patients aged 56, 58 and 62 years, respectively. **CONCLUSION:** Fluvastatin could be used safely to increase the response to PEG-IFN and ribavirin, especially in aged women who respond poorly to combined PEG-IFN/ribavirin.

Systemic autoimmune diseases in patients with hepatitis C virus infection: Characterization of 1020 Cases (The HISPAMEC Registry). Ramos-Casals M, Muñoz S, Medina F, et al. *J Rheumatol*. 2009 Apr 15. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19369460?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To describe the clinical and immunologic characteristics of a large series of patients with systemic autoimmune diseases (SAD) associated with chronic hepatitis C virus (HCV) infection. **METHODS:** The HISPAMEC Registry is a multicenter international study group dedicated to collecting data on patients diagnosed with SAD with serological evidence of chronic HCV infection. The information sources are cases reported by physicians of the HISPAMEC Study Group and periodic surveillance of reported cases by a Medline search updated up to December 31, 2007. **RESULTS:** One thousand twenty HCV patients with SAD were included in the registry. Patients were reported from Southern Europe (60%), North America (15%), Asia (14%), Northern Europe (9%), South America (1%), and Australia (1%). Countries reporting the most cases were Spain (236 cases), France (222 cases), Italy (144 cases), USA (120 cases), and Japan (95 cases). The most frequently reported SAD were Sjögren's syndrome (SS; 483 cases), rheumatoid arthritis (RA; 150 cases), systemic lupus erythematosus (SLE; 129 cases), polyarteritis nodosa (78 cases), antiphospholipid syndrome (59 cases), inflammatory myopathies (39 cases), and sarcoidosis (28

cases). Twenty patients had 2 or more SAD. Epidemiological data were available in 677 cases. Four hundred eighty-seven (72%) patients were female and 186 (28%) male, with a mean age of 49.5 +/- 1.0 years at SAD diagnosis and 50.5 +/- 1.1 years at diagnosis of HCV infection. The main immunologic features were antinuclear antibody (ANA) in 61% of patients, rheumatoid factor (RF) in 57%, hypocomplementemia in 52%, and cryoglobulins in 52%. The main differential aspect between primary and HCV-related SAD was the predominance of cryoglobulinemic-related markers (cryoglobulins, RF, hypocomplementemia) over specific SAD-related markers (anti-ENA antibodies, anti-dsDNA, anti-cyclic citrullinated peptide) in patients with HCV. **CONCLUSION:** In the selected cohort, the SAD most commonly reported in association with chronic HCV infection were SS (nearly half the cases), RA and SLE. Nearly two thirds of SAD-HCV cases were reported from the Mediterranean area. In these patients, ANA, RF and cryoglobulins are the predominant immunological features.

Hepatic steatosis in chronic hepatitis C: study of risk factors and relationship with the fibrosis stage. [Article in Spanish] Antón MD, Roselló E, Gómez F, Paredes JM, López A, Moreno-Osset E. Med Clin (Barc). 2009 Apr 13. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19368934?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND AND OBJECTIVE: Liver steatosis (LS) is a frequent histological finding in chronic hepatitis C virus (HCV) infection with prognostic implications. The aim of the present prospective study was to analyse the risk factors of steatosis and its relationship with the fibrosis stage in patients with chronic HCV infection. **MATERIAL AND METHOD:** Eighty four consecutive HCV RNA positive patients, not treated previously, in whom a liver biopsy was performed, were enrolled. In each patient demographic, clinical, laboratory, viral, and histological variables were obtained at the time of biopsy. Bivariate and multivariate analysis, calculating the odds ratio (OR) and the 95% confidence interval (95%CI), were performed. **RESULTS:** LS was present in 69% of patients. Risk factors of steatosis were an increase of the body mass index (OR: 1.17; 95%CI: 1.01-1.35) and chronic alcohol consumption (OR: 3.58; 95%CI: 1.1-11.6) whereas those of fibrosis were chronic alcohol consumption (OR: 3.58; 95%CI: 1.1-11.6) and increase of the liver inflammatory activity (OR: 1.31; 95%CI: 1.13-1.53). LS was associated with genotype 3 virus infection, which was present in all patients with this infection who had severe steatosis in a significantly greater proportion than in patients with non-genotype 3 virus infection (41.7% vs 2.8%; P<.001). LS was more frequent in patients with advanced fibrosis stages than in patients with non-advanced fibrosis (78,9% vs 60,9%; P=.074). **CONCLUSIONS:** LS is a frequent finding in HCV chronic infection related to both host and viral factors. LS could be a worsening factor of hepatic injury.

Predicting mortality risk in patients with compensated HCV-induced cirrhosis: A long-term prospective study. Bruno S, Zuin M, Crosignani A, et al. [J]50: Am J Gastroenterol. 2009 Apr 7.

[Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19352340?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: The identification of prognostic factors associated with mortality is crucial in any clinical setting. **METHODS:** We enrolled in a prospective study 352 patients with compensated hepatitis C virus (HCV)-induced cirrhosis, consecutively observed between 1989 and 1992. At entry, patients underwent upper endoscopy to detect esophageal varices, and were then surveilled by serial clinical and ultrasonographic examination. The model for end-stage liver disease (MELD) score was calculated with information collected at enrollment. Baseline predictors and intercurrent events

associated with mortality were assessed using the Cox regression model. **RESULTS:** During a median follow-up of 14.4 years, 194 subjects received a single course of interferon monotherapy, 131 patients developed decompensation (ascites, bleeding, hepatic encephalopathy), 109 patients had hepatocellular carcinoma (HCC), 9 had liver transplant, and 158 died. Esophageal varices were associated with development of decompensation (hazard ratio (HR), 2.09; 95% confidence interval (CI), 1.33-3.30) and liver-related death (HR, 2.27; 95% CI, 1.41-3.66). A MELD score of 10 predicted overall mortality (HR, 2.15; 95% CI, 1.50-3.09). Overall survival of patients with MELD ≤ 10 was 80% at 10 years. HCC occurrence increased the risk of decompensation fivefold (HR, 5.52; 95% CI, 3.77-8.09). Hepatic and overall mortality hazard ratios were 8.62 (95% CI, 5.57-13.3) and 3.80 (95% CI, 2.67-5.42), respectively, for patients who developed HCC, and 16.9 (95% CI, 9.97-28.6) and 7.08 (95% CI, 4.88-10.2) for those who experienced decompensation.

CONCLUSIONS: In patients with compensated HCV-induced cirrhosis, the presence of esophageal varices at baseline predicted decompensation and mortality. The development of HCC during follow-up strongly hastens the occurrence of decompensation, which is the main determinant of death. Patients with a MELD score ≤ 10 at study entry had a prolonged life expectancy.

Prevalence and treatment of hyperlipidemia in patients with chronic hepatitis C infection.

Murthy GD, Vu K, Venugopal S. Eur J Gastroenterol Hepatol. 2009 Apr 24. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Murthy%20GD%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Patients with chronic hepatitis C (HCV) infection can also have hyperlipidemia. Glucose intolerance has been associated with HCV infection and treating hyperlipidemia in this and other high-risk groups is warranted. We hypothesized that hyperlipidemia is common in patients with hepatitis C and that it is under-treated for fear of worsening liver function. **DESIGN:** From the Stratton Veterans Affairs Medical Center computerized database, we collected information on patients with HCV infection enrolled in hepatology clinic. We collected information on age, sex, duration of HCV infection, concomitant diagnoses, medications they were on, laboratory values including hepatic function, glucose, and lipid levels. We collected information on the lipid levels and various cardiovascular risk factors. **METHODS:** This is a retrospective study involving record review. We analyzed the data collected from the records for prevalence of high cholesterol (as defined by the National Cholesterol Education Program) and for prevalence of various cardiovascular risk factors. We analyzed prevalence of treatment of hyperlipidemia in various risk groups. In the patients who were treated for hyperlipidemia, we collected information on any worsening hepatic function that led to treatment discontinuation. **RESULTS:** Six hundred and twenty-eight (70.5%) out of 891 patients with hepatitis C had hyperlipidemia. Of the 628 patients who had hyperlipidemia, 81 (12.7%) had positive antibody and RNA not tested; 162 (25.4%) had positive antibody but negative RNA testing; and 385 (61.3%) had positive testing for viral RNA. Two hundred and eighty-four (45.2%) of 628 patients with hyperlipidemia were eligible for treatment to lower it. Of 146 patients with hyperlipidemia and diabetes mellitus or arterial disease who were qualified for treatment (LDL > 99), 95 (65.1%) were treated with lipid-lowering medication. Of 148 patients with hyperlipidemia and without diabetes or arterial disease who were qualified for treatment, 64 (43.3%) were treated with lipid-lowering medication. **CONCLUSION:** A high prevalence of hyperlipidemia in patients infected with HCV is observed. Prevalence is highest among those who are positive for viral RNA. About half the patients with hyperlipidemia were eligible for treatment with drugs to lower it. Treatment of hyperlipidemia with medication though surprisingly common could improve.

Hepatitis C virus-infected patients are 'spared' from the metabolic syndrome but not from insulin resistance. A comparative study of nonalcoholic fatty liver disease and hepatitis C virus-related steatosis. Lonardo A, Ballestri S, Adinolfi LE, et al. []14: Can J Gastroenterol. 2009 Apr;23(4):273-8.

http://www.ncbi.nlm.nih.gov/pubmed/19373421?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C feature steatosis and insulin resistance (IR), conditions associated with the metabolic syndrome (MS).

OBJECTIVES: To assess the prevalence of MS and determinants of IR in patients with NAFLD and chronic hepatitis C.

METHODS: Ninety-three consecutive patients with NAFLD, 97 with chronic hepatitis C virus (HCV) genotypes 1 and 2, and 182 'healthy' controls without steatosis were enrolled in the present study. The prevalence of MS was assessed by modified Adult Treatment Panel III criteria and IR by the homeostasis model assessment of insulin resistance (HOMA-IR). IR was defined as the 75th percentile of the HOMA-IR of control subjects.

RESULTS: While the prevalence of IR was similar in NAFLD and HCV-infected subjects (70.0% and 78.7%, respectively), the prevalence of MS was significantly higher in NAFLD patients than in HCV-infected patients (27.9% versus 4.1%) and in controls (5.6%). With multivariate analysis, IR was predicted by body mass index (OR 1.263; 95% CI 1.078 to 1.480) and triglyceridemia (OR 1.011; 95% CI 1.002 to 1.020) in NAFLD and by sex (OR for female sex 0.297; 95% CI 0.094 to 0.940) and fibrosis stage (OR 2.751; 95% CI 1.417 to 5.340) in chronic hepatitis C. **CONCLUSIONS:** IR is independently associated with body mass index and triglyceridemia in NAFLD, sex and fibrosis in chronic HCV infection, and has a higher prevalence in NAFLD and chronic hepatitis C than in controls. However, the frequency of MS in HCV-infected patients, similar to that of controls, is significantly lower than that seen in NAFLD patients. The current diagnostic criteria of MS are more likely to 'capture' patients with NAFLD than with chronic hepatitis C, although both groups are insulin resistant.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Clinical features and effect of antiviral therapy on anti-liver/kindey microsomal antibody type 1 positive chronic hepatitis C. Ferri S, Muratori L, Quarneti C, et al. J Hepatol. 2009 Mar 26. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19398235?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND/AIMS: Anti-liver/kidney microsomal antibody type 1 (anti-LKM1), a serological marker of type 2 autoimmune hepatitis, is also detected in a small proportion of patients with hepatitis C. This study aimed to evaluate clinical features and effect of antiviral therapy in patients with hepatitis C who are anti-LKM1 positive. **METHODS:** Sixty consecutive anti-LKM1 positive and 120 age and sex-matched anti-LKM1 negative chronic hepatitis C patients were assessed at diagnosis and during follow-up. Of these, 26 anti-LKM1 positive and 72 anti-LKM1 negative received antiviral therapy. Anti-LKM1 was detected by indirect immunofluorescence and immunoblot. Number of HCV-infected hepatocytes and intrahepatic CD8+ lymphocytes was determined by immunohistochemistry. **RESULTS:** At diagnosis anti-LKM1 positive patients had higher IgG levels and more intrahepatic CD8+ lymphocytes (p 0.022 and 0.046, respectively). Viral genotypes distribution and response to therapy were identical. Hepatitic flares during antiviral treatment only occurred in a minority of patients in concomitance with anti-LKM1 positivity.

CONCLUSIONS: Immune system activation is more pronounced in anti-LKM1 positive patients

with hepatitis C, possibly representing the expression of autoimmune mechanisms of liver damage. Antiviral treatment is as beneficial in these patients as in anti-LKM1 negative patients, and the rare necroinflammatory flares are effectively controlled by corticosteroids, allowing subsequent resumption of antiviral therapy.

Roles for endocytic trafficking and phosphatidylinositol 4-kinase III alpha in hepatitis C virus replication. Berger KL, Cooper JD, Heaton NS, et al. Proc Natl Acad Sci U S A. 2009 Apr 17. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Berger%20KL%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Hepatitis C virus (HCV) reorganizes cellular membranes to establish sites of replication. The required host pathways and the mechanism of cellular membrane reorganization are poorly characterized. Therefore, we interrogated a customized small interfering RNA (siRNA) library that targets 140 host membrane-trafficking genes to identify genes required for both HCV subgenomic replication and infectious virus production. We identified 7 host cofactors of viral replication, including Cdc42 and Rock2 (actin polymerization), EEA1 and Rab5A (early endosomes), Rab7L1, and PI3-kinase C2gamma and PI4-kinase IIIalpha (phospholipid metabolism). Studies of drug inhibitors indicate actin polymerization and phospholipid kinase activity are required for HCV replication. We found extensive co-localization of the HCV replicase markers NS5A and double-stranded RNA with Rab5A and partial co-localization with Rab7L1. PI4K-IIIalpha co-localized with NS5A and double-stranded RNA in addition to being present in detergent-resistant membranes containing NS5A. In a comparison of type II and type III PI4-kinases, PI4Ks were not required for HCV entry, and only PI4K-IIIalpha was required for HCV replication. Although PI4K-IIIalpha siRNAs decreased HCV replication and virus production by almost 100%, they had no effect on initial HCV RNA translation, suggesting that PI4K-IIIalpha functions at a posttranslational stage. Electron microscopy identified the presence of membranous webs, which are thought to be the site of HCV replication, in HCV-infected cells. Pretreatment with PI4K-IIIalpha siRNAs greatly reduced the accumulation of these membranous web structures in HCV-infected cells. We propose that PI4K-IIIalpha plays an essential role in membrane alterations leading to the formation of HCV replication complexes.

Angiotensin 1-7, an alternative metabolite of the renin-angiotensin system, is upregulated in human liver disease and has antifibrotic activity in the bile duct ligated rat. Lubel JS, Herath CB, Tchongue J, et al. Clin Sci (Lond). 2009 Apr 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19371232?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Angiotensin 1-7 (Ang-(1-7)) a peptide product of the recently described angiotensin converting enzyme (ACE) homologue, ACE2, opposes the harmful actions of angiotensin II (Ang II) in cardiovascular tissues, but its role in liver disease is unknown. Our objective was to assess plasma levels of Ang-(1-7) in human liver disease and determine its effects in experimental liver fibrosis. Angiotensin peptide levels were measured in cirrhotic and non-cirrhotic patients with hepatitis C. The effects of Ang-(1-7) on experimental fibrosis were determined using the rat bile duct ligation (BDL) model. Liver histology, hydroxyproline quantification and expression of fibrosis related genes were assessed. Expression of renin-angiotensin system components and the effects of Ang-(1-7) were examined in rat hepatic cells (HSC). In human cirrhotics both plasma Ang-(1-7) and Ang II concentrations were markedly elevated ($P < 0.001$). Non-cirrhotic hepatitis C patients had elevated Ang-(1-7) levels compared with controls ($P < 0.05$), but Ang II concentrations were not increased. In BDL rats, Ang-(1-7) improved fibrosis stage, collagen picrosirius red staining, and reduced

hydroxyproline content together with reduced gene expression of collagen 1A1, alpha-SMA, VEGF, CTGF, ACE and mas (the Ang-(1-7) receptor). Cultured HSC expressed AT1 and mas receptors, and when treated with Ang-(1-7) or the mas receptor agonist AVE 0991 produced less alpha-SMA and hydroxyproline, an effect reversed by the mas receptor antagonist, A779. Ang-(1-7) is upregulated in human liver disease and has antifibrotic actions in a rat model of cirrhosis. The ACE2/Ang-(1-7)/mas axis represents a potential target for antifibrotic therapy in humans.

Hepatitis C virus and disrupted interferon signaling promote lymphoproliferation via type II CD95 and interleukins. Machida K, Tsukiyama-Kohara K, Sekiguch S, et al. [144]:

Gastroenterology. 2009 Apr 8. [Epub ahead of print] Related Articles, LinkOut

http://www.ncbi.nlm.nih.gov/pubmed/19362089?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND & AIMS: The molecular mechanisms of lymphoproliferation associated with the disruption of interferon (IFN) signaling and chronic hepatitis C virus (HCV) infection are poorly understood. Lymphomas are an extrahepatic manifestations of HCV infection; we sought to clarify the molecular mechanisms of these processes. **METHODS:** We established interferon regulatory factor-1null (irf-1 ^{-/-}) mice with inducible and persistent expression of HCV structural proteins (irf-1 / CN2 mice). All the mice (n =900) were observed for at least 600 days after Cre/loxP switching. Histologic analyses, as well as analyses of lymphoproliferation, sensitivity to Fas-induced apoptosis, colony formation, and cytokine production were performed. Proteins associated with these processes were also assessed. **RESULTS:** Irf-1 / CN2 mice had extremely high incidences of lymphomas and lymphoproliferative disorders and displayed increased mortality. Disruption of irf-1 reduced the sensitivity to Fas-induced apoptosis and decreased the levels of caspases -3/7 and -9 mRNA species and enzymatic activities. Furthermore, the irf-1 / CN2 mice showed decreased activation of caspases -3/7 and -9 and increased levels of IL-2, IL-10, and Bcl-2, as well as increased Bcl-2 expression, which promoted oncogenic transformation of lymphocytes. IL-2 and IL-10 were induced by the HCV core protein in splenocytes. **CONCLUSIONS:** Disruption of IFN signaling resulted in lymphoma development, indicating that differential signaling occurs in lymphocytes compared with liver. This mouse model, in which HCV expression and disruption of IFN signaling synergize to promote lymphoproliferation, will be an important tool for the development of therapeutic agents that target the lymphoproliferative pathway.

HIV/HCV COINFECTION

Hepatitis B and C virus coinfection: A novel model system reveals the absence of direct viral interference. Bellecave P, Gouttenoire J, Gajer M, et al. Hepatology. 2009 Mar 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Bellecave%20P%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Coinfection with hepatitis B virus (HBV) and hepatitis C virus (HCV) has been associated with severe liver disease and frequent progression to cirrhosis and hepatocellular carcinoma. Clinical evidence suggests reciprocal replicative suppression of the two viruses, or viral interference. However, interactions between HBV and HCV have been difficult to study due to the lack of appropriate model systems. We have established a novel model system to investigate interactions between HBV and HCV. Stable Huh-7 cell lines inducibly replicating HBV were transfected with selectable HCV replicons or infected with cell culture-derived HCV. In this system, both viruses were found to replicate in the same cell without overt interference. Specific inhibition of one virus

did not affect the replication and gene expression of the other. Furthermore, cells harboring replicating HBV could be infected with cell culture-derived HCV, arguing against superinfection exclusion. Finally, cells harboring replicating HBV supported efficient production of infectious HCV. Conclusion: HBV and HCV can replicate in the same cell without evidence for direct interference in vitro. Therefore, the viral interference observed in coinfecting patients is probably due to indirect mechanisms mediated by innate and/or adaptive host immune responses. These findings provide new insights into the pathogenesis of HBV-HCV coinfection and may contribute to its clinical management in the future.

Hepatitis C virus coinfection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. Peters L, Mocroft A, Soriano V, Rockstroh JK, Losso M, Valerio L, Aldins P, Reiss P, Ledergerber B, Lundgren JD; EuroSIDA Study Group. *J Acquir Immune Defic Syndr.* 2009 Apr 15;50(5):457-63.

http://www.ncbi.nlm.nih.gov/pubmed/19360931?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Conflicting data exist whether hepatitis C virus (HCV) affects the CD4 cell recovery in patients with HIV starting antiretroviral treatment. **OBJECTIVE:** To investigate the influence of HCV coinfection on the CD4 recovery in patients with maximum virologic suppression within the EuroSIDA cohort. **METHODS:** Patients tested for anti-HCV antibodies and with at least 2 consecutive HIV viral loads (VLs) <50 copies per milliliter after starting combination antiretroviral therapy were eligible for inclusion. For each pair of VL <50 copies per milliliter, the annual change in CD4 count was calculated and compared between (1) HCV-seronegative vs. HCV-seropositive patients, (2) HCV genotypes 1-4 in HCV-RNA+ patients, and (3) viremic vs. aviremic (HCV-RNA < 615 IU/mL) in HCV-seropositive patients. Results were adjusted for known confounders. **RESULTS:** Four thousand two hundred eight patients were included, representing 39,474 pairs of HIV VL measurements with VL <50 copies per milliliter and 12,492 person-years of follow-up. The unadjusted annual change in CD4 count for HCV-seropositive and HCV-seronegative patients was 35.5 cells per milliliter (95% confidence interval 27.2 to 43.9) and 38.3 cells per milliliter (95% confidence interval 34.8 to 41.9), respectively. After adjustment, there was no difference in CD4 change when comparing, according to HCV serostatus ($P = 0.17$), between genotypes ($P = 0.23$) or when comparing HCV viremic vs. aviremic patients ($P = 0.57$). Adjusting additionally for HCV treatment and HCV-RNA VL did not change the findings.

CONCLUSIONS: HCV serostatus did not influence the CD4 recovery in patients with HIV with maximum virologic suppression after starting combination antiretroviral therapy. Furthermore, no difference in CD4 gain was found when comparing distinct HCV genotypes in HCV-RNA+ patients or when comparing HCV viremic vs. aviremic HCV-seropositive patients.

Pegylated interferon α 2a plus ribavirin versus pegylated interferon α 2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. Berenguer J, González-García J, López-Aldeguer J, et al. *Antimicrob Chemother.* 2009 Apr 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19363085?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: The two currently available types of pegylated interferon (peg-IFN) used to treat hepatitis C have different pharmacokinetic properties. It is unclear how these differences affect response to therapy. We compared the effectiveness and safety of peg-IFN- α 2a and peg-IFN- α 2b, both with ribavirin, against chronic hepatitis C virus (HCV) infection in HIV-infected patients. **METHODS:** From the GESIDA HIV/HCV cohort, we analysed patients treated with

peg-IFN-alpha2a (n = 315) or peg-IFN-alpha2b (n = 242). The primary endpoint was a sustained virological response (SVR). **RESULTS:** Both groups were well matched in baseline characteristics except for a higher frequency of injection drug users in the peg-IFN-alpha2b group than in the peg-IFN-alpha2a group (85% versus 76%; P = 0.01) and a higher frequency of bridging fibrosis and cirrhosis (F3-F4) in the peg-IFN-alpha2b group than in the peg-IFN-alpha2a group (42% versus 33%; P = 0.04). End-of-treatment response was significantly lower among patients treated with peg-IFN-alpha2b [40% versus 52%; odds ratio (OR), 1.63; 95% confidence interval (95% CI), 1.16-2.29; P < 0.01]. However, no significant differences were found in SVR between patients treated with peg-IFN-alpha2b and those treated with peg-IFN-alpha2a (31% versus 33%; OR, 1.09; 95% CI, 0.75-1.59; P = 0.655). Therapy was interrupted due to adverse events in 33 (14%) patients treated with peg-IFN-alpha2b and 47 (15%) patients treated with peg-IFN-alpha2a. **CONCLUSIONS:** No differences in effectiveness and safety were found between peg-IFN-alpha2b and peg-IFN-alpha2a for the treatment of chronic HCV infection in HIV-infected patients.

Hepatitis C seropositivity and kidney function decline among women with HIV: Data from the Women's Interagency HIV Study. Tsui J, Vittinghoff E, Anastos K, Augenbraun M, et al. [42: Am J Kidney Dis. 2009 Apr 24. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Tsui%20J%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: How coinfection with hepatitis C virus (HCV) impacts on the trajectory of kidney function in human immunodeficiency virus (HIV)-infected patients is unclear. This study examined the effect of HCV infection on kidney function over time in women infected with HIV. **STUDY DESIGN:** Retrospective observational cohort. **SETTING & PARTICIPANTS:** Study sample included participants from the Women's Interagency HIV Study who were HIV infected and had undergone HCV antibody testing and serum creatinine measurement at baseline. **PREDICTOR:** HCV seropositivity. **OUTCOMES & MEASUREMENT:** Estimated glomerular filtration rate (eGFR) calculated from semi-annual serum creatinine measurements using the 4-variable Modification of Diet in Renal Diseases (MDRD) Study equation. Linear mixed models were used to evaluate the independent effect of HCV seropositivity on eGFR over time, adjusting for demographic factors, comorbid conditions, illicit drug use, measures of HIV disease status, use of medications, and interactions with baseline low eGFR (<60 mL/min/1.73 m²). **RESULTS:** Of 2,684 HIV-infected women, 952 (35%) were found to be HCV seropositive. In 180 women with chronic kidney disease (CKD) at baseline (eGFR < 60 mL/min/1.73 m²), HCV seropositivity was independently associated with a fully adjusted net decrease in eGFR of approximately 5% per year (95% confidence interval, 3.2 to 7.2) relative to women who were seronegative. In contrast, HCV infection was not independently associated with a decrease in eGFR in women without low eGFR at baseline (P < 0.001 for interaction). **LIMITATIONS:** The MDRD Study equation has not been validated as a measure of GFR in persons with HIV or HCV infection. Proteinuria was not included in the study analysis. Because the study is observational, effects of residual confounding cannot be excluded. **CONCLUSIONS:** In HIV-infected women with CKD, coinfection with HCV is associated with a modest, but statistically significant, decrease in eGFR over time. More careful monitoring of kidney function may be warranted for HIV-infected patients with CKD who are also coinfecting with HCV.

Perceived knowledge of blood-borne pathogens and avoidance of contact with infected patients. Kagan I, Ovadia KL, Kaneti T. *J Nurs Scholarsh.* 2009 Mar;41(1):13-9.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kagan%20I%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

PURPOSE: To examine the relationship between nurses' knowledge of blood-borne pathogens (BBPs), their professional behavior regarding handwashing, compliance with standard precautions (SPs), and avoidance of therapeutic contact with BBP-infected patients. **DESIGN:** This cross-sectional design study took place in a regional medical center in Central Israel during 2003.

METHODS: Of the 180 participants, 159 (88.3%) were women with an average educational level of 16.40 years (SD=2.66). The mean age of the sample was 39.41 (SD=10.1). Data were collected using a structured questionnaire including sociodemographic information, level of knowledge concerning three BBPs (human immunodeficiency virus [HIV], hepatitis B virus [HBV], and hepatitis C virus [HCV]), level of compliance with SPs, understanding of SP principles, and avoidance of therapeutic contact with BBP-infected patients.

FINDINGS: Levels of HIV-related knowledge were significantly higher than were those of HBV- and HCV-related knowledge. Only 96 participants (54.5%) stated that all patients should be treated as BBP-carriers. The understanding of the basic principle of SPs did not influence the relationship between perceived knowledge and self-reported compliance with SPs; 77.3% of the sample reported that they avoid therapeutic contact with BBP-infected patients. The level of perceived knowledge did not contribute to the nurses' avoidance of care of BBP carriers. **CONCLUSIONS:** Perceived knowledge of BBPs has a weak effect on compliance with SPs and willingness to care for BBP-infected patients.

RECOMMENDATIONS: Nurses must identify their preconceptions when caring for BBP-carriers. Further research on this issue is needed to attempt to understand the forces acting on our nursing staff, in order to ensure appropriate care of BBP-infected patients. **CLINICAL**

RELEVANCE: Our study indicated some reluctance among nurses to care for patients with blood-borne pathogens. This appears to be the result of value systems and not a lack of knowledge, indicating a need to integrate a psychoeducational approach to education of nurses.

Treatment of chronic hepatitis C in Asia: when East meets West. Yu ML, Chuang WL. *J Gastroenterol Hepatol.* 2009 Mar;24(3):336-45.

http://www.ncbi.nlm.nih.gov/pubmed/19335784?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The issue of best treatment for chronic hepatitis C virus (HCV) infection is in constant flux, not only in Western countries but also in Asia. Currently, pegylated-interferon plus ribavirin is the standard of care. Studies from Asia provide evidence to support the same broad treatment strategies for Asian patients as recommended in Western countries. Nevertheless, there is increasing evidence that Asians have a higher likelihood of achieving a sustained virological response (SVR) than their Caucasians counterparts when treated with the corresponding regimen. With the recommended 'standard dose and duration treatment regimens', SVR is achieved in Asia for around 70% of HCV genotype 1 (HCV-1) infected cases, approximately 90% of HCV-2/3, approximately 65% of HCV-4, and approximately 80% of HCV-6 patients. Difference of body weight in race might contribute the superior response in Asian patients. HCV genotype distribution in Asia also differs from North-America/Europe. HCV-6 and its variants, previously mistyped as HCV-1, needs accurate genotyping. Increasing data support the proposal that HCV genotype, baseline viral load and on-treatment virological response provide information for decision-making so that treatment can be individualized. Beyond the older recommendations, an abbreviated 24-week regimen could be suggested for HCV-1/4 patients with baseline viral loads < 400 000 IU/mL and a rapid virological response (RVR, HCV RNA undetectable at week 4), and an abbreviated 12-16 weeks of pegylated-

interferon with weight-based doses of ribavirin could be suggested for HCV-2/3 patients with a RVR. Such tailored treatment regimens can reduce the costs of treatment and incidence of adverse events without compromising efficacy. Hepatitis C virus (HCV) infection is one of the most important causes of cirrhosis worldwide, and particularly in some countries of Asia (notably Japan) where it is now more prevalent than chronic hepatitis B virus infection. Hepatitis C virus infection can also lead to hepatocellular carcinoma (HCC). It is estimated that there are more than 170 million people chronically infected with HCV, and 3 to 4 million persons are newly infected each year. The risk for developing cirrhosis 20 years after initial HCV infection among those chronically infected varies between studies, but is estimated at around 10%-15% for men and 1-5% for women. Once cirrhosis is established, the rate of developing HCC is at 1%-4% per year. Approximately 280 000 deaths per year are related to HCV infection. Hepatitis C virus-related end-stage liver disease and HCC have become the leading cause for liver transplantation worldwide. In the Asia-Pacific area, the estimated prevalence of antibodies to HCV (anti-HCV) range from 0.3% in New Zealand to 5.6% in Thailand. In Japan, Middle East, Vietnam and Taiwan, several HCV hyper-endemic areas have been reported with an anti-HCV prevalence rate of 12% to as high as 58%. In addition to the well-known endemic status of HBV infection in most countries of the Asia-Pacific region, HCV infection presents another critical scenario of public health issue in this region, as outlined in Guidelines by the Asia-Pacific Association for Study of the Liver (APASL). Given the lack of an effective vaccine, optimal treatment of chronic HCV infection is now perceived as a 'must' in terms of public health strategies, as well as of the clinical setting for individual patients.

The impact of needle and syringe programs on HIV and HCV transmissions in injecting drug users in Australia: A model-based analysis. Kwon JA, Iversen J, Maher L, Law MG, Wilson DP. *J Acquir Immune Defic Syndr.* 2009 Apr 21. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kwon%20JA%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: We aim to estimate how changes in sterile syringe distribution through needle-syringe programs (NSPs) may affect HIV and hepatitis C virus (HCV) incidence among injecting drug users (IDUs) in Australia. **METHODS:** We develop a novel mathematical model of HIV and HCV transmission among IDUs who share syringes. It is calibrated using biological and Australian epidemiological and behavioral data. Assuming NSP syringe distribution affects the number of times each syringe is used before disposal, we use the model to estimate the relationship between incidence and syringe distribution. **RESULTS:** HIV is effectively controlled through NSP distribution of sterile syringes {with the effective reproduction ratio below 1 [0.66 median, interquartile range (0.63-0.70)] under current syringe distribution}. In contrast, HCV incidence is expected to remain high and its control is not feasible in the foreseeable future. The proportion of injections that are shared and the number of times each syringe is used before disposal are the driving factors of HCV incidence. The frequency in which each syringe is used can potentially be influenced by changes in syringe distribution. We estimate that if syringe distribution or coverage doubled, then annual incidence is likely to reduce by 50%. However, if it was decreased to one third of the current level, then approximately 3 times the incidence could be expected.

CONCLUSIONS: This research highlights the large benefits of NSPs, puts forward a quantitative relationship between incidence and syringe distribution, and indicates that increased coverage could result in significant reductions in viral transmissions among IDUs.

Evaluation of a patient referral contact tracing programme for hepatitis B and C virus infection in drug injectors. Brewer DD, Hagan H. *Euro Surveill.* 2009 Apr 9;14(14):5-9.

http://www.ncbi.nlm.nih.gov/pubmed/19371508?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Effective contact tracing for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection could enhance disease control, especially in populations with low HBV vaccination rates and high prevalence of untreated HCV infection. We evaluated a low-cost approach to HBV/HCV contact tracing in injection drug users (IDUs). Index cases (n=26) were IDUs who seroconverted to HBV and/or HCV during a prospective cohort study in Seattle. Interviewers elicited index cases' recent injection partners and administered recall cues and other techniques to boost recall. Index cases received vouchers for free hepatitis testing, which they were to give to locatable partners. Persons redeeming vouchers also received small monetary incentives. Most (26/40) seroconverters participated in the paid contact interviews. Index cases reported many partners (mean=17), and in the aggregate, index cases indicated they could refer more than one third of their elicited partners for testing. Overall, only 17 persons were ultimately referred and just eight of these were confirmed as partners sought for referral. The supplementary elicitation techniques, and especially the recall cues, increased reporting of injection partners substantially. The injection network constructed from reported partnerships was mostly connected and cyclic. Successful contact tracing in IDUs likely requires active involvement by public health staff to locate and notify exposed injection partners.

Psychopathological changes and quality of life in hepatitis C virus-infected, opioid-dependent patients during maintenance therapy. Schäfer A, Wittchen HU, Backmund M, et al. *Addiction*. 2009 Apr;104(4):630-40.

http://www.ncbi.nlm.nih.gov/pubmed/19335661?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIMS: To examine among maintenance patients (methadone or buprenorphine) with and without hepatitis C virus (HCV) infection (i) the frequency of psychopathological symptoms at baseline and 1-year follow-up; (ii) the association between antiviral interferon (IFN) treatment and psychopathological symptoms; and (iii) to explore whether IFN therapy has an effect on 1-year outcome of maintenance treatment. **DESIGN:** Naturalistic prospective longitudinal cohort design. **SETTING:** A total of 223 substitution centres in Germany. **PARTICIPANTS:** A nationally representative sample of 2414 maintenance patients, namely 800 without and 1614 with HCV infection, of whom 122 received IFN therapy. **MEASURES:** HCV infection (HCV+/HCV-), IFN (IFN+/IFN-) treatment status and clinical measures. Diagnostic status and severity (rated by clinician), psychopathology (BSI--Brief Symptom Inventory) and quality of life (EQ-5D--EuroQol Group questionnaire). **FINDINGS:** HCV+ patients revealed indications for a moderately increased psychopathological burden and poorer quality of life at baseline and follow-up compared to HCV- patients. HCV+ patients showed a marked deterioration over time only in the BSI subscale somatization (P = 0.002), and the frequency of sleep disorders almost doubled over time (12.8% at baseline; 24.1% at follow-up; P < 0.01). IFN treatment, received by 10% of HCV+ patients, did not impair efficacy or tolerability of maintenance therapy and was associated overall with neither increased psychopathological burden nor reduced quality of life. **CONCLUSIONS:** Findings suggest no increased risk among HCV+ patients on maintenance therapy for depressive or other psychopathological syndromes. In our patient sample, IFN treatment was not associated with increased psychopathological burden, reduced quality of life or poorer tolerability and efficacy of maintenance treatment.