

Caring Ambassadors Hepatitis C Program Newsletter  
www.HepCChallenge.org  
July 2008



IN THE NEWS	1 – 10
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	11 – 14
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	14 – 24
HIV/HCV COINFECTION	18 – 19
COMPLEMENTARY & ALTERNATIVE THERAPY	19 – 20
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS	20 – 24

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**IN THE NEWS**

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**Company developing non-nucleoside polymerase inhibitor for treatment of hepatitis C**

<http://www.earthtimes.org/articles/show/anadys-pharmaceuticals-initiates-phase-i-clinical-trial-of-ana598,416557.shtml>

“Anadys Pharmaceuticals, Inc. announced today the initiation of dosing in a Phase I clinical trial of ANA598, an investigational oral non-nucleoside polymerase inhibitor for the treatment of chronic hepatitis C virus (HCV) infection. The objectives of this trial are to assess safety, tolerability, and pharmacokinetics following ascending single oral doses of ANA598 in healthy volunteers. Approximately 40 healthy subjects will participate in the study, which is being conducted in the United States.

Following successful completion of the healthy volunteer study, Anadys plans to begin a Phase Ib study of ANA598 in HCV-infected patients in the third quarter of 2008. ‘Based on its very favorable preclinical profile, including potency, pharmacokinetics, and tolerability, we believe ANA598 has the potential to become an important component of future combination therapy for patients with HCV infection,’ said James Freddo, M.D., Anadys’ Chief Medical Officer. ‘We are excited about initiating this clinical program and look forward to future trials of ANA598 in HCV patients, first as a single agent and then in subsequent combination studies. We expect the full benefit of direct antivirals to be demonstrated when studied as components of novel combination regimens incorporating multiple anti-HCV agents.’ ” [truncated]

**Immtech announces results from hepatitis c discovery program**

<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/06-03-2008/0004825490&EDATE=>

“Immtech Pharmaceuticals, Inc. announced today positive results against the hepatitis C virus (HCV) of a compound from its drug discovery portfolio. The prototype compound belongs to an expanding class of compounds that has previously demonstrated activity against a related surrogate virus, bovine viral diarrhea virus (BVDV). The compound was found to have significant activity against HCV under assay conditions designed to demonstrate inhibition of the virus entry process, using a newly available in vitro cell culture system that employs infectious and replicating virus.

Norman Abood, Ph.D., Sr. Vice President, Discovery Programs, stated, ‘We aim to develop a compound with a novel mechanism of action that is complementary to the currently recognized treatments of HCV. It appears that Immtech’s class of compounds inhibits an early, non-replicative

step in the virus life cycle, based upon our earlier work in BVDV. The majority of the industry's efforts have focused on programs to identify drug candidates, such as protease and polymerase inhibitors, which inhibit HCV virus replication. Our latest findings provide an approach that will allow us to potentially identify a drug candidate with a new and complementary mechanism of action.’ ” [truncated]

### **Biochips fighting viruses**

<http://www.russia-ic.com/news/show/6460/>

“Hepatitis C virus particle Scientists from Russian Institute of Molecular Biology started certification of biological chips for distinguishing strains of hepatitis C virus. New technology has enormous market potential, since traditional techniques cannot tell viral strain in one case out of three. Biochips allow predicting disease development and prescribing appropriate therapy, which is nearly 100% effective.

Hepatitis C virus requires precise diagnostics, since virus’s mutability is extremely high; moreover, various viral subtypes need specific treatment with individual adjustment of drugs and doses. Some cases allow therapy reduction, which is important due to high treatment costs. Hepatitis C virus was chosen due to several reasons. First, hepatitis C is a socially significant disease, which has no vaccine. Second, biochips are the best way to detect this virus, because biochips perform multiparameter analysis, which identifies all possible pathogens in a single sample of biological fluids (blood, serum or urine).

Biochip project will be finished before the end on this year. Several hundreds of virus samples will be analyzed within this project, and then scientists will submit protocols to health authorities in order to get registration certificate for using biochips in Russia.”

### **Avexa, Chinese firm in hepatitis C program**

<http://www.businessspectator.com.au/bs.nsf/Article/Avexa-announces-research-with-TargetDrug-F9V2X?OpenDocument>

“Australian biotech company Avexa Ltd has announced an agreement to work with Shanghai-based TargetDrug Co Ltd on its Hepatitis C virus (HCV) program to develop a novel lead inhibitor. Chief executive of Avexa, Dr Julian Chick, says HCV affects 180 million people globally. ‘With only half of all HCV patients benefiting from current therapy, unmet medical needs are clearly very high. We see the development of new HCV treatments as an opportunity to put Avexa’s proven experience in pure drug discovery into play,’ Dr Chick said. ” [truncated]

### **I tried to deny I had hepatitis C. Now I’m glad I had treatment**

<http://www.worcesternews.co.uk/news/2317020.m5ec/?from=ec&to=2317020&l=i tried to deny i had hepatitis c now im glad i had treatment>

“When Phil noticed his skin was turning yellow he pushed it to the back of his mind. It was the 1970s and, at the time, he was in the throes of alcohol and drug addiction. He assumed the jaundice, which would come and go for periods of three or four weeks, was due to his lifestyle and forgot about it.

Even when, in 1989, a former partner rang and told him she had been diagnosed with Hepatitis C, Phil, who is now in his 50s, still took no action. He said: ‘I thought, I’ll deal with it when it starts affecting me, but when you are using very powerful painkillers, like heroin, you don’t feel aches and

pains. 'It wasn't until 10 years later in 1999 when I found myself in rehab I decided to get myself checked out.'

The results were a mixed bag. Phil, who lives in Worcester but whose identity we have concealed, was clear of HIV and, although he had had Hepatitis B - probably the cause of his earlier jaundice - his body had already fought the virus off. The bad news was he had contracted a form of Hepatitis C known as genotype one, the most difficult to treat. It was no great surprise for Phil as Hep C, a blood-borne virus causing inflammation of the liver, is most commonly - but not exclusively - seen among users of intravenous drugs and, initially, he was not too concerned. He said: 'At the time I thought, let's look on the positive side, you've only got Hep C, you could be living with a death sentence like HIV.' He was offered treatment but decided to concentrate on his rehab and recovery and it was only when, four years later he began to feel ill, that he changed his mind. ” [truncated]

### **Reduced hepatitis C viral level achieved with DNA vaccine delivered by Inovio Biomedical's electroporation delivery system in phase I/II clinical study**

[http://www.businesswire.com/portal/site/google/?ndmViewId=news\\_view&newsId=20080604005476&newsLang=en](http://www.businesswire.com/portal/site/google/?ndmViewId=news_view&newsId=20080604005476&newsLang=en)

“Inovio Biomedical Corporation, a leader in enabling the development of DNA vaccines using electroporation-based DNA delivery, announced today that its partner, Tripep AB, reported preliminary results indicating a dramatic reduction in hepatitis C viral load in its ongoing phase I/II clinical study of its ChronVac-C® therapeutic DNA vaccine, which is delivered using Inovio’s electroporation-based DNA delivery system. This result is from the first patient in the middle dose group to complete treatment against hepatitis C virus infection. Samples taken before, during and after treatment show that the viral levels in blood successively decreased by more than 95% during treatment. Inovio's electroporation delivery technology is intended to enhance the potency of DNA vaccines against cancers and infectious diseases.

ChronVac-C® is a therapeutic vaccine given to individuals already infected with the hepatitis C virus with the aim to clear the infection by boosting the immune response against the virus. This clinical study is being conducted at the Infectious Disease Clinic and Center for Gastroenterology at the Karolinska University Hospital in Huddinge and Solna, respectively, in Sweden. The intended enrollment of 12 patients will be divided into three dose groups with increasing doses of ChronVac-C(R). Each patient receives four vaccinations one month apart. After the last vaccination, patients are followed for another six months. The study's main purpose is to assess safety. It is also testing whether the treatment boosts the immune response to HCV (immunogenicity) and its effect on virus replication in the liver. If the patient is completely virus-free six months after completing treatment, he/she will be considered cured.

In the lowest dose group, two patients who completed treatment developed a T-cell response to hepatitis C. The preliminary result from this first patient to complete treatment in the intermediate dose group is the first to indicate a significant reduction in viral load. There have been no severe adverse events. “The benefit we would hope to see from a successful hepatitis C virus DNA vaccine would be a dramatic reduction in viral levels,” stated Avtar Dhillon, MD, Inovio's president and CEO. ‘We look forward to seeing the longer term results of this DNA vaccine and its potential to address this multi-billion dollar market.’ ” [truncated]

### **Endoscopy Center of Southern Nevada: More hepatitis C tests positive**

<http://www.lawyersandsettlements.com/articles/10709/endoscopy-center-more-hepatitis-positive.html>

“Las Vegas, NV: The largest patient notification in US history that centered around the Endoscopy Center of Southern Nevada continues to worry current and former patients of the facility, that they might be next to receive a positive test for hepatitis C. The latest count is 84—that's the number of people who are suspected of contracting hepatitis C as the result of unsafe injection practices at the Endoscopy Center. Among the 50,000 current and former patients of the facility who have been contacted, and urged to get screened, about 400 have tested positive for hepatitis.

It has also been confirmed by the Southern Nevada Health District that the hepatitis C virus can be linked back to one person, on a single day, for at least half of the confirmed acute cases, which in late May stood at eight. Seven of the eight confirmed cases linked back to the Endoscopy Center, and four of those seven links to one person on September 21st, 2007.” [truncated]

### **Tattooed Irish should be tested for hepatitis C**

[http://www.imt.ie/news/2008/06/tattooed\\_irish\\_should\\_be\\_tested.html](http://www.imt.ie/news/2008/06/tattooed_irish_should_be_tested.html)

“Irish people should consider being tested for hepatitis C if they have ever had a tattoo or body piercing using an unsterilised needle, or are uncertain about the sterility of a tattoo or piercing they received, said Ms Olivia Carr of the Blood Borne Virus Forum. In 2005, Ireland had the highest rate of reported cases of hepatitis C of all European member states who provided data. The 2007 Irish figures showed a 29 per cent increase in the number of hepatitis C notifications. ‘People should also be tested if they have ever injected illicit drugs, or received medical treatment in a country with high hepatitis rates,’ Ms Carr said. ‘Some 20,000 Irish people may be infected with hepatitis C, but only a fraction know they are infected,’ she added.” [truncated]

### **Greater hepatitis testing needed**

<http://www.independent.ie/health/latest-news/greater-hepatitis-testing-needed-1402456.html>

“Pregnant women should be routinely tested for hepatitis C during their clinic visits, according to a study carried out in Dublin's Rotunda, Mater and Temple Street hospitals. Currently, only women with risk factors, such as a history of injecting drugs, are tested. However, over the final six months of last year doctors in the Rotunda asked all women booking their antenatal visits to be tested for hepatitis C.

Hepatitis C can seriously damage the liver over many years causing cirrhosis, cancer or even liver failure. Mothers can pass on the virus to their unborn child although the risk is low -- about five-10pc of babies become infected. The doctors said the vast majority of the 4,118 mothers attending the clinics agreed to the tests. The tests showed that 34 of the women were positive for the virus and six in 10 of these were Irish. Three quarters reported one or more risk factor which could have exposed them to the virus -- mostly sharing needles while injecting drugs. But the rest had no risk factors, which meant the virus would not otherwise have been picked up. ” [truncated]

### **Vertex Reports 52% SVR 12 Rate for a 24-week Telaprevir-based regimen in genotype 1 hepatitis C patients who failed prior treatment**

<http://www.tradingmarkets.com/.site/news/Stock%20News/1668589/>

“Vertex Pharmaceuticals Incorporated today announced positive results from a planned interim analysis of PROVE 3, an ongoing Phase 2b study evaluating Telaprevir-based treatment in patients with genotype 1 chronic hepatitis C virus (HCV) infection who did not achieve sustained virologic

response (SVR) with at least one prior pegylated interferon (peg-IFN) and ribavirin (RBV) regimen. Vertex is developing Telaprevir in collaboration with Tibotec.

In the interim analysis, 52% (60 of 115; intent-to-treat analysis) of patients randomized to receive treatment with a 24-week telaprevir-based regimen (12 weeks of telaprevir in combination with peg-IFN and RBV, followed by 12 weeks of peg-IFN and RBV alone) maintained undetectable HCV RNA 12 weeks post-treatment (SVR 12). In the interim analysis, adverse events were similar to those commonly observed with peg-IFN and RBV including fatigue, nausea, rash, headache, gastrointestinal disorders and anemia, and were consistent with those previously reported in patients being treated with telaprevir-based therapy in the PROVE 1 and 2 studies in treatment-naïve subjects.” [truncated]

### **Act now if you're at risk for hepatitis C**

<http://www.heraldnet.com/article/20080610/LIVING/716321058>

“Dixie contracted hepatitis C from a blood transfusion during surgery years ago. She had no symptoms and, if it weren't for a routine blood test, Dixie wouldn't have known she had the disorder. She certainly wouldn't have known she had chronic liver disease that is treatable. The test made Dixie aware that she had a condition contagious to others and that could potentially shorten her life. So she decided to act.” [truncated]

### **Silent no more: viral hepatitis B and C**

<http://thechronicleherald.ca/Columnists/1061339.html>

“There are many diseases in Canada that generate the awareness, funding, advocacy and research that they deserve. As terrible and serious as these diseases are, they are not silent. Viral hepatitis B and C are not among them. As a practising liver specialist and chairman of the Canadian Liver Foundation, I often ask myself: What is it about viral hepatitis that makes it almost invisible? Why is no one talking about it?

One of the reasons is the stigma that the more than 600,000 Canadians who suffer from hepatitis B and C live with. Indeed, hepatitis B and C affect one in 12 people worldwide – a phenomenally huge number. It can affect anybody at any time, but is often viewed to be only a problem for the more marginalized populations. Not only can it be deemed socially unacceptable to talk about it, but it can be difficult to diagnose because there may be few, if any, symptoms. If left untreated, however, hepatitis B and C can lead to scarring (cirrhosis), severe chronic illness, cancer and death.

Liver cancer is most frequently a result of hepatitis B and C and its incidence is increasing more rapidly than almost any other cancer. Proper care can prevent this cancer, but due to gaps in the health care system, the majority of patients who develop liver cancer will die from their disease. Almost half a billion people worldwide have either hepatitis B or C and while this is far higher than the prevalence of HIV or any cancer, awareness is inexplicably low and the majority of those infected are unaware until it is too late.

A colleague of mine compares this disease to an iceberg – one that the health care system is steaming directly toward. The need is immense. And that is why patients, physicians and others who care about this disease have come together to call on the federal government to do more than just piecemeal funding and stopgap measures. In Canada, with no national strategy to deal with this disease, limited funding for research and a shortage of physicians and nurses, the result is a sub-

standard level of care. In a country that prides itself on its publicly funded health care system, this is unacceptable.” [truncated]

### **Valeant says hepatitis C drug causes less anemia**

Valeant says hepatitis C candidate could replace drug that can cause anemia

<http://money.cnn.com/news/newsfeeds/articles/apwire/4cde66d4ec6c40e949ee88502404e3db.htm>

“Valeant Pharmaceuticals International said Thursday that its mid-stage hepatitis C candidate taribavirin could replace a drug used in a common treatment regimen. Ribavirin and peginterferon are considered the standard of care regimen for hepatitis C. Speaking at the Goldman Sachs Global Healthcare Conference, Valeant Senior Vice President of Drug Development Harry Mansbach said that many patients, however, develop anemia upon taking ribavirin.

Mansbach said that because fewer cases of anemia have been associated with Valeant's taribavirin drug, it could be prescribed instead of ribavirin for hepatitis C patients at risk for anemia, such as those who also are HIV-positive. Chief Executive J. Michael Pearson said, though, that the company won't move taribavirin into late-stage trials until a partner for the drug is found. ” [truncated]

### **Sanford vetoes bill to halt HIV notifications at schools**

[http://www.charleston.net/news/2008/jun/13/sanford\\_vetoes\\_bill\\_halt\\_hiv\\_notifications44410/](http://www.charleston.net/news/2008/jun/13/sanford_vetoes_bill_halt_hiv_notifications44410/)

“South Carolina schools will continue to be notified when students test positive for HIV following a governor's veto that brought warnings Thursday from critics who contend requiring the notice will dissuade people from seeking medical testing. Gov. Mark Sanford issued the veto Wednesday night, saying federal privacy laws are flawed and that ending notification to school superintendents and nurses is a step in the wrong direction. He said Hepatitis B and C should be added to the notifications.

‘We believe that as a matter of public policy that more highly contagious diseases should be added to this notification list rather than deleted. Instead, this bill would move in the opposite direction by removing what many consider to be a very deadly disease,’ Sanford wrote. ‘If my son or daughter was sitting in class or was on the sporting field with a fellow student who happened to have Hepatitis C, as a parent I would want to know.’

Critics said sending HIV test results to schools discourages students from being screened and runs afoul of federal laws. Casting concerns about HIV and Hepatitis C in the context of classroom or sport event ‘shows a misunderstanding of the transmission of HIV, a misunderstanding or lack of knowledge of how one acquires HIV,’ said Dr. Jacob White, deputy director of the South Carolina HIV/AIDS Council. ”

### **Bike races raise hepatitis C research funds**

<http://www.mlive.com/news/annarbornews/index.ssf?/base/news-28/1213627239150060.xml&coll=2As>

“Scott Mahler, of Ypsilanti, ascended the winners podium on South University Avenue on Sunday, his four children rushed to congratulate him. Minutes earlier, Mahler had won an Ann Arbor Tour de Kids race - on his seven-year-old son's tricycle. ‘I wanted them to come out and participate, and they thought it was only fair I participate, too. This is good family fun,’ said Mahler, laughing.

Mahler beat about nine other fathers - riding tricycles and unicycles - in the Dads' Dash, a Father's Day-themed race in the Tour de Kids. The daylong Tour de Kids, staged on streets around the University of Michigan Diag, raised money for the Greenview Hepatitis C Fund for research at the University of Michigan Medical Center.” [truncated]

**Vertex Pharmaceuticals announces the appointment of Freda C. Lewis-Hall, M.D., as Executive Vice President, Medicines Development**

[http://www.istockanalyst.com/article/viewarticle+articleid\\_2295603~title\\_Vertex-Pharmaceuticals.html](http://www.istockanalyst.com/article/viewarticle+articleid_2295603~title_Vertex-Pharmaceuticals.html)

“Vertex Pharmaceuticals Incorporated today announced the appointment of Freda C. Lewis-Hall, M.D. as Executive Vice President, Medicines Development. Dr. Lewis-Hall joins Vertex from Bristol-Myers Squibb, Incorporated, and has extensive leadership experience across multiple functional areas in the pharmaceutical industry. At Vertex, Dr. Lewis-Hall will be responsible for Regulatory Affairs, Clinical and Non-clinical Development, Medical Affairs and Commercial Development. Dr. Lewis-Hall will serve on the Company’s executive management team and will report directly to Joshua Boger, Ph.D., President and CEO of Vertex.” [truncated]

**Novel agents will drive the hepatitis C virus drug market to increase nearly five-fold to more than \$10 billion in 2017**

<http://www.earthtimes.org/articles/show/novel-agents-will-drive-the,439498.shtml>

“Decision Resources, one of the world's leading research and advisory firms for pharmaceutical and healthcare issues, finds that market to treat hepatitis C virus will grow by nearly five-fold during the next decade, increasing from approximately \$2 billion in 2007 to more than \$10 billion in 2017 in the United States, France, Germany, Italy, Spain, United Kingdom and Japan. The new Pharmacor report entitled Hepatitis C Virus finds that, as drug makers have recognized the high unmet need and significant commercial potential that exists, the hepatitis C virus market has been one of the most active areas of infectious disease drug development in recent years.” [truncated]

**Insulin resistance means coinfecting patients have a poorer response to hepatitis C treatment**

<http://www.aidsmap.com/en/news/54612FB7-87B1-41C8-8DE1-044782E70851.asp>

“Insulin resistance means a poorer response to anti-hepatitis C treatment in HIV/hepatitis C coinfecting patients, according to a French study presented to the Fourth International Workshop on HIV and Hepatitis C Coinfection in Madrid on June 19th. Measures to improve insulin resistance, such as exercise or weight loss could, the investigators suggest, improve the chances of hepatitis C therapy achieving good results.

HIV/hepatitis C coinfecting patients have a poorer response to hepatitis C therapy than patients who are only infected with hepatitis C. A number of factors have been associated with response to treatment for hepatitis C including patient characteristics. Some patient characteristics, such as age, gender and race, cannot be changed. But others, such as body mass index (BMI) and, importantly for the purposes of this study, insulin resistance, are potentially modifiable.” [truncated]

**Vertex CEO preparing for '09 hepatitis drug launch**

<http://www.reuters.com/article/marketsNews/idUSN1948277620080619>

“Vertex Pharmaceuticals Inc will be prepared to launch its experimental hepatitis C drug next year even though U.S. regulators have not said whether they would review it based on a mid-stage trial,

the company's chief executive said. 'That's Plan B,' CEO Joshua Boger said late on Wednesday at an event at the BIO International Convention in San Diego.

He said Plan A continues to be completion of a pivotal trial of the drug, telaprevir, in hepatitis C patients not previously treated, with data expected in the first half of 2010. If positive, Vertex would then file for regulatory approval in the second half of 2010. But the company 'has to be ready,' despite the expense, to launch in the third quarter of next year should the U.S. Food and Drug Administration agree to a faster timeline, Boger said." [truncated]

### **Anti-HIV treatment may mean that progression of hepatitis C no worse in coinfecting patients than in those with only hepatitis C**

<http://www.aidsmap.com/en/news/0095A06D-982A-4E89-952E-06379CCC64E8.asp>

"Anti-HIV treatment may mean that the rate of liver fibrosis is significantly slowed in patients with HIV and hepatitis C coinfection, according to a German study presented to the Fourth International Conference on HIV and Hepatitis C Coinfection in Madrid. The investigators found that there was no difference in degree of liver damage between HIV/hepatitis C coinfecting patients who received antiretroviral therapy and that seen in individuals who were only infected with hepatitis C.

This finding adds weight to the recommendation in the recently revised British HIV treatment guidelines that early initiation of HIV therapy is especially important in HIV/hepatitis C-coinfecting patients. It is now well established that HIV/hepatitis C coinfecting patients experience faster hepatitis C disease progression than patients who are only infected with hepatitis C. It is thought that this is because of the damage to the immune system that HIV causes. There is some evidence that the use of anti-HIV treatment can help slow the rate of liver disease in coinfecting patients, but this is still a controversial area."

### **Genelabs provides update on hepatitis C drug development with collaboration partners**

[http://www.businesswire.com/portal/site/google/?ndmViewId=news\\_view&newsId=20080623005407&newsLang=en](http://www.businesswire.com/portal/site/google/?ndmViewId=news_view&newsId=20080623005407&newsLang=en)

"Genelabs Technologies, Inc. (Nasdaq:GNLB) announced today that based on progress to date, its hepatitis C drug development and commercialization collaboration with Novartis is continuing to the next phase. In September 2006, Genelabs and Novartis entered into a two-year collaboration to discover and develop certain non-nucleoside inhibitors (NNI) of the NS5b polymerase in HCV. Genelabs was responsible for drug discovery research and Novartis is responsible for development and commercialization. The research phase of the collaboration was completed on June 2, 2008. Genelabs and Novartis will continue to hold joint research committee meetings to monitor the progress of compounds discovered during this phase as they advance.

Genelabs also announced that Gilead has exercised its right to terminate a similar research collaboration agreement for nucleoside-based inhibitors for the NS5b HCV polymerase, and will return to Genelabs all rights to the compounds developed in the program. 'We are very pleased that Novartis is continuing to advance compounds identified in the research phase of our collaboration,' said Ronald C. Griffith, Genelabs' Chief Scientific Officer. 'We look forward to the potential of future milestone achievements with this program. At the same time, we are continuing to independently discover and develop nucleoside-based inhibitors for this important NS5b HCV target and are discussing further collaboration in this area with various third parties.' "

### **African American Council On Liver Awareness convenes in Washington D.C.**

<http://www.medicalnewstoday.com/articles/114525.php>

“Concerns over the increasing number of hepatitis C cases in the past four months has brought together African Americans in the fields of medicine, social work and advocacy to the nation's capitol to discuss its implications in their community. The AACLA summit took place at the Capital Hilton hotel, June 26-29, 2008, hosted by its Chief Executive Officer and President, Johanna Blanding-Koskinen, and included key health providers of the African American community: Mark Colomb, Ph.d, of ‘My Brother's Keeper,’ Luther Virgil, M.D. and CEO of the National Minority Clinical Research Association. (NMCRA) and Terrence Young, Program Manager/Outreach Coordinator of the ‘Community Education Group’ based in Washington, D.C.” [truncated]

### **Suit alleges inadequate care of hepatitis C outbreak in California prisons**

<http://www.latimes.com/features/health/la-me-prison9-2008jul09,0,2618115.story>

“An attorney in the federal class-action lawsuit says up to 40% of the 171,000 inmates in state prisons may be infected by hepatitis C. California prison officials are failing to adequately treat an outbreak of hepatitis C that has infected thousands of inmates, a federal class-action lawsuit alleged Tuesday.

The lawsuit was filed in Los Angeles on behalf of inmates including Kevin Jackson, who is at the California State Prison at Solano and alleges that he has not received proper treatment since being diagnosed with the disease in August 2007. Up to 40% of the 171,000 inmates in state prisons may be infected with hepatitis C, said Shawn Khorrami, an attorney for Jackson.

The lawsuit alleges that the California Department of Corrections and Rehabilitation is wrongly excluding thousands of inmates from liver biopsies and antiviral treatments and allowing their diseases to progress to more advanced stages of liver damage. Khorrami said the lack of proper diagnostic testing and treatment further spreads the disease among inmates. ” [truncated]

### **Hepatitis C virus may need enzyme's help to cause liver disease**

<http://www.sciencedaily.com/releases/2008/07/080709091717.htm>

“A key enzyme may explain how hepatitis C infection causes fatty liver -- a buildup of excess fat in the liver, which can lead to life-threatening diseases such as cirrhosis and liver cancer, report University of Pittsburgh Graduate School of Public Health and School of Medicine researchers. The study shows that an enzyme known to play a major role in lipid production, fatty acid synthase (FAS), was highly elevated in human liver cells exposed to the hepatitis C virus. While preliminary, the research suggests that testing for elevated levels of FAS could help determine which patients with hepatitis C virus may go on to develop more serious, long-lasting health consequences brought on by fatty liver. ” [truncated]

### **Anadys Pharma resumes Clinical Investigation of TLR7 Mechanism to treat HCV**

<http://www.rttnews.com/ArticleView.aspx?Id=648079&SMap=1>

“Anadys Pharmaceuticals Inc. said that it is resuming clinical investigation of the Toll-Like Receptor-7 or TLR7 mechanism for the treatment of chronic hepatitis C. Based on preclinical pharmacology testing and the results of completed 13-week GLP animal toxicology studies, Anadys has received clearance to initiate a clinical trial of ANA773, the company's oral TLR7 agonist prodrug, under a clinical trial application in the Netherlands.

Following initial dosing in healthy volunteers, this trial will explore every-other-day dosing over 28 days in HCV patients, the company noted. Anadys also said it continues to enroll patients in a separate Phase I clinical trial of ANA773 in oncology that is ongoing under an IND in the United States.”

### **Hepatitis records ready for release**

<http://www.fox5vegas.com/news/16821945/detail.html>

“LAS VEGAS -- Former patients of the Endoscopy Center of Southern Nevada will now be able to retrieve their medical records, four months after being seized by police. According to the Review-Journal, the company Metro hired to alphabetize the records has completed the task, saying the files are ready for release.

Metro has set up a hot line for records request and will release the number to the public next week. More than 50,000 former patients were exposed to blood-borne pathogens by unhealthy medical practices at the facility, health officials said. Between March 2004 and January 2008, the staff at the facility reused medical vials and syringes on multiple patients, leading to cross contamination, officials said.” [truncated]

### **Doctors concerned about diseases**

<http://www.kitv.com/mostpopular/16815875/detail.html>

“HONOLULU -- Some are calling for tougher new regulations for the piercing and tattoo industry as doctors say diseases like HIV and Hepatitis C can easily be spread by tattoos and piercing. Tattoos have become more and more popular in recent years. Hawaii's law regulating the industry was written back in 1981. It was revised 10 years ago, but many said it is time to make it stronger.

‘I think tattooing and body piercings are dangerous. You really need to know what you're doing,’ said Dr. Alan Tice, of Queen's Medical Center. Tice testified at a hearing Monday that there is a silent epidemic of Hepatitis C in Hawaii. One in 50 people have the disease, and tattooing and piercing can spread it.” [truncated]

### **Grand Jury recommends needle exchange program in Stanislaus County, Calif., To reduce cases of HIV, hepatitis C**

[http://www.kaisernet.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=53136](http://www.kaisernet.org/daily_reports/rep_index.cfm?DR_ID=53136)

“A civil grand jury last week recommended that Stanislaus County, California, create a needle exchange program to decrease the number of hepatitis C and HIV infections, the Modesto Bee reports. According to the grand jury report, the county is on pace to record 620 new hepatitis C cases this year, up from 519 in 2007. According to the grand jury, a needle exchange program could reduce the number of infections and help diminish the threat to public employees who come into contact with discarded syringes.

‘Both the public health and law enforcement approaches can coexist with the common goal of harm reduction in Stanislaus County ... by providing new syringes to injection drug users in exchange for dirty syringes,’ the grand jury wrote. The grand jury recommended that the county follow the guidelines of a 2006 state law, which clarified the use of public funds in the creation of needle exchange programs.’ [truncated]

**Pathological evolution of hepatitis C virus-"Healthy carriers"**. Sobesky R, et al. World J Gastroenterol. 2008 Jun 28;14(24):3861-5  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18609710&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18609710&dopt=Abstract)

**AIM:** To determine factors associated with fibrosis progression in hepatitis C virus (HCV)-infected patients without significant initial pathological lesions. **METHODS:** Seventy six untreated HCV-infected patients with initially normal liver as defined by a Knodell score  $\leq 3$ , with 2 liver biopsies and detectable HCV-RNA were included. Markers of fibrosis progression were assessed.

**RESULTS:** Median duration of infection and time between paired biopsies was 13 (95% CI: 1-28) and 4 (95% CI: 2-16) years respectively. Alanine-transaminase (ALT) activity was normal in 43.4% of cases. 50% demonstrated progression of the necro-inflammation and 34% of fibrosis after a median time evolution of 4 years (95% CI: 2-16). The median difference in the necro-inflammation and fibrosis score between biopsies was low, 1.5 and 0.0 respectively. Univariate analysis showed there was no difference between fibrosis activity or evolution according to genotype or viral load. A higher fibrosis progression ( $P = 0.03$ ) was observed in patients with body mass index (BMI)  $> 25$ . Fibrosis progression correlated with the time interval between biopsies ( $P = 0.01$ ). A significant progression of activity (1.7 vs 0.4,  $P < 0.05$ ) or fibrosis (0.9 vs 0.0,  $P < 0.01$ ) was observed in patients with elevated ALT. There was a significant correlation between activity progression and fibrosis progression ( $P = 0.003$ ). Multivariate analysis demonstrated that fibrosis progression was associated with elevated ALT, BMI  $> 25$  and the time interval between 2 biopsies.

**CONCLUSION:** There is no fibrosis progression in 66% of patients without significant initial histopathological lesion. Fibrosis progression is associated with elevated ALT and BMI  $> 25$ .

**Peg-interferon alfa-2b and ribavirin for the treatment of genotype 1 hepatitis C recurrence after liver transplantation.** Lodato F, et al. Aliment Pharmacol Ther. 2008 Jun 11; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18549463&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18549463&dopt=Abstract)

**BACKGROUND/AIMS:** Treatment of HCV recurrence after LT is difficult with low response rates. Aims of present study was to assess the safety and efficacy of pegylated-Interferon (PEG-IFN) alfa-2b+Ribavirin (RBV) in patients with post-LT recurrent genotype-1 HCV and to establish stopping rules according to response. **MATERIALS AND METHODS:** Fifty-three patients with post-LT HCV recurrence, were enrolled. Patients received PEG-IFN alfa-2b 1.0 mcg/Kg/weekly plus RBV 8-10 mg/Kg/daily for 24 weeks. Those with "early virological response at week 24 (EVR24) " continued treatment for 24 weeks (Group A). Patients without EVR24 were randomized to continue (Group B) or to discontinue (Group C). **RESULTS:** overall SVR was 26% (14/53). ALT, Rapid Virological Response, EVR, EVR24, undetectable serum HCV-RNA at weeks 12 (cEVR12) and 24 (cEVR24) were related to SVR. cEVR12 and cEVR24 (OR: 14.7; 95% CI: 2.02-106.4) were independent predictors of SVR. All patients with SVR, had cEVR12 No patient in Group B and group C achieved ETR. One patient in Group B had SVR. **CONCLUSIONS:** PEG-IFN alfa-2b was effective in 1/4 of patients with HCV genotype 1 after LT. Treatment should be discontinued in patients with no virological response at week 12. Further studies are needed to evaluate whether a longer treatment period might be beneficial in patients with  $\geq 2 \log_{10}$  drop in HCV-RNA at week 24.

### **Living as a drug addict in Oslo, Norway - a study focusing on nutrition and health.**

Sæland M, et al. Public Health Nutr. 2008 Jun 13;:1-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18549520&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18549520&dopt=Abstract)

**OBJECTIVES:** To investigate nutritional status and related living conditions among drug addicts in Oslo. **DESIGN:** A cross-sectional study of nutritional status evaluated by anthropometric and biochemical measurements; a structured interview concerning education, living conditions, income source, drug history and sex practice; and biochemical testing of sexually transmitted infections. **SETTING:** The present study was conducted between November 2001 and April 2003 in locations where the drug addicts reside in Oslo. **SUBJECTS:** A total of 123 male and seventy-two female addicts using drugs by injections regularly. **RESULTS:** We found that 20 % of the women were moderately underweight (BMI in kg/m<sup>2</sup>) (16.5 < BMI < 18.5), 7 % were severely underweight (BMI <= 16.5) and 3 % of the men were moderately underweight (16.5 < BMI < 18.5). BMI was positively correlated with days institutionalised and number of eating events per day. Respondents sleeping rough had significantly reduced BMI compared to those in hostels and shelters. The concentrations of Hb, serum ferritin and albumin supported a higher prevalence of malnutrition among the women. Hepatitis C was found in 85 %, active hepatitis B in 6 % and less than 2 % were HIV positive. Also, 84 % received public financial support, 38 % of the women had prostitution as a significant income source, while burglary was most prevalent among the men; 20 % were pushing drugs. **CONCLUSION:** Malnutrition among the drug addicts varied from 5 % to 30 %, independent of drug history, education and income. Moderate and severe underweight was most prevalent among the women. Being previously institutionalised and having increased number of eating events increased BMI. Sleeping rough correlated with reduced body weight. Hepatitis C infection was common; hepatitis B and HIV were rare.

### **The efficacy of short-term interferon-beta therapy for type C cirrhotic patients with genotype 2a and low virus load.**

Arase Y, et al. Intern Med. 2008;47(12):1085-90

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18552464&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18552464&dopt=Abstract)

**OBJECTIVE:** The aim of this study was to elucidate the efficacy of short-term interferon (IFN) therapy for type C cirrhotic patients with genotype 2a and low virus load. **METHODS:** The present study was retrospective cohort study. Inclusion criteria were liver cirrhosis, hepatitis C virus (HCV) genotype 2a, the serum HCV RNA level of less than 100 KIU/mL, and IFN period of 6 or 8 weeks. Twenty-five consecutive patients who satisfied the above criteria were treated with IFN-beta daily at the dosage of 6 MU for 6 or 8 weeks. Independent factors that might have influenced sustained virologic response (SVR) were studied using multiple logistic regression analysis. **RESULTS:** Background of clinical profiles were as follows: median (range) age=64 (53-76) years, male/female=13/12, and median (range) HCV-RNA=31 (8-90) KIU/mL. Out of 25, 14 patients (56.0%) had SVR by the intention-to-treat analysis. The SVR was significantly associated with serum HCV RNA level. Logistic analysis showed that SVR occurred when HCV RNA level was <50 KIU/mL (p=0.047). Based on the difference of the serum HCV RNA level, the SVR rate was 68.4% (13/19) in patients with a serum HCV RNA level of <50 KIU/mL and 16.7% (1/6) in patients with a serum HCV RNA level of > or =50 KIU/mL. **CONCLUSIONS:** The 6 or 8-week IFN-beta therapy is a possible selection of therapy for cirrhotic patients with HCV genotype 2a and a serum HCV RNA level of <50 KIU/mL.

**Safety and efficacy of pegylated interferon {alpha}-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia.** Harmatz P, et al. Haematologica. 2008 Jun 12; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18556414&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18556414&dopt=Abstract)

Antiviral treatment of HCV in thalassemia has raised concerns of ribavirin-induced hemolysis and increased iron loading. This study examined the change in liver iron concentration (LIC), transfusion requirement, virological response, and iron-related toxicities after pegylated interferon alpha-2a/ribavirin treatment in patients with thalassemia. Median transfusions increased by 44%.

However, only 29% (4/14) of patients showed an increase of LIC > 5mg/g dry wt. and overall liver iron remained stable. One of 4 patients with genotype 2 or 3 demonstrated sustained viral response, compared with 50% with genotype 1 (6/12). No patient developed cardiac, liver or endocrine toxicities, although neutropenia occurred in 52%. The molar efficacy of deferoxamine improved with reduction in liver inflammation on biopsy ( $p=0.001$ ). **In conclusion**, antiviral treatment is safe if transfusion requirement, iron toxicities and neutropenia are monitored.

**Antiviral therapy completion and response rates among hepatitis C patients with and without schizophrenia.** Huckans M, et al. Schizophr Bull. 2008 Jun 17; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18562341&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18562341&dopt=Abstract)

**BACKGROUND:** Despite disproportionately high rates of hepatitis C (HCV) among patients with severe mental illness, to date, there is scant empirical data available regarding antiviral therapy outcomes within this population. **OBJECTIVE:** To compare antiviral therapy completion and response rates between HCV patients with vs those without schizophrenia (SCHZ). **METHODS:** A regional Veterans Healthcare Administration database was used to identify veterans meeting criteria for this retrospective chart review. All patients confirmed to have SCHZ and to have received antiviral therapy between 1998 and 2006 ( $n = 30$ ) were compared with a control group of demographically matched (HCV genotype, age, race, gender) patients with no history of SCHZ ( $n = 30$ ). **RESULTS:** For HCV patients with genotype 1, antiviral completion, end of treatment response (ETR), and sustained viral response (SVR) rates did not significantly differ between groups. For those with genotypes 2 and 3 combined, antiviral therapy completion rates did not significantly differ between groups; however, the SCHZ group was significantly ( $P < 0.050$ ) more likely to achieve an ETR and an SVR. For all genotypes combined, the SCHZ patients were no more likely than controls to discontinue therapy early for psychiatric symptoms, medical complications, or other adverse events, and groups did not significantly differ in terms of hospitalization rates during antiviral therapy. **CONCLUSION:** Our retrospective chart review suggests that patients with SCHZ complete and respond to antiviral therapy for HCV at rates comparable with those without SCHZ. Based on these data, SCHZ should not be considered a contraindication to antiviral therapy for HCV.

**A simple noninvasive score predicts gastroesophageal varices in patients with chronic viral hepatitis.** Gentile I, et al. J Clin Gastroenterol. 2008 Jun 16; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18562980&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18562980&dopt=Abstract)

**BACKGROUND:** Guidelines recommend upper endoscopic screening of cirrhotic patients for gastroesophageal varices. Cirrhosis is not always distinguishable from chronic hepatitis. **GOALS:** To identify low-risk patients who can be spared upper endoscopy irrespective of a diagnosis of

cirrhosis. **STUDY:** We evaluated 13 nonendoscopic variables as predictors of esophagogastric varices in 254 patients with hepatitis B or hepatitis C-related chronic liver disease who underwent upper endoscopy. **RESULTS:** Any size varices occurred in 30.3% (77/254), and large varices in 12.2% of patients (31/254). Age >50 years [odds ratio (OR): 11.29; 95% confidence interval (CI): 2.33-54.67], platelet count <150,000/mm<sup>3</sup> (OR: 4.40; 95% CI: 1.85-10.45), albumin <3.6 g/dL (OR: 2.99; 95% CI: 1.31-6.79), and aspartate aminotransferase/alanine aminotransferase ratio >1 (OR: 2.83; 95% CI: 1.26-6.34) independently predicted varices by logistic regression. Using a score based on age >50 years, platelets <150,000/mm<sup>3</sup>, and aspartate aminotransferase/alanine aminotransferase ratio >1 (1 point/predictor), only 3.2% of patients with a score <2 had varices, all small. **CONCLUSIONS:** Patients with chronic viral hepatitis and a score <2 need not undergo upper endoscopy, as they are unlikely to have large varices. Because about 50% of our patients had this score, 50% of upper endoscopies may be safely avoided.

**R1626 plus peginterferon Alfa-2a provides potent suppression of hepatitis C virus RNA and significant antiviral synergy in combination with ribavirin.** Pockros PJ, et al. Hepatology. 2008 Jun 20; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18570306&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18570306&dopt=Abstract)

R1626, a prodrug of the hepatitis C virus (HCV) RNA polymerase inhibitor R1479, showed time-dependent and dose-dependent reduction of HCV RNA levels in a previous study. The present study evaluated the efficacy and safety of R1626 administered for 4 weeks in combination with peginterferon alfa-2a +/- ribavirin in HCV genotype 1-infected treatment-naïve patients. Patients were randomized to: DUAL 1500 (1500 mg R1626 twice daily [bid] + peginterferon alfa-2a; n = 21); DUAL 3000 (3000 mg R1626 bid + peginterferon alfa-2a; n = 32); TRIPLE 1500 (1500 mg R1626 bid + peginterferon alfa-2a + ribavirin; n = 31); or standard of care (SOC) (peginterferon alfa-2a + ribavirin; n = 20). At 4 weeks HCV RNA was undetectable (<15 IU/mL) in 29%, 69%, and 74% of patients in the DUAL 1500, DUAL 3000, and TRIPLE 1500 arms, respectively, compared with 5% of patients receiving SOC, with respective mean reductions in HCV RNA from baseline to week 4 of 3.6, 4.5, 5.2, and 2.4 log<sub>10</sub> IU/mL. Synergy was observed between R1626 and peginterferon alfa-2a and between R1626 and ribavirin. There was no evidence of development of viral resistance. Adverse events (AEs) were mainly mild or moderate; seven patients had nine serious AEs (including one patient with one serious AE in SOC). The incidence of Grade 4 neutropenia was 48%, 78%, 39%, and 10% in DUAL 1500, DUAL 3000, TRIPLE 1500, and SOC, respectively, and was the main reason for dose reductions. **CONCLUSION:** A synergistic antiviral effect was observed when R1626 was combined with peginterferon alfa-2a +/- ribavirin; up to 74% of patients had undetectable HCV RNA at week 4. Dosing of R1626 was limited by neutropenia; a study of different dosages of R1626 in combination with peginterferon alfa-2a and ribavirin is underway.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**Impact of immunosuppressive regimen on survival of kidney transplant recipients with hepatitis C.** : Luan FL, et al. Transplantation. 2008 Jun 15;85(11):1601-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18551066&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18551066&dopt=Abstract)

**BACKGROUND:** Hepatitis C virus (HCV) infection is common among end-stage renal disease patients receiving hemodialysis and a kidney transplant. HCV-positive kidney transplant recipients have worse clinical outcomes than those who are HCV negative. The optimal immunosuppressive

regimen in this group of patients remains uncertain. **METHODS:** Using data obtained from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients, we studied the impact of induction and maintenance immunosuppression on risk of patient death, with death-censored graft failure and death with a functioning graft as secondary endpoints. Cox regression analysis was used to estimate hazard ratios (HR) adjusted for donor, recipient, and transplant variables. A total of 3708 HCV-positive and 75,629 HCV-negative kidney transplant recipients were analyzed. **RESULTS:** Patient survival was negatively affected by HCV-positive serology. Among HCV-positive kidney transplant recipients, a reduced HR for patient death was observed with the use of induction therapy (HR=0.75, 95% CI 0.61-0.90, P=0.003) and with the use of mycophenolate mofetil (HR=0.77, 95% CI 0.64-0.92, P=0.005). **CONCLUSIONS:** In kidney transplant recipients with HCV-positive serology, the use of antibody induction did not negatively affect patient survival and the use of mycophenolate mofetil as part of maintenance immunosuppression was associated with better patient survival.

**Proteasome activation by hepatitis C core protein is reversed by ethanol-induced oxidative stress.** Osna NA, et al. *Gastroenterology*. 2008 Jun;134(7):2144-52

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18549882&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18549882&dopt=Abstract)

**BACKGROUND & AIMS:** The proteasome is a major cellular proteinase. Its activity is modulated by cellular oxidants. Hepatitis C core protein and ethanol exposure both cause enhanced oxidant generation. The aim was to investigate whether core protein, by its ability to generate oxidants, alters proteasome activity and whether these alterations are further affected by ethanol exposure.

**METHODS:** These interactions were examined in Huh-7 cell lines that expressed inducible HCV core protein and/or constitutive cytochrome P450 2E1 (CYP2E1) and as purified components in a cell-free system. Chymotrypsin-like proteasome activity was measured fluorometrically. **RESULTS:** Proteasome activity in core-positive 191-20 cells was 20% higher than that in core-negative cells and was enhanced 3-fold in CYP2E1-expressing L14 cells. Exposure of core-positive cells to glutathione ethyl ester, catalase, or the CYP2E1 inhibitor diallyl sulfide partially reversed the elevation of proteasome activity in core-positive cells, whereas ethanol exposure suppressed proteasome activity. The results indicate that proteasome activity was up-regulated by low levels of core-induced oxidative stress but down-regulated by high levels of ethanol-elicited stress. These findings were partially mimicked in a cell-free system. Addition of core protein enhanced the peptidase activity of purified 20S proteasome containing the proteasome activator PA28 and was further potentiated by addition of liver mitochondrial and/or microsome fractions. However, proteasome activation was significantly attenuated when fractions were obtained from ethanol-fed animals. **CONCLUSIONS:** HCV core protein interacts with PA28, mitochondrial, and endoplasmic reticulum proteins to cause low levels of oxidant stress and proteasome activation, which is dampened during ethanol metabolism when oxidant generation is higher.

**Iron increases translation initiation directed by internal ribosome entry site of hepatitis C virus.** Cho H, Lee HC, Jang SK, & Kim YK. *Virus Genes*. 2008 Jun 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18566883&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18566883&dopt=Abstract)

Although increased liver iron in individuals with chronic hepatitis C virus (HCV) is associated with a poor response to interferon therapy, the underlying molecular mechanisms are poorly understood. In this study, we show that iron enhances the translation initiation mediated by the internal ribosome entry site (IRES) of HCV. We also demonstrate by UV cross-linking analysis that specific

cellular proteins bind to HCV 5' untranslated region (5' UTR) in an iron-dependent manner. Notably, p85 and p110 are competed out for their binding to HCV 5' UTR when excess amounts of iron-responsive element (IRE) competitor RNAs are treated. This indicates that at least these two factors are common proteins for binding to HCV 5' UTR and IRE. Our results, taken together, suggest that intracellular iron modulates the iron sensing pathway and HCV IRES-dependent translation by changing the binding affinities of the common cellular factors to IRE and HCV IRES, respectively. As a consequence, the coordinated regulation of gene expression by intracellular iron could provide favorable conditions for HCV proliferation.

### **CD81 is a central regulator of cellular events required for HCV infection of human hepatocytes.**

Bazzoli M, et al. J Virol. 2008 Jun 25[Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18579606&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18579606&dopt=Abstract)

Infection with hepatitis C virus (HCV) is still a major public health problem, and the events leading to hepatocyte infection are not yet fully understood. Combining confocal microscopy with biochemical analysis and studies of infection requirement using pharmacological inhibitors and siRNAs, we show here that engagement of CD81 activates the Rho GTPase family members Rac, Rho and Cdc42, and that the block of these signaling pathways drastically reduces HCV infectivity. Activation of Rho GTPases mediates actin-dependent relocalization of the HCV-E2/CD81 complex to cell-cell contact areas where CD81 gets in contact with the tight junction proteins occludin, ZO-1 and claudin-1, recently described as a HCV co-receptor. Finally, we show that CD81 engagement activates the Raf/MEK/ERK signaling cascade and that this pathway affects post-entry events of the virus life cycle. In conclusion, we describe a range of cellular events that are manipulated by HCV to coordinate interactions with its multiple co-receptors and to establish productive infections and find that CD81 is a central regulator of these events.

### **Hepatitis C virus infection, mixed cryoglobulinemia cryoglobulinemia and BLyS**

**upregulation: Targeting the infectious trigger, the autoimmune response, or both?** De Vita S, Quartuccio L, & Fabris M. Autoimmun Rev. 2008 Jun 24[Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18589005&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18589005&dopt=Abstract)

Mixed cryoglobulinemia syndrome (MCsn) is a systemic vasculitis prevalently mediated by immune complexes, i.e., mixed cryoglobulins, and characterized by non-neoplastic B-cell lymphoproliferation favouring the progression into frank B-cell non-Hodgkin lymphoma (NHL) in 5-10% of patients. The hepatitis C virus (HCV) infection is the etiologic agent in the large majority of MCsn cases and chronic antigenic stimulation by HCV is considered a key mechanism sustaining the proliferation of the RF-secreting B-cell clones. Besides chronic antigenic stimulation, cytokines and growth factors may also play a key role in sustaining B-cell overactivation. B-lymphocyte stimulator (BlyS) was recently described as a critical survival factor for B cells, promoting their activation and maturation. Abnormal production of BLyS alters immune tolerance by allowing the survival of autoreactive B cells, thus triggering autoimmune disorders. BlyS inhibits B-cell apoptosis, and B-cell apoptosis is implicated in the pathogenesis of MCsn, as well as of other autoimmune diseases. Both antiviral therapy and B-cell depletive therapy in MCsn may influence BlyS expression. Antiviral therapy, monotherapy against biologic targets downstream viral infection, or the combination of the two, should be optimized in the single patient and stage of the disease, based on disease pathobiology, efficacy and safety issues.

**Combinations of a cyclophilin inhibitor NIM811 with HCV NS3-4A protease or NS5B polymerase inhibitors enhance antiviral activity and suppress the emergence of resistance.**

Mathy JE, Ma S, Compton T, & Lin K. Antimicrob Agents Chemother. 2008 Jun 30 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18591281&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18591281&dopt=Abstract)

Chronic hepatitis C virus (HCV) infection remains a major global health burden while current interferon-based therapy is suboptimal. Efforts to develop more effective antiviral agents mainly focus on two viral targets, NS3-4A protease and NS5B polymerase. However, resistant mutants against these viral specific inhibitors emerge quickly both in vitro and in patients particularly in the case of monotherapy. An alternative and complementary strategy is to target host factors such as cyclophilins that are also essential for viral replication. Future HCV therapies will most likely be combinations of multiple drugs of different mechanisms to maximize antiviral activity and to suppress the emergence of resistance. Here, the effects of combining a host cyclophilin inhibitor NIM811 with other viral specific inhibitors were investigated in vitro using HCV replicon. All the combinations led to more pronounced antiviral effects than any single agent with no significant increase of cytotoxicity. Moreover, the combination of NIM811 with a nucleoside (NM107) or a non-nucleoside (thiophene-2-carboxylic acid) polymerase inhibitor was synergistic, while the combination with a protease inhibitor (BILN2061) was additive. Resistant clones were selected in vitro with these inhibitors. Interestingly, it was much more difficult to develop resistance against NIM811 than viral specific inhibitors. No cross-resistance was observed among these inhibitors. Most notably, NIM811 was highly effective in blocking the emergence of resistance when used in combination with viral protease or polymerase inhibitors. Taken together, these results illustrate the significant advantages of combining inhibitors targeting both viral and host factors as key components of future HCV therapies.

**Elevated serum ALT levels during pegylated interferon monotherapy may be caused by hepatic iron overload.** Nagashima M, et al. Intervirology. 2008;51 Suppl 1:76-85

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18544952&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18544952&dopt=Abstract)

**OBJECTIVE:** Persistently elevated serum alanine aminotransferase (ALT) levels have been observed in chronic hepatitis C (CHC) patients during pegylated interferon (PEG-IFN) therapy. We investigated whether elevated serum ALT levels during PEG-IFN therapy are associated with iron overload. **METHODS:** Sixty-three CHC patients treated with PEG-IFNalpha-2a monotherapy were evaluated. The associations between elevated serum ALT levels ( $>$  or  $=70$  IU/l) were investigated before and 24 weeks after therapy. We classified patients as follows: patients with no elevated serum ALT levels (group NE:  $n = 35$ ), patients with elevated serum ALT levels (group E:  $n = 28$ ), and patients with no elevated serum ALT level and negative HCV RNA (group NE-:  $n = 24$ ), and patients with elevated serum ALT level and negative HCV RNA (group E-:  $n = 19$ ). We also compared total iron score (TIS) and fibrosis stage in liver specimens obtained before and during therapy from 3 patients with elevated serum ALT levels. **RESULTS:** Serum ferritin levels were significantly increased after 24 weeks compared to baseline levels in group E ( $218 \pm 273$  vs.  $438 \pm 308$  ng/ml;  $p < 0.0001$ ) and group E- ( $146 \pm 152$  vs.  $410 \pm 291$  ng/ml;  $p < 0.0001$ ). Serum ALT and ferritin levels were significantly correlated after 24 weeks. The liver specimens revealed that TIS and fibrosis progressed during therapy. **CONCLUSION:** Our findings suggest that the elevation in serum ALT levels during therapy is caused by iron overload which may be induced by PEG-IFNalpha-2a.

**Low levels of hepatitis C virus (HCV) neutralizing antibodies in patients coinfecting with HCV and human immunodeficiency virus.** Castelain S, et al. *J Infect Dis.* 2008 Jun 17; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18558868&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18558868&dopt=Abstract)

The hepatitis C virus (HCV) neutralizing antibody (nAb) response in 37 subjects with HCV monoinfection and 37 HCV-infected subjects with well-controlled human immunodeficiency virus (HIV) infection was evaluated using a focus reduction neutralization assay. HCV nAb levels were retrospectively studied in both groups of patients, who were matched on the basis of sex, age, and HCV genotype. The mean HCV nAb level (+/- standard deviation) among coinfecting patients ([Formula: see text]) was significantly less than that among monoinfected patients ([Formula: see text]) ([Formula: see text]). Lower HCV nAb titers in coinfecting patients could help worsen the outcome of HCV infection. These results favor starting HCV therapy as soon as possible in coinfecting patients.

**Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe.** Landes M, et al. *HIV Med.* 2008 Jun 11; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18554310&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18554310&dopt=Abstract)

**OBJECTIVES** The aim of the study was to investigate the prevalence of and risk factors for hepatitis C or B virus (HCV or HBV) coinfection among HIV-infected pregnant women, and to investigate their immunological and virological characteristics and antiretroviral therapy use.

**METHODS** Information on HBV surface antigen (HBsAg) positivity and HCV antibody (anti-HCV) was collected retrospectively from the antenatal records of HIV-infected women enrolled in the European Collaborative Study and linked to prospectively collected data. **RESULTS** Of 1050 women, 4.9% [95% confidence interval (CI) 3.6-6.3] were HBsAg positive and 12.3% (95% CI 10.4-14.4) had anti-HCV antibody. Women with an injecting drug use(r) (IDU) history had the highest HCV-seropositivity prevalence (28%; 95% CI 22.8-35.7). Risk factors for HCV seropositivity included IDU history [adjusted odds ratio (AOR) 2.92; 95% CI 1.86-4.58], age (for >=35 years vs. <25 years, AOR 3.45; 95% CI 1.66-7.20) and HBsAg carriage (AOR 5.80; 95% CI 2.78-12.1). HBsAg positivity was associated with African origin (AOR 2.74; 95% CI 1.20-6.26) and HCV seropositivity (AOR 6.44; 95% CI 3.08-13.5). Highly active antiretroviral therapy (HAART) use was less likely in HIV/HCV-seropositive than in HIV-monoinfected women (AOR 0.34; 95% CI 0.20-0.58). HCV seropositivity was associated with a higher adjusted HIV RNA level (+0.28log<sub>10</sub> HIV-1 RNA copies/mL vs. HIV-monoinfected women; P=0.03). HIV/HCV-seropositive women were twice as likely to have detectable HIV in the third trimester/delivery as HIV-monoinfected women (AOR 1.95; P=0.049). **CONCLUSIONS** Although HCV serostatus impacted on HAART use, the association between HCV seropositivity and uncontrolled HIV viraemia in late pregnancy was independent of HAART.

**Prevalence of infection with hepatitis B and C virus and coinfection with HIV in medical inpatients in Malawi.** Nyirenda M, et al. *J Infect.* 2008 Jul;57(1):72-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18555534&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18555534&dopt=Abstract)

**BACKGROUND:** Coinfection with hepatitis B (HBV) or hepatitis C (HCV) adversely affects the prognosis of HIV infection and vice versa, and results in complex interactions with antiretroviral therapy. These infections are common in sub-Saharan Africa but there are few data on prevalence of coinfection. All three components of the most common ART regimen used in Africa, stavudine, lamivudine and nevirapine, can cause hepatic problems and lamivudine resistant HBV is known to emerge after HBV monotherapy in coinfecting patients. Point of care (POC) tests for HBV and HCV are widely used but have not been validated in field tests in sub-Saharan Africa. **METHODS:** Prospective observational study of sequential adult inpatients in medical wards of a large urban teaching hospital in Malawi in 2004. Comparison of demographic risk factors with HIV antibody status determined using local double POC test protocols, and with HBsAg and HCV antibody prevalence as estimated in a reference laboratory in Liverpool, UK. Results of locally performed POC tests for HBV using Determine HBsAg (Abbott) and for HCV antibody using HCV-SPOT (Genelabs) were compared with results of reference methods in the UK. **RESULTS:** Of 226 adults (39% male), median (range) age 35 (14-80) years, 81% had a history of traditional scarification, 12% a history of blood transfusion and 11% a history of jaundice. HIV antibodies were present in 76.1%, HBsAg in 17.5% and HCV in 4.5%, with HIV/HBV coinfection in 20.4% and HIV/HCV coinfection in 5% of those with HIV. There was no correlation between prevalence of any of the three viruses and demographic risk factors or presence of either of the other two viruses. Point of care tests gave misleading results with prevalence estimates of 38% for HBV and 4.5% for HCV. For both of these POC tests the performance indices were unacceptable for individual patient management or epidemiological survey purposes. **CONCLUSIONS:** The high prevalence of hepatitis/HIV coinfections may impact on treatment with antiretroviral therapy, especially if there are unintended interruptions of therapy, and studies are needed to document the possible clinical impact on ART programmes. The poor performance of POC tests for HBV and HCV may be due to local operational problems or to unexpected technical issues not revealed by early validation tests. These tests are widely used in resource poor settings and should be revalidated in prospective field studies in areas of the tropics with high HIV prevalence rates.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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### **The pharmacokinetics of silymarin is altered in patients with hepatitis C virus and nonalcoholic fatty liver disease and correlates with plasma caspase-3/7 activity.**

Schrieber SJ, et al. Drug Metab Dispos. 2008 Jun 19; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18566043&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18566043&dopt=Abstract)

**BACKGROUND/AIMS:** Silymarin, used by 30 - 40% of liver disease patients, is comprised of 6 major flavonolignans each of which may contribute to silymarin's hepatoprotective properties. Previous studies have only described the pharmacokinetics for two flavonolignans, silybin A and silybin B, in healthy volunteers. The aim of this study was to determine the pharmacokinetics of the major silymarin flavonolignans in liver disease patients. **METHODS:** Healthy volunteers and three patient cohorts were administered a single, 600 mg oral dose of milk thistle extract and fourteen blood samples were obtained over 24 hours. **RESULTS:** Silybin A and B accounted for 43% of the exposure to the sum of total silymarin flavonolignans in healthy volunteers and only 31 - 38% in liver disease cohorts due to accumulation of silychristin (20 - 36%). AUC<sub>0-24h</sub> for the sum of total silymarin flavonolignans were 2.4-, 3.3-, and 4.7-fold higher for hepatitis C virus (HCV) noncirrhosis, nonalcoholic fatty liver disease ( $p \leq 0.03$ ), and HCV cirrhosis cohorts ( $p \leq 0.03$ ), respectively, compared to healthy volunteers (AUC<sub>0-24h</sub>=2021 ng\*h/ml). Caspase-3/7 activity

correlated with the AUC<sub>0-24h</sub> for the sum of all silymarin conjugates among all subjects ( $R^2=0.52$ ), and was 5-fold higher in HCV cirrhosis cohort ( $p \leq 0.005$  vs healthy). No correlation was observed with other measures of disease activity including plasma ALT, IL-6, and 8-isoprostane F<sub>2</sub>alpha, a measure of oxidative stress. **CONCLUSIONS:** These findings suggest that the pharmacokinetics of silymarin is altered in patients with liver disease. Patients with cirrhosis had the highest plasma caspase-3/7 activity and also achieved the highest exposures for the major silymarin flavonolignans.

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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### **Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients.**

Lup Scedil Or M, et al. J Gastrointestin Liver Dis. 2008 Jun;17(2):155-163

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18568136&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18568136&dopt=Abstract)

**AIM.** The current study aims to assess the role of the histological parameters in liver biopsy for explaining the variance of liver stiffness, as well as the performance of transient elastography in quantifying liver fibrosis in patients with chronic hepatitis C. **METHODS.** 324 consecutive CHC patients were prospectively included in this study. All of them had positive HCV-RNA in serum and had undergone percutaneous liver biopsy for grading and staging the diseases (METAVIR scoring system). All were referred to liver stiffness measurement 1 day prior to biopsy. **RESULTS.** Liver stiffness values were strongly correlated with fibrosis ( $r=0.759$ ,  $p < 0.0005$ ). They also correlated with steatosis ( $r=0.255$ ,  $p < 0.0005$ ), necroinflammatory activity ( $r=0.378$ ,  $p < 0.0005$ ) and hepatic iron deposition ( $r=0.143$ ,  $p=0.03$ ). The univariate regression analysis demonstrated that fibrosis ( $\text{sq.R}=0.610$ ,  $p < 0.0005$ ), activity ( $\text{sq.R}=0.145$ ,  $p < 0.0005$ ) and steatosis ( $\text{sq.R}=0.037$ ,  $p=0.002$ ) were correlated with liver stiffness. In multiple regression analysis, all three variables independently influenced liver stiffness: fibrosis ( $p < 0.0005$ ), activity ( $p=0.039$ ) and steatosis ( $p=0.025$ ). Together they explained 62.4% of the variance of the liver stiffness. The areas under ROC curve for the diagnosis of fibrosis F $\geq$ 1, F $\geq$ 2, F $\geq$ 3, and F=4 were 0.936, 0.862, 0.910 and 0.938, for the cut-off values of 4.9 kPa, 7.4 kPa, 9.1 kPa and 11.85 kPa respectively. **CONCLUSIONS.** Transient elastography is a useful method for chronic hepatitis C assessment. Fibrosis is the main predictor of liver stiffness, but activity and steatosis also influence liver stiffness.

### **Probabilistic graphical model, Network-based medical tool for the prognosis of chronic hepatitis C patients treated with peginterferon plus ribavirin.**

Trapero-Marugan M, et al. Aliment Pharmacol Ther. 2008 Jun 12; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18549464&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18549464&dopt=Abstract)

**AIMS:** To develop an easy bioinformatics-platform based on algorithm decisions (Bayesian network) for a more efficient prediction of treatment response. **PATIENTS AND METHODS:** 385 consecutive CHC treated patients were included. More than 40 variables were analysed. Data from 308 patients were used to build the variable model network using dLife-platform based on probabilistic-graphical-models. The prediction accuracy of the bioinformatics-network was compared to the true data collected in a retrospective study. The model was then validated twice with external data from CHC patients treated in other hospitals. **RESULTS:** The accuracy of this bioinformatics network for treatment response in our 308 patients was 83.3%, which is higher than accuracy obtained by physicians based on the study of clinical data and their own experience (50-

65%). The ROC curve areas after validation with another cohort of patients were: 0.91 for SVR, 1 for non-response, and 0.81 for relapse. dLife offered a diagnostic accuracy of 81.3%, which is a clear improvement compared to unassisted prognosis (50-65%). **CONCLUSION:** dLife accurately predicts the outcome of CHC combination therapy, improving treatment decisions and reducing costs. This bioinformatics platform allows integrating widespread data sources and permits to predict the clinical outcome of a particular patient using a general probabilistic-graphical-model.

**Usefulness of a new immunoradiometric assay of HCV core antigen to predict virological response during PEG-IFN/RBV combination therapy for chronic hepatitis with high viral load of serum HCV RNA genotype 1b.** Sasase N, et al. Intervirology. 2008;51 Suppl 1:70-5  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18544951&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18544951&dopt=Abstract)

We investigated the clinical usefulness of a new immunoradiometric (IRM) assay of hepatitis C virus (HCV) core antigen in predicting virological response during pegylated interferon plus ribavirin (PEG-IFN/RBV) combination therapy for chronic hepatitis with high viral loads of serum HCV RNA genotype 1b. Thirty-nine patients received a regimen of PEG-IFNalpha-2b (1.5 microg/kg/week s.c.) in combination with RBV (600-1,000 mg/day). Of the 39 patients, 18 (46.2%) achieved sustained virological response (SVR), 11 (28.2%) attained partial response (PR) and 10 (25.6%) showed no response (NR). Four weeks after the start of therapy, 1- and 2-log reductions in the amount of HCV core antigen were observed in 20 (2/10) and 0% (0/10) showing NR, 91 (10/11) and 63.6% (7/11) with PRs, and 88.9 (16/18) and 55.6% (10/18) of patients with SVR, respectively. The 1- and 2-log reductions 4 weeks after the start of therapy were not a defining condition for PR and SVR. The amount of HCV core antigen was significantly different between SVR and PR patients on days 1 and 7, and between patients with NR and SVR at all points of time. In conclusion, this new IRM assay is useful in predicting virological response during PEG-IFN/RBV therapy.

**The development of a qualitative real-time RT-PCR assay for the detection of hepatitis C virus.** Clancy A, Crowley B, Niesters H, & Herra C. Eur J Clin Microbiol Infect Dis. 2008 Jun 13 [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18551325&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18551325&dopt=Abstract)

Real-time polymerase chain reaction (PCR) represents a favourable option for the detection of hepatitis C virus (HCV). A real-time reverse transcriptase PCR (RT-PCR) assay was developed as a qualitative diagnostic screening method for the detection of HCV using the ABI PRISM(R) 7500 Sequence Detection System. The primers and probe were designed to target the 5'-untranslated region of the hepatitis C viral genome. A second heterologous probe assay was developed for the detection of the haemagglutinin gene of phocine distemper virus (PDV) and was used as an internal control. A semi-automated HCV extraction method was also implemented using the ABI PRISMtrade mark 6100 Nucleic Acid PrepStation. The HCV assay was optimised as a qualitative singleplex RT-PCR assay with parallel testing of the target and internal control. The assay results (n = 200) were compared to the COBAS AMPLICORtrade mark HCV Test v2.0 assay. The assay demonstrated a high rate of sensitivity (99%), specificity (100%) and an acceptable limit of detection (LOD) of 100 IU/ml. The development of a qualitative multiplex assay for the simultaneous detection of HCV and internal control indicates the same high rates of sensitivity and specificity. This sensitive real-time assay may prove to be a valuable method for the detection of HCV.

**Development and evaluation of a sensitive enzyme-linked oligonucleotide-sorbent assay for detection of polymerase chain reaction-amplified hepatitis C virus of genotypes 1-6.** Huang RY, et al. J Virol Methods. 2008 Jun 17 [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18565599&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18565599&dopt=Abstract)

A high-throughput polymerase chain reaction (PCR)-based enzyme-linked oligonucleotide-sorbent assay (ELOSA) was developed for use in the diagnostic testing of serum from patients who may be infected with different hepatitis C virus (HCV) genotypes. Twelve genotype-specific 5'-aminated DNA-coated probes were designed based on the variable 5'-untranslated region sequences of the HCV genotypes 1-6. Using 100 clinical serum samples, the performance of the PCR-ELOSA method was compared with Roche's COBAS Amplicor HCV Monitor V2.0 assay and the VERSANT HCV genotype assay (LiPA), and the overall agreement was 99% at the level of HCV genotypes with a detection range of  $2.0 \times 10^2$  to  $1.0 \times 10^7$  IU/ml for PCR-ELOSA. The PCR-ELOSA was more comprehensive as demonstrated by the fact that approximately 20% of the samples with different subtypes could be discriminated by this method but not by LiPA. In addition, the PCR-ELOSA system showed high accuracy ( $CV \leq 6.36\%$ ) and even higher reproducibility ( $CV \leq 5.55\%$ ). Thus, this novel PCR-ELOSA system provides a sensitive and versatile alternative to current HCV detection assays.

**HCV infection in voluntary donors and its influence on recruitment of donors in chongqing area.** Zhao SM, et al. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2008 Jun;16(3):676-80

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18549653&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18549653&dopt=Abstract)

Blood donor recruitment models have changed from paid donors to employer-organized donors and to voluntary donors in China. Reports on the hepatitis C virus (HCV) infection among voluntary blood donors in China have been rarely found at present. The prevalence of anti-HCV and genotypes among the first-time voluntary blood donors was investigated in Chongqing area of China. A total of 13620 serum samples were collected from the first-time voluntary blood donors in Chongqing, China. Anti-HCV antibody was tested by ELISA. The Core/E2 region of HCV RNA from HCV seropositive samples was amplified by RT-PCR for genotyping. The results indicated that the prevalence of anti-HCV averaged 0.49% (67/13620), and the highest rate (0.86%) was obtained in the group aged 40 to 49. A higher prevalence was observed among the more educated donors, and metropolitan donors. The ratios of following genotypes 1b, 2a, 3a and 3b were 4 (18%), 5 (23%), 9 (41%) and 4 (18%) in all the 22 samples respectively. Genotype 3 (3a and 3b) was the predominant genotype. **In conclusion**, the prevalence of anti-HCV was low among the population of voluntary blood donors in Chongqing area. The genotyping results showed the possibility of presence of druggies among the voluntary blood donors. Therefore, more attention should be paid to exclude those high-risk persons from the volunteers.

**Previously infected chimpanzees are not consistently protected from reinfection or persistent infection following reexposure to the identical hepatitis C virus strain.** Bukh J, et al. J Virol. 2008 Jun 11; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18550671&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18550671&dopt=Abstract)

Protective immunity following resolved hepatitis C virus (HCV) infection has been reported. However, the breadth of this immunity has remained controversial and the role of neutralizing antibodies has not been well defined. In the present study, two chimpanzees (CH96A008 and

CH1494) with resolved monoclonal H77C (genotype 1a) infection were re-challenged with low-dose homologous H77C virus about 12 months after viral clearance; CH96A008 became persistently infected and CH1494 had transient viremia lasting 2 weeks. CH1494 was subsequently either partially or completely protected following five homologous re-challenges with monoclonal H77C or polyclonal H77, and after 6 heterologous re-challenges with HC-J4 (genotype 1b) or HC-J6 (genotype 2a) viruses. Subsequently, a final challenge with H77C resulted in persistent HCV infection. In both chimpanzees, serum neutralizing antibodies against retroviral pseudo-particles bearing the H77C envelope proteins were not detected during the initial infection and during re-challenge. However, anamnestic cellular immune responses developed during the initial homologous re-challenge, in particular in CH96A008, which developed a persistent infection. Polyprotein sequences of viruses recovered from CH1494 after the two homologous re-challenges that resulted in transient viremia were identical with the H77C virus. In contrast, the polyprotein sequences of viruses recovered from both chimpanzees following homologous re-challenge resulting in persistent infection had numerous changes. These findings have important implications for our understanding of immunity against HCV; even in the best-case scenario with autologous re-challenge, low-level viral persistence was seen in the presence of primed T-cell responses.

**Factors associated with quality of life in chronic hepatitis C patients who received interferon plus ribavirin therapy.** Chang SC, et al. J Formos Med Assoc. 2008 Jun;107(6):454-62  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18583216&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18583216&dopt=Abstract)

**BACKGROUND/PURPOSE:** Antiviral treatment leading to impaired quality of life in chronic hepatitis C patients has been reported in the West. To promote high quality care, we explored the quality of life in Taiwanese chronic hepatitis C patients treated with antiviral therapy by means of comparing quality of life, social support and its factors. **METHODS:** One hundred and fifteen patients with chronic hepatitis C, enrolled from hospitals in Central Taiwan, were treated with interferon plus ribavirin. A structured questionnaire was used for data collection, including the Hepatitis Quality of Life Questionnaire (HQLQ), Inventory of Socially Supportive Behaviors (ISSB) and clinical demographics. The data were analyzed by the methods of means, correlation and regression. **RESULTS:** The study patients included 60 men (52.2%) and 55 women (47.8%), with 98 (85.2%) older than 40 years. The drug expenses of 71 (61.7%) patients were paid for by the Bureau of National Health Insurance of Taiwan. The patients had a low mean HQLQ score of 58.13 +/- 17.21. Three scales which had HQLQ scores below 50 were general health perceptions (49.39), vitality (49.32) and role disability: physical (47.48). The mean ISSB score was 71.15 +/- 19.61. Only financial stress ( $p = 0.006$ ) had significant difference in HQLQ. Treatment duration ( $r = -0.23$ ) correlated negatively with the general health domain of HQLQ, and tangible support ( $r = -0.21$ ) correlated negatively with HQLQ scales. Financial stress and tangible support were significant predicting variables for HQLQ. **CONCLUSION:** The study found that patients with chronic hepatitis C who received interferon plus ribavirin therapy had poor quality of life during the treatment period. There was significant difference among patients with different financial stress, and a negative relationship between tangible support and hepatitis quality of life. Financial stress and tangible support are predictors of quality of life for all subjects. The results of this study might assist healthcare personnel to comprehend the quality of life and its related factors in patients with chronic hepatitis C treated with antiviral therapy.

**Extended-therapy duration for chronic hepatitis C, genotype 1: The long and the short of it.** Pearlman BL., World J Gastroenterol. 2008 Jun 21;14(23):3621-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18595128&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18595128&dopt=Abstract)

With pegylated interferon and ribavirin, more than half of all chronically-infected hepatitis C patients can achieve a sustained virologic response; however, patients with genotype 1 infections and those with other poor prognostic factors have relatively inferior treatment response rates. Since new therapies are still years away from approval, it is incumbent upon providers to maximize the therapeutic efficacy of today's treatment. The later the virus is undetectable in serum during treatment, the less likely it will be eradicated. Patients with a delayed or slow virologic response to therapy (at least a 2-log(10) decrease in baseline hepatitis C RNA yet detectable viremia at 12 wk of therapy and undetectable virus 12 wk subsequently) may, therefore, benefit from an extended therapy course beyond one of standard duration. Although higher rates of treatment discontinuation may plague this approach, 72 wk of treatment for genotype 1-infected slow-responders may improve response rates and diminish relapse rates relative to those of 48 wk. Based on data from both viral kinetic and clinical studies, therapy prolongation in slow responders may be a reasonable strategy to improve response rates in these treatment-refractory patients.

**Anti-hepatitis C virus-positive blood donors: are women any different?** Narciso-Schiavon JL, et al. *Transfus Med.* 2008 Jun;18(3):175-83

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18598280&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18598280&dopt=Abstract)

We sought to assess clinical, epidemiological, biochemical, serological and histological characteristics of anti-hepatitis C virus (HCV)-positive female blood donors and compare them with men. As women are frequently the minority among blood donors, studies evaluating this population usually reflect characteristics of male gender. This retrospective study included 380 blood donors with confirmed positive anti-HCV. The mean age was 36.9 +/- 11.3 years and 33.2% were women. Compared with men, female donors showed higher prevalence of prior transfusion of blood products (P = 0.031) and lower prevalence of intravenous drug use (P = 0.001) and alcohol abuse (P < 0.001). Women exhibited lower medians of alanine aminotransferase (P < 0.001) and gamma-glutamyltransferase (P < 0.001). They also showed higher platelet count (P < 0.001) and prothrombin activity (P = 0.049), and a lower frequency of antibody against core antigen of hepatitis B virus (anti-HBc) positivity (P = 0.032). A higher proportion of spontaneous viral clearance (P = 0.001) and a lower frequency of viraemia (P < 0.001) were observed among women. On liver biopsy, women had lower prevalence of fibrosis stage > or = 2. Multivariate analysis identified age (OR = 1.050, 95% CI: 1.019-1.081, P = 0.001) and anti-HBc positivity (OR = 2.184, 95% CI: 1.010-4.722, P = 0.047) as independent predictors of significant fibrosis. Female blood donors presented higher prevalence of spontaneous viral clearance as well as biochemical and histological evidence of less advanced liver disease. These findings could be because of intrinsic characteristics of female gender or secondary to associated factors such as younger age or anti-HBc positivity.