

Caring Ambassadors Hepatitis C Program Newsletter  
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**CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

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**Response to therapy with pegylated interferon and ribavirin for chronic hepatitis C in hispanics compared to non-hispanic whites.** Yu S, Douglass JM, Qualls C, Arora S, Dunkelberg JC. *Am J Gastroenterol.* 2009 May 12. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19436272?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19436272?ordinalpos=7&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVES:** Ethnicity has been shown to play an important role in hepatitis C virus (HCV) treatment response. However, few studies have examined the treatment response of Hispanics to combination therapy with pegylated interferon and ribavirin. The aim of this study was to compare the treatment responses of Hispanics and non-Hispanic whites (NHW) treated with pegylated interferon and ribavirin for chronic HCV. **METHODS:** A retrospective review was conducted of all treatment-naïve Hispanics and NHW with HCV who were treated at the University of New Mexico Hospital or Albuquerque VA Medical Center between October 2001 and January 2007. Genotype 1 patients received 48 weeks of therapy with pegylated interferon and ribavirin; genotype 2 and 3 patients received 24 weeks of treatment. **RESULTS:** A total of 396 patients were included in the analysis, consisting of 179 Hispanics and 217 NHW. Overall, fewer Hispanics completed therapy compared with NHW (64.8% vs. 80.2%,  $P < 0.001$ ). In genotype 1 patients, early virologic response (EVR), end-of-treatment response (ETR), and sustained virologic response (SVR) did not differ significantly between the two ethnic groups. In genotype 2 and 3 patients, Hispanics had similar EVR compared with NHW (81.3% vs. 88.2%,  $P = 0.25$ ), but lower ETR (64.1% vs. 83.1%,  $P = 0.01$ ) and SVR (45.3% vs. 75.3%,  $P < 0.001$ ). After correcting for patients who prematurely discontinued therapy, genotype 2 and 3 Hispanics continued to have a reduced SVR compared with NHW (65.9% vs. 87.3%,  $P = 0.014$ ). The attenuated SVR in Hispanics was because of a higher relapse rate after achieving ETR compared with NHW (25% vs. 7.5%,  $P = 0.02$ ). **CONCLUSIONS:** Hispanics with genotype 2 and 3 HCV infection treated with pegylated interferon and ribavirin are less likely to achieve SVR compared with NHW. The lower rate of SVR in Hispanic patients is, in part, because of an increased rate of relapse after ETR.

**Artichoke leave extract for chronic hepatitis C - A pilot study.** Huber R, Müller M, Naumann J, Schenk T, Lüdtke R. *Phytomedicine.* 2009 May 7. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19427774?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19427774?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Artichoke leave extracts (ALE) have hepatoprotective properties and are used by patients with chronic liver disease. Effects in patients with chronic hepatitis C are unclear. **METHODS:** 17 patients with chronic hepatitis C and persistently elevated aminotransferase levels were treated for 12 weeks with 3200mg standardized ALE per day. Primary outcome parameter was

the rate of alanine aminotransferase (ALT) normalisation after 12 weeks. Secondary parameters were the course of ALT, aspartate aminotransferase and gamma glutamyltransferase levels, quantitative HCV RNA, subjective symptoms frequently associated with chronic hepatitis C (fatigue, discomfort upper abdomen, joint problems) and safety. **RESULTS:** None of the patients had normalized ALT levels after 12 weeks of treatment. There was no significant change of aminotransferase levels or viral load compared to baseline levels. Fatigue and joint problems significantly improved after 4 weeks of treatment. However, after 12 weeks, there was no significant difference to baseline. Tolerability of ALE was rated as good to excellent. Severe side effects did not occur. **CONCLUSION:** ALE seem not to be effective to improve aminotransferase levels in patients with chronic hepatitis C.

**Positive and negative prediction of sustained virologic response at weeks 2 and 4 of treatment with albinterferon alfa-2b or peginterferon alfa-2a in treatment-naïve patients with genotype 1, chronic hepatitis C.** Neumann AU, Pianko S, Zeuzem S, Yoshida EM, et al. *J Hepatol.* 2009 Mar 11. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19447518?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19447518?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND/AIMS:** Albinterferon alfa-2b is a novel, long-acting, fusion polypeptide that is dosed q2wk or q4wk. The predictive value of early virologic response during albinterferon alfa-2b or peginterferon alfa-2a treatment was investigated in interferon-naïve patients with genotype 1, chronic hepatitis C. **METHODS:** Four hundred and fifty-eight patients were randomized to: albinterferon 900 or 1200µg q2wk, or 1200µg q4wk, or peginterferon 180µg qwk. HCV RNA was measured by real-time PCR. A linear exhaustive search algorithm was used to determine the best SVR prediction algorithm in the per-protocol population (n=368), with inclusion of key ITT analyses to assess impact. **RESULTS:** SVR rate: 54-67% (P=NS between arms). Rapid initial virologic response rate at week 2 (RIVR; viral decline >2log<sub>10</sub>IU/mL) was 32-50% and gave rise to positive predictive value of 88-97% for SVR. No initial virologic response at week 4 (NIVR; viral decline <2log<sub>10</sub>IU/mL; viral load >5.5log<sub>10</sub>IU/mL) demonstrated a 100% negative predictive value for SVR. A sequential prediction algorithm based on viral kinetics at weeks 2 and 4 identified four prediction groups that reliably predicted SVR, positively or negatively, in 65-72% of patients. **CONCLUSIONS:** Improved SVR prediction was obtained by integrating absolute levels and reduction of HCV RNA at treatment week 2 and 4. Patients with RIVR had a high likelihood of achieving SVR.

**Overestimation of liver fibrosis staging using transient elastography in patients with chronic hepatitis C and significant liver inflammation.** Vispo E, Barreiro P, Del Valle J, et al. *Antivir Ther.* 2009;14(2):187-93.

[http://www.ncbi.nlm.nih.gov/pubmed/19430093?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19430093?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Transient elastography (TE) is a non-invasive method that allows liver fibrosis staging on the basis of hepatic stiffness measurements. Little is known about the influence of chronic liver inflammation on the stiffness of hepatic tissue. **METHODS:** A total of 112 patients with chronic hepatitis C underwent a liver biopsy and TE. **RESULTS:** Mean values of liver stiffness (in kPa) by inflammation strata were 4.8, 6.4, 9.4 and 12.6 for A0, A1, A2 and A3, respectively, in hepatitis C virus (HCV)-monoinfected individuals (P=0.018). These figures were 8.0, 10.4, 12.9 and 12.6 for A0, A1, A2 and A3, respectively, in HIV-HCV-coinfected patients (P=0.35). In HCV-monoinfected patients with fibrosis staging F3-F4, mean liver stiffness was greater if inflammation was ≥A2 versus A0-A1 (14.6 versus 6.2 kPa; P=0.04). By contrast, no differences in liver stiffness

according to inflammation were seen in HCV-monoinfected patients with <F3 or in HIV-HCV-coinfected patients regardless of liver fibrosis staging. Among HCV-monoinfected patients, mean liver stiffness was greater for alanine aminotransferase >100 versus <100 IU/l (10.5 versus 8.5 kPa; P=0.04). **CONCLUSIONS:** The extent of liver inflammation might affect the accuracy of TE for staging liver fibrosis, particularly in HCV-monoinfected patients with advanced fibrosis on liver biopsy and/or increased alanine aminotransferase levels.

**Epidemiological, immunological and clinical characteristics of acute hepatitis C.** Boykinova OB, Stoilova YD, Tsvetkova TZ, Baltadjiev IG. *Folia Med (Plovdiv)*. 2009 Jan-Mar;51(1):61-9. [http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Boykinova%20OB%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Boykinova%20OB%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**The aim of the study** was to make a clinical and epidemiological and immunological characteristic of patients with acute hepatitis C infection (AHC). **PATIENTS AND METHODS:** The study included 178 patients with AHC; they were studied in terms of clinical course, biochemical constellations, T and B lymphocyte subpopulations, level of TNF-alpha in the blood serum, presence of autoantibodies, and the outcome of the disease in a five-year follow-up period. Methods: anti-HCV (EIA), HCV-RNA (PCR), HCV genotyping; ALT, AST, AP, gamma-GT; ultrasonography and liver biopsy. **RESULTS:** AHC incidence increased six-fold between 2000 and 2006. The prevalence of the disease among intravenous drug-users (IDUs) was 46.07%. Young people (31.71 +/- 1.21) and males (67.98%) were prevalent. The genotype HCV-1 was prevalent. AHC ran with icterus in 70.22% of all cases, while it was anicteric in 29.78%; ALT-activity was high--it was mean 1007.94 +/- 59.87 U/l; intrahepatic cholestasis was found in 38.80%. A light form of the disease was found in 43.26%, mild--in 50.56%, and severe--in 6.18%, without reaching acute liver failure. In the acute stage of the disease, an increase of helper/inducer CD3+CD4+ (p = 0.001), memory T helper CD4+CD29+ (p < 0.0001), activated CD3+HLA-DR+ (p < 0.0001), mature CD3+ T cells (p < 0.05), naive CD2+T (p < 0.01), and B-lymphocytes CD19+ (p < 0.001) was found, together with a non-significant increase of the suppressor/cytotoxic CD3+CD8+ T lymphocytes in comparison with the controls. The total killer CD56+ were reduced, as well as the MHC restricted killer cells CD8+CD56+. TNF-alpha was elevated in the serum in the light and mild forms (p < 0.0001). The participation of non-organ-specified antibodies (NOSAs) was minimal. Anti-MLA titer was 1/80 in two patients. Five years after the outset of AHC, a spontaneous viral clearance was established in 36.67% and chronic hepatitis in 63.33%. **CONCLUSION:** Despite the initially activated immune cellular response strongly correlating with a well expressed cytolytic syndrome around 2/3 of the AHC patients develop a chronic form of the disease.

**Weight related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial.** Everhart JE, Lok AS, Kim HY, Morgan TR, et al.

*Gastroenterology*. 2009 May 12. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19445938?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19445938?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND AND AIMS:** With the limited efficacy of current therapy for chronic hepatitis C, modifiable risk factors for liver disease progression are important to identify. Because obesity is associated with liver disease, we examined the effects of weight related conditions on disease outcomes in the HALT-C trial. **METHODS:** Of 1050 patients, 985 could be evaluated for pre-defined progression of liver disease not related to hepatocellular carcinoma. Clinical outcomes were determined over 3.5 years for all patients and progression to cirrhosis on protocol biopsy among patients who had bridging fibrosis (56.5% of cohort) at entry. **RESULTS:** At study entry, median

BMI was high (29.2 kg/m<sup>2</sup>) and accompanied by other weight related conditions, including diabetes (24.9%), high median waist circumference, and insulin resistance (by HOMA 2 IR). Among non-invasive measures, HOMA 2 IR was most strongly associated with outcomes with hazard ratio (HR) of 1.26 per quartile increase (95% confidence interval (CI) 1.09-1.45). Presence of steatosis on baseline biopsy was associated with an increased outcome rate among patients with bridging fibrosis (p < 0.0001) and a decreased rate among patients with cirrhosis (p = 0.006). Presence of Mallory bodies was associated with outcomes (HR = 1.59, 95% CI 1.10-2.31) as was significant weight change of at least 5 percent in the first year after randomization (HR=1.25 per category increase in weight, 95% CI 1.01-1.55). **CONCLUSIONS:** Insulin resistance, histological features of fatty liver disease, and weight change were associated with outcomes of chronic hepatitis C. Improvement in these weight related factors might modify disease progression.

**Evaluation of VCH-759 monotherapy in hepatitis C infection.** Cooper C, Lawitz EJ, Ghali P, Rodriguez-Torres M, et al. J Hepatol. 2009 Apr 23. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19446909?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19446909?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** VCH-759 is a non-nucleoside inhibitor of HCV RNA-dependent polymerase with sub-micromolar IC<sub>50</sub> values versus genotype 1a/1b replicons. **METHODS:** The antiviral activity, pharmacokinetics and tolerability of VCH-759 administered as monotherapy for 10 days with a 14 day follow-up period were evaluated in 31 treatment-naïve genotype 1 participants. Three cohorts received: 400mg thrice (t.i.d.), 800mg twice (b.i.d.), 800mg t.i.d or placebo. **RESULTS:** VCH-759 was well tolerated with the most frequent adverse event being gastrointestinal upset in both the active and placebo groups attributable, in part, to the dosing vehicle. VCH-759 was rapidly absorbed and trough plasma levels were at or above the IC<sub>90</sub> (non protein-adjusted) for all dosing regimens. The mean maximal decrease in HCV RNA log<sub>10</sub> (IU/mL) was 1.97, 2.30 and 2.46 for 400mg t.i.d., 800mg b.i.d. and 800mg t.i.d. doses. Viral polymerase genotypic sequencing revealed emergence of HCV variants in a majority of participants that coincided with on-treatment viral rebound. **CONCLUSIONS:** VCH-759 was well tolerated and achieved a 2 log<sub>10</sub> decline in HCV RNA with 800mg b.i.d. and t.i.d. doses. In a subset of participants, viral rebound was observed and associated with resistant variants. This data supports further evaluation of VCH-759 in combination with interferon-ribavirin treatment.

**Treatment of hepatitis C virus carriers with persistently normal alanine aminotransferase levels with peginterferon alpha-2a and ribavirin: a multicentric study.** Puoti C, Pellicelli AM, Romano M, et al. Liver Int. 2009 Apr 17. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19422478?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19422478?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**ABSTRACT BACKGROUND/AIMS:** To evaluate, in clinical practice, the efficacy and safety of combined antiviral treatment in hepatitis C virus (HCV) carriers with normal alanine aminotransferase (ALT) levels. **METHODS:** Eighty-eight HCV carriers with persistently normal ALT levels were enrolled. All patients received peginterferon (PEG-IFN) alpha-2a 180 µg once weekly plus ribavirin (RBV) 800 mg/day for 24 weeks (HCV-2 and -3) or 1000-1200 mg/day for 48 weeks (HCV-1). **RESULTS:** Rapid virological response (RVR) was seen in 66/88 patients (75%): 19/32 HCV-1 (59%), 40/46 HCV-2 (87%) and 7/10 HCV-3 patients. Younger patients, leaner subjects and patients with non-1 genotype or lower baseline HCV RNA levels were more likely to achieve an RVR. Sustained virological response (SVR) was seen in 69/88 patients (78%): 20/32 HCV-1 patients (62%), 41/46 HCV-2 patients (89%) and 8/10 (80%) HCV-3 patients. The overall SVR rate was 88% in patients with RVR (58/66) and 50% in those without RVR.

**CONCLUSIONS:** The combination of PEG-IFN alpha-2a and RBV produces, in patients with normal ALT, virological response rates that are comparable or even higher than those obtained in patients with elevated ALT levels. Thus, we suggest that in selected cases immediate therapy might be preferred to a 'wait-and-see' policy.

**The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin.** Ogawa E, Furusyo N, Toyoda K, Takeoka H, Maeda S, Hayashi J. *Antiviral Res.* 2009 Apr 14. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19443053?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19443053?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**The aim of this study** was to assess the association between liver stiffness measured by transient elastography (FibroScan((R))) and the efficacy of pegylated interferon alpha-2b plus ribavirin combination treatment for patients with chronic hepatitis C virus (HCV) infection. We prospectively studied 145 Japanese patients with chronic HCV infection. FibroScan was done at baseline, at the end of treatment, and at 48 and 96 weeks after the end of treatment. The FibroScan values were significantly decreased for sustained virological response (SVR) patients (the mean rate of change; -16.2%, -32.2% and -43.5%) in comparison with non-SVR patients (-7.2%, -2.1% and +17.3%) at the end of treatment (P=0.0127), and 48 weeks (P<0.0001) and 96 weeks (P<0.0001) after the end of treatment. Among the non-SVR patients, the FibroScan values were significantly decreased for patients with biochemical response (BR) (-17.9%, -30.0% and -27.1%) in comparison with non-BR (-4.1%, +6.4% and +30.6%) at the end of treatment (P=0.0270), and 48 weeks (P<0.0001) and 96 weeks (P<0.0001) after the end of treatment. The FibroScan values may predict a progressively better clinical outcome for patients with successful virological and biochemical responses.

**Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial.** Kharaziha P, Hellström PM, Noorinayer B, et al. *Eur J Gastroenterol Hepatol.* 2009 May 16. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kharaziha%20P%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kharaziha%20P%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** End-stage liver disease is a medical problem with high morbidity and mortality. We have investigated the feasibility, safety, and efficacy of using autologous mesenchymal stem cells (MSCs) as a treatment. **METHODS:** Eight patients (four hepatitis B, one hepatitis C, one alcoholic, and two cryptogenic) with end-stage liver disease having Model for End-Stage Liver Disease score  $\geq 10$  were included. Autologous MSCs were taken from iliac crest. Approximately, 30-50 million MSCs were proliferated and injected into peripheral or the portal vein. Liver function and clinical features were evaluated at baseline and 1, 2, 4, 8, and 24 weeks after injection. **RESULTS:** Treatment was well tolerated by all patients. Liver function improved as verified by the Model for End-Stage Liver Disease score, which decreased from  $17.9 \pm 5.6$  to  $10.7 \pm 6.3$  (P<0.05) and prothrombin complex from international normalized ratio  $1.9 \pm 0.4$  to  $1.4 \pm 0.5$  (P<0.05). Serum creatinine decreased from  $114 \pm 35$  to  $80 \pm 18$   $\mu\text{mol/l}$  (P<0.05). Serum albumin changed from  $30 \pm 5$  to  $33 \pm 5$  g/l and bilirubin from  $46 \pm 29$  to  $41 \pm 31$   $\mu\text{mol/l}$ . No adverse effects were noted. **CONCLUSION:** Our data show that MSCs injection can be used for the treatment of end-stage liver disease with satisfactory tolerability. Furthermore, this treatment may improve clinical indices of liver function in end-stage liver disease.

**Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the heart and soul study.** Tsui JI, Whooley

MA, Monto A, Seal K, Tien PC, Shlipak M. [15: J Card Fail. 2009 Jun;15(5):451-6. Epub 2009 Feb 10.

[http://www.ncbi.nlm.nih.gov/pubmed/19477406?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19477406?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** How hepatitis C virus (HCV) affects coronary heart disease (CHD) risk factors and outcomes is largely unknown. **METHODS AND RESULTS:** Among a cohort of patients with stable CHD, we examined the association between HCV seropositivity and levels of inflammatory markers (C-reactive protein [CRP], fibrinogen, interleukin-6, and tumor necrosis factor [TNF]-alpha) and risk for the following outcomes: death, cardiovascular (CV) events, and heart failure events. A total of 84 (8.6%) participants were found to be seropositive for HCV. HCV-seropositive patients were found to have significantly lower adjusted mean levels of CRP (2.6 vs. 4.4;  $P < .01$ ) and fibrinogen (340 vs. 398;  $P < .01$ ), but higher levels of TNF-alpha (7.1 vs. 4.8;  $P < .01$ ). Age-adjusted rates for HCV seropositive vs. seronegative were as follows: death 93 vs. 42/1,000p-y ( $P < .01$ ), CV events 62 vs. 40 ( $P = .13$ ), and heart failure 76 vs. 29 ( $P < .01$ ). After adjustment for demographic and clinical factors, HCV remained significantly associated with an increased risk for heart failure events (HR=2.13; 95% CI: 1.19-3.80). **CONCLUSIONS:** In this cohort with CHD, HCV seropositive participants had higher rates of death, CV events, and heart failure hospitalizations during follow-up. After adjustment for CV risk factors, HCV seropositivity remained independently associated with risk for heart failure events.

#### **Peginterferon alpha-2b and ribavirin for the treatment of chronic hepatitis C in Japanese pediatric and young adult patients: a survey of the Japan Society of Pediatric Hepatology.**

Tajiri H, Inui A, Kiyohara Y, Suzuki M, Kagimoto S, Etani Y, Shimizu T, Fujisawa T. Eur J Gastroenterol Hepatol. 2009 May 23. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19474745?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19474745?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVES:** Only a few studies on the treatment with peginterferon-2b and ribavirin are available in children with chronic hepatitis C virus (HCV). The aim of this study was to evaluate both the efficacy and the safety of the treatment in Japanese children and young adults.

**METHODS:** Twenty-two of 41 members of the Japan Society of Pediatric Hepatology reported on 37 cases who were treated with peginterferon and ribavirin. **RESULTS:** Of the 37 patients, 29 have completed the treatment and all of them cleared the HCV virus. Three patients are still being treated, whereas the remaining five failed to complete the treatment. Cessation of the treatment was because of the nonresponsiveness ( $n=3$ ), the expense of the treatment ( $n = 1$ ), or lethargy ( $n=1$ ). After excluding the three patients, who were continuing the treatment and one who has not completed the 24-week follow-up period, from the 37 patients, 33 were available for sustained virologic response (SVR) analysis. After 4 weeks of follow-up, one of the 33 relapsed. An intention-to-treat analysis showed that 27 of the 33 (81.8%) achieved a SVR. The only factor significantly associated with SVR was their virologic response status at week 4. **CONCLUSION:** The results showed that the present patients infected with HCV and treated with peginterferon-2b and ribavirin achieved a remarkably high SVR rate. In addition, most of the patients achieved a SVR once they showed a virologic response at week 4. The combination of peginterferon-alpha with ribavirin may be considered as a standard therapy for children and young adults.

**Absence of intrafamilial transmission of hepatitis C virus and low risk for sexual transmission in rural central Africa indicate a cohort effect.** Ndong-Atome GR, Njouom R, Padilla C, et al. J Clin Virol. 2009 May 25. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19473878?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19473878?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Intrafamilial and sexual transmission of hepatitis C virus (HCV) are still being debated, and little is known about such transmission in central Africa. **OBJECTIVE:** To examine the rate of intrafamilial transmission of HCV between patients and their household members. **STUDY DESIGN:** A cross-sectional study was conducted in Dienga, a remote village in Gabon, involving 195 household members of 14 index cases of HCV infection. After a questionnaire on the risk factors for parenteral exposure, blood samples were obtained and tested for antibody to HCV by an enzyme immunoassay (Monolisa anti-HCV plus version 2). Positive samples were tested for HCV RNA and genotyped by amplification and phylogenetic analysis of a fragment of the NS5B gene. **RESULTS:** HCV antibody was found in 13/195 (6.7%) household contacts, comprising 5/14 (35.7%) sexual partners and 8/114 (7%) relatives. None of the children of index patients tested positive. HCV RNA was detected in only five household members with HCV antibody. The same genotypes were found in only two of five couples, both couples being sexual partners. Parenteral risk factors were not more likely to be reported by people positive for HCV antibody than by those who were negative. Age over 50 years was the only independent predictor of positivity for HCV antibody. **CONCLUSIONS:** This study indicates, as previously suggested, that the spread of HCV in central Africa is due to a cohort effect, with previous, possibly iatrogenic, transmission rather than intrafamilial or sexual transmission.

**Multiple cytokine profiling of the therapeutic responses to ribavirin and pegylated interferon-alpha2b using an "induction" approach with natural interferon-beta in difficult-to-treat chronic hepatitis C.** Kishida Y, Haruna Y, Naitoh M, Katayama K, Kashiwagi T. J Interferon Cytokine Res. 2009 Jun;29(6):353-68.

[http://www.ncbi.nlm.nih.gov/pubmed/19441887?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19441887?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Cyclic and periodic IFN treatment (CPIT) consisting of induction treatment with nIFN-beta followed by maintenance treatment with IFN-alpha could prevent viral breakthrough and achieve rapid virological response (RVR) and early virological response (EVR) in chronic hepatitis C (CHC). The efficacy and immune response of RBV+PEG-IFN-alpha2b using induction approach with CPIT (novel combination treatment: NCT) in 7 CHC patients with genotype 1b and high viral load were evaluated. A biometric multiplex serum cytokine assay was utilized to characterize the immunomodulatory effect. RVR and EVR were 7/7 and 7/7, respectively. Viral titers dropped below detectable levels in five patients with sustained virological response (SVR) before the end of CPIT (early virological responder: EAVR), and two patients without SVR after the end of CPIT (late virological responder: LAVR). At baseline, in EAVR compared with the controls, IL-6 and IL-15, CXCL-8 and CXCL-10 levels were significantly higher ( $P < 0.05$ ); IL-10 and IL-13 levels were significantly lower ( $P < 0.05$ ); and the IL-12 level was lower. In LAVR, GM-CSF, CXCL-8 and CXCL-10, and CCL-4 levels were significantly higher ( $P < 0.05$ ); and IL-10 and IL-12 were lower than the controls. In EAVR but not LAVR, the IL-12 increased and the CXCL-8 decreased significantly ( $P < 0.05$ ). In conclusion, NCT-induced viral clearance leading to improvement in the innate immune response resulting in SVR in CHC with genotype 1b and high viral load.

**Short-term prolongation of pegylated interferon and ribavirin therapy for genotype 1b chronic hepatitis C patients with early viral response.** Ikeda H, Suzuki M, Okuse C, Yamada N, Okamoto M, Kobayashi M, Nagase Y, et al. Hepatol Res. 2009 May 7. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19467024?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19467024?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**AIM:** We tailored extended treatments using pegylated interferon (PEG IFN) and ribavirin (RBV) to viral responses after initiation of therapy and investigated the efficacy and safety of its therapy for chronic hepatitis C (CHC) patients. **METHODS:** Eighty-two genotype 1b CHC patients were enrolled in the present study. All patients received PEG IFN- $\alpha$ -2b and weight-based RBV therapy. We defined a viral response in which serum HCV-RNA is undetectable at week 4 as rapid viral response (RVR), detectable at week 4 and undetectable by week 12 as early viral response (EVR), and detectable at week 12 and undetectable by week 24 as late viral response (LVR). We set the treatment duration depending on viral response; 48 weeks for RVR patients and 72 weeks for LVR. Furthermore, EVR patients received a short-term extension of treatment duration to 52-60 weeks. We prospectively investigated sustained viral response (SVR) rates of these groups.

**RESULTS:** Overall SVR rate for the total patient group was 57.3%. SVR rates of the RVR, EVR and LVR patients were 100%, 80.5% and 40.0%, respectively. Nine patients could not complete this treatment protocol. Baseline platelet count and mutation in the interferon sensitivity-determining region of NS5A were significant independent predictors of SVR, and amino acid substitution of the core region was a significant independent predictor of non-viral response by multivariate logistic regression analyses. **CONCLUSION:** The results indicate that short-treatment extension of PEG IFN plus RBV treatment protocols in EVR patients can improve overall SVR rates.

### **Interleukin 18 promoter variants (-137G>C and -607C>A) in patients with chronic hepatitis**

**C: Association with Treatment Response.** Haas SL, Weiß C, Bugert P, Gundt J, Witt H, Singer MV, Berg T, Böcker U. J Clin Immunol. 2009 May 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19455410?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19455410?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Recently, two functional IL18 promoter variants, -607C>A (rs1946518) and -137G>C (rs187238), were associated with viral clearance in patients with hepatitis C. The present study focused on their relevance for treatment response. **METHODS:** Seven hundred fifty-seven chronically infected European patients and 791 controls were enrolled in the study. IL18 genotyping was performed by allele-specific PCR. Liver histology was available in 67.9%. **RESULTS:** Genotype and allele frequencies were equally distributed in patients and controls. No significant association with various disease characteristics was observed. However, when comparing patients with sustained virological response (SR) and non-SR, statistically significant associations were found for both variants ( $p = 0.0416$  and  $p = 0.0274$ , respectively). In viral genotype 1, the -607A allele was positively associated with treatment response ( $p = 0.0190$ ; OR 1.537; 95% CI, 1.072-2.205) and the -137G allele with a higher rate of nonresponse ( $p = 0.0302$ ; OR 1.524; 95% CI, 1.040-2.233).

**CONCLUSIONS:** The association of IL18 variants with treatment response in genotype 1 hepatitis C patients implies a predictive and modifying role of these genetic variants.

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

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### **Novel serum markers of fibrosis progression for the follow-up of hepatitis C virus-infected patients.**

Caillot F, Hiron M, Gorla O, et al. [14: Am J Pathol. 2009 May 28. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19477948?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19477948?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Liver biopsy is considered the gold-standard method for the assessment of liver fibrosis during follow-up of hepatitis C virus-infected patients, but this invasive procedure is not devoid of complications. The aim of the present study was to identify novel non-invasive markers of fibrosis progression. By microarray analysis, we compared transcript levels in two extreme stages of fibrosis

from 16 patients. Informative transcripts were validated by real-time PCR and used for the assessment of fibrosis in 23 additional patients. Sixteen transcripts were found to be dysregulated during the fibrogenesis process. Among them, some were of great interest because their corresponding proteins could be serologically measured. Thus, the protein levels of inter-alpha inhibitor H1, serpin peptidase inhibitor clade F member 2, and transthyretin were all significantly different according to the four Metavir stages of fibrosis. In conclusion, we report here that dysregulation, at both the transcriptional and protein levels, exists during the fibrogenesis process. Our description of three novel serum markers and their potential use as serological tests for the non-invasive diagnosis of liver fibrosis open new opportunities for better follow-up of hepatitis C virus-infected patients.

**Diabetes pattern on the 75 g oral glucose tolerance test is a risk factor for hepatocellular carcinoma in patients with hepatitis C virus.** Konishi I, Hiasa Y, Shigematsu S, et al. *Liver Int.* 2009 Apr 17. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19422477?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19422477?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**ABSTRACT BACKGROUND:** Patients with hepatitis C virus (HCV) frequently show glucose intolerance. Diabetes mellitus (DM) has been proposed to be a risk factor for hepatocellular carcinoma (HCC). **AIMS:** The aim of this study is to clarify the influence of glucose intolerance as evaluated by the 75 g oral glucose tolerance test (OGTT) on hepatocarcinogenesis in patients with HCV. **METHODS:** This study was carried out in a cohort of 197 patients with HCV who had not been previously diagnosed as having DM. All patients underwent the 75 g OGTT at entry. They were also screened for HCC and, thereafter, the rate of hepatocarcinogenesis was compared between the patients with and without glucose intolerance. **RESULTS:** Based on the results of the 75 g OGTT, 125 (63%) had normal glucose tolerance (NGT), 49 (25%) had impaired glucose tolerance (IGT) and 23 (12%) had the DM pattern. HCC occurred more frequently in patients with the DM pattern than in patients with either NGT or IGT. Even in patients without advanced liver fibrosis, HCC was more frequently observed in patients with DM than in patients with NGT. A multiple logistic regression analysis showed advanced liver fibrosis, the DM pattern on the 75 g OGTT, an older age and gamma-glutamyltransferase to all be independent risk factors related to hepatocarcinogenesis. **CONCLUSIONS:** A DM pattern on the 75 g OGTT was thus found to be associated with hepatocarcinogenesis and the 75 g OGTT is considered to be useful for identifying this risk factor for HCC in patients with HCV.

**Progress towards improving antiviral therapy for hepatitis C with hepatitis C virus polymerase inhibitors. Part I: Nucleoside analogues.** Brown NA. *Expert Opin Investig Drugs.* 2009 May 9. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19426125?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19426125?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** With an increasing worldwide burden of liver failure and liver cancer from chronic hepatitis C virus (HCV) infection, discovery and development efforts for new antiviral medicines for HCV are expanding rapidly. Two HCV protease inhibitors (PIs), telaprevir (VX950) and boceprevir (SCH503034), are now furthest along in clinical development, with Phase II data suggesting a potential treatment advance with triple combination regimens comprising a protease inhibitor, pegylated interferon and ribavirin. However, the current data suggest that such regimens will fail to produce sustained virologic responses in  $\geq 30 - 40\%$  of patients, and tolerance of interferon/ribavirin treatment regimens is often problematic; hence, there is a need for continued development of new anti-HCV agents to further optimize treatment efficacy and safety. The HCV

polymerase (HCV Pol) is an attractive target for antiviral therapy because the gene sequences encoding HCV Pol are relatively conserved across the six main HCV genotypes and the emergence of viral resistance is expected to be relatively slow for pharmaceutical agents, such as nucleoside analogues, that are targeted to the active (catalytic) site of HCV Pol. **METHODS:** This review (Part I) of HCV Pol inhibitors focuses on the scientific rationale and recent development progress for nucleoside-type HCV Pol inhibitors; a subsequent review (Part II) will assess progress with non-nucleosidic HCV Pol inhibitors. **RESULTS/CONCLUSIONS:** Early clinical data for several nucleosides targeted to HCV Pol indicate marked antiviral effects and a likelihood of relatively slow HCV resistance, consistent with the profile of nucleosidic inhibitors of HIV and hepatitis B virus infection and supporting potentially important roles for nucleoside agents in optimizing combination therapies for HCV infection. Optimally effective future anti-HCV therapies are likely to be based on multi-class treatment regimens combining polymerase and PIs, together with pegylated interferon and ribavirin or pharmaceutical agents from other mechanistic classes.

**Prediction of asymptomatic cirrhosis in chronic hepatitis C patients: accuracy of artificial neural networks compared with logistic regression models.** Cazzaniga M, Salerno F, Borroni G, Ceriani R, Stucchi G, et al. *Eur J Gastroenterol Hepatol.* 2009 Jun;21(6):681-7.

[http://www.ncbi.nlm.nih.gov/pubmed/19445042?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19445042?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVE:** Models based on logistic regression analysis are proposed as noninvasive tools to predict cirrhosis in chronic hepatitis C (CHC) patients. However, none showed to be sufficiently accurate to replace liver biopsy. Artificial neural networks (ANNs), providing a prediction based on nonlinear algorithms, can improve the diagnosis of cirrhosis, a syndrome characterized by complex, nonlinear biological alterations. We compared ANNs with two logistic regression analysis-based models in predicting CHC histologically proven cirrhosis. **METHODS:** Liver biopsy was obtained in CHC patients of two different cohorts (an internal cohort including 244 patients and an external cohort including 220 patients). One hundred and forty-four patients from the internal cohort served as a training set to construct ANNs and a logistic regression model (LOGIT). These two models and the aspartate aminotransferase-to-platelet ratio index (APRI) were tested in the remaining 100 patients (internal validation set) and in the external cohort (external validation set). Diagnostic performances were evaluated by standard indices of accuracy. **RESULTS:** In the internal validation set, ANNs, LOGIT, and APRI showed similar discrimination powers (0.88, 0.87, and 0.87 respectively). However, ANNs showed the best positive predictive value (0.86 vs. 0.67 and 0.56) and positive likelihood ratio (40.2 vs. 13.4 and 8.4). In the external validation set, the discrimination power of ANNs (0.76) was significantly higher than those of LOGIT (0.67) and APRI (0.67). **CONCLUSION:** Compared to conventional models, ANNs performance in predicting CHC cirrhosis is slightly better and more reproducible.

**T(CD8) response in diverse outcomes of recurrent exposure to hepatitis C virus.** Bharadwaj M, Thammanichanond D, Aitken CK, et al. *Immunol Cell Biol.* 2009 May 12. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19434069?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19434069?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**To analyse** the immune correlates in a setting of recurrent exposure to hepatitis C virus (HCV), we studied T(CD8) responses in injecting drug users (IDUs) with different disease outcomes. Ex vivo HCV-specific T(CD8) responses assessed by interferon-gamma (IFN $\gamma$ ) enzyme-linked immunospot (ELISPOT) were comparable in human lymphocyte antigen (HLA)-matched IDUs with spontaneous HCV clearance or persistent infection. A detailed characterization of these T(CD8) cells in age and HLA-matched IDUs demonstrated that HCV clearance and protection

from reinfection correlated with HCV-specific T(CD8) cells that could proliferate in vitro, possessed cytotoxic potential and produced IFN $\gamma$  and tumour-necrosis factor- $\alpha$ , rather than with the circulating frequency of responding T(CD8) cells determined ex vivo. While validating the importance of multifunctional T(CD8) in mediating protection in IDUs with recurrent exposure to HCV our findings highlight that the magnitude and/or breadth of HCV-specific T(CD8) determined in ex vivo ELISPOT may not be the sole determinant of protection especially in a setting of recurrent exposure.

**King's Score: an accurate marker of cirrhosis in chronic hepatitis C.** Cross TJ, Rizzi P, Berry PA, Bruce M, Portmann B, Harrison PM. Eur J Gastroenterol Hepatol. 2009 May 7. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19430302?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19430302?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVES:** Histological assessment of patients with chronic hepatitis C infection is no longer performed routinely; consequently, a simple test is needed to identify patients with significant hepatic fibrosis. **METHODS:** Data were collected, retrospectively, on 923 consecutive patients undergoing percutaneous liver biopsy for chronic hepatitis C at King's College Hospital between 1 January 2000 and 30 June 2006; 602 patients were accepted to form the training set and a further 105 patients to form the validation set. **RESULTS:** On liver biopsy, 132 (22%) had cirrhosis (Ishak F5-6) in the training set and 19 (18%) in the validation set. Factors found by multivariate analysis to be associated with fibrosis in the training set were used to construct the King's Score:  $\text{agexaspartate aminotransferase} / \text{international normalized ratio} / \text{platelets}$ . Area under receiver operating characteristic curves for predicting cirrhosis and significant fibrosis (F3-6) were 0.91 and 0.79, respectively. A King's Score of greater than or equal to 16.7 predicted cirrhosis in 34% of patients (odds ratio 36.2, 95% confidence interval, 22.0-59.6;  $P < 0.0001$ ) with sensitivity 86%, specificity 80% and a high negative predictive value of 96%; a score greater than or equal to 12.3 predicted F3-6 (odds ratio 33.9, 95% confidence interval, 15.2-34.4;  $P < 0.001$ ). The validation set confirmed the utility of this index, area under receiver operating characteristic curves 0.94 and 0.89 for cirrhosis and F3-6, respectively. **CONCLUSION:** The King's Score is a simple and accurate index for predicting cirrhosis in chronic hepatitis C. Patients with a score of less than 16.7 have a low risk of cirrhosis.

**Circulating levels of interferon-gamma in course of hepatitis C virus-related arthritis.**

Tarantino G, Sabatini P, Soriente I, Amato P, Sangiolo MG, Riccio A. J Interferon Cytokine Res. 2009 May 18. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19450146?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19450146?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**The aim** was to weigh the serum concentrations of interferon gamma (IFN- $\gamma$ ), a cytokine that enhances Th1-cell differentiation and suppresses collagen synthesis and angiogenesis, in two apparently distinct diseases, hepatitis C virus-related arthritis (HCVrA) and rheumatoid arthritis (RA), which share some overlapping immunological features. In this study, IFN- $\gamma$  serum levels were assayed by an ELISA method in 21 HCVrA patients and in 16 with RA. Very low IFN- $\gamma$  serum levels were found in five out of 21 patients with HCVrA and only in three out of 16 RA patients. Median value (range) resulted decrease in both HCVrA and RA groups, that is, 0.29 (0.04-1.49) versus 0.20 (0.05-1.18) IU/mL,  $P = 0.58$ . No correlation was evidenced with hepatic and arthritic involvements, nor between IFN- $\gamma$  serum levels and viral replication and moreover with the positivity of antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptides antibodies. **These results** show that IFN- $\gamma$  behavior appears similar in HCVrA and RA

groups reinforcing the lack of significant differences between HCVrA and RA patients. Low circulating levels could be explained with the fact that IFN-gamma is not an isolate cytokine, but a piece of composite system regulated in a complex fashion, with many different factors contributing.

**Modeling hepatitis C virus kinetics: the relationship between the infected cell loss rate and the final slope of viral decay.** Dahari H, Shudo E, Cotler SJ, Layden TJ, Perelson AS. *Antivir Ther.* 2009;14(3):459-64.

[http://www.ncbi.nlm.nih.gov/pubmed/19474480?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19474480?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Patients infected with hepatitis C virus (HCV) who respond to treatment with interferon-alpha plus ribavirin exhibit biphasic or triphasic viral load decreases. While the rapid first phase is indicative of the effectiveness of therapy in blocking viral production ( $\epsilon$ ), the slope of the final phase ( $\lambda$ ), that is, the second phase in biphasic decreases and the third phase in triphasic decreases, depends on the infected cell loss rate ( $\delta$ ). In standard models,  $\lambda$  is approximately  $\epsilon\delta$  when the viral clearance rate  $c \gg \delta$ , as has been previously estimated.

**METHODS:** The relationship among  $\epsilon$ ,  $\delta$ ,  $\lambda$  and the baseline fraction of HCV-infected hepatocytes ( $\pi$ ) was investigated in a model that included proliferation of hepatocytes.

**RESULTS:** We found that  $\lambda$  was not proportional to  $\epsilon$ , but rather obeyed a complex relationship that could lead to dramatic increases in estimates of  $\delta$  as  $\epsilon$  increased. In particular, when  $\epsilon < 99\%$ ,  $\lambda$  moderately underestimated  $\delta$  in patients with a small  $\pi$ , whereas  $\delta$  might be up to 10-fold larger than  $\lambda$  in patients with a large  $\pi$ . Interestingly, when  $\epsilon > 99\%$ ,  $\delta \sim \lambda$  regardless of  $\pi$ . **CONCLUSIONS:** Our results indicated that in patients undergoing therapy who achieved a 2 log(10) reduction in viral load ( $\epsilon < 99\%$ ), previously estimated  $\delta$  values might represent only a minimal estimate of the infected cell loss rate. Moreover, combining interferon-alpha with new antiviral agents to achieve  $\epsilon > 99\%$  should allow for a more accurate estimate of  $\delta$  in HCV RNA kinetic studies. This might be important when using viral kinetics to estimate the effect of the immune response on viral elimination and the attainment of sustained virological response.

**Natural killer cell functional dichotomy in chronic hepatitis B and chronic hepatitis C virus infections.** Oliviero B, Varchetta S, Paudice E, et al. *Gastroenterology.* 2009 May 23. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19470388?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19470388?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND AND AIMS:** The phenotypic and functional characteristics of natural killer (NK) cells in chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are incompletely defined and largely controversial. **METHODS AND RESULTS:** We studied NK cell receptor (NKR) expression, cytotoxic activity and cytokine production in peripheral blood mononuclear cells (PBMC) from 35 patients with chronic hepatitis C, 22 with chronic hepatitis B and 30 healthy controls. Patients with chronic HBV infection had an increased proportion of NKG2C+ NK cells with normal inhibitory receptor expression and a lower proportion of activated NK cells compared with HCV+ patients, which was associated with normal or reduced cytolytic activity and markedly dysfunctional TNF and IFN production. Patients with chronic HCV infection showed a predominantly activating phenotype, featuring a decreased percentage of cells expressing the inhibitory receptor KIR3DL1 and a concomitant increase in the proportion of NKG2D+ NK cells. Expression of the CD69 early activation antigen on NK cells positively correlated with serum alanine aminotransferase and HCV RNA values, suggesting participation of virus-induced effector NK cells in liver necroinflammation. Phenotypic changes in HCV+ patients were associated with

enhanced cytokine-induced cytolytic activity and increased usage of natural cytotoxicity and NKG2D receptor pathways, accompanied by defective cytokine production, although to a lesser extent than patients with chronic HBV infection. **CONCLUSIONS:** These findings provide evidence for a functional dichotomy in patients chronic HBV and HCV infections, featuring conserved or enhanced cytolytic activity and dysfunctional cytokine production which may contribute to virus persistence.

**Age- and sex-related reference ranges of alanine aminotransferase levels in children:**

**European Paediatric HCV Network.** England K, Thorne C, Pembrey L, Tovo PA, Newell ML. J Pediatr Gastroenterol Nutr. 2009 May 19. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19465871?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19465871?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Serum alanine aminotransferase (ALT) levels are commonly used to indicate liver damage. Although elevated levels indicate possible liver injury, abnormalities, or disease, some patients with "normal" ALT levels have minimal to mild liver disease. Recently, ALT reference ranges for adults were queried and revised ranges proposed with lower upper limits of normality. The appropriateness of current paediatric ALT reference ranges is unclear. **MATERIAL AND METHODS:** Hepatitis C virus (HCV)-uninfected children from the European Paediatric HCV Network represent a large population of healthy children born to HCV-infected mothers, with ALT observations collected prospectively from birth. Linear regression identified factors associated with ALT levels while accounting for within-child repeated measurements. ALT centiles stratified by sex were calculated using maximum penalized likelihood methods and LMS software. **RESULTS:** A total of 1293 HCV-uninfected children had 5011 ALT measurements during follow-up. ALT levels significantly decreased with increasing age, whilst ALT levels were significantly lower in girls than boys. Reference cutoffs representing the 95th centiles before 18 months of age were 60 U/L for boys and 55 U/L for girls, decreasing to 40 U/L for boys and 35 U/L for girls after 18 months of age. **CONCLUSIONS:** These reference ranges represent a unique investigation of ALT levels in a healthy child population. We show lower and more detailed age-related cutoffs of normality than available. Additionally, we demonstrate a significant effect of sex on ALT reference ranges, which has not previously been described in children younger than 5 years of age.

**Rifampicin as an oral angiogenesis inhibitor targeting hepatic cancers.** Shichiri M, Fukai N, Kono Y, Tanaka Y. Cancer Res. 2009 May 19. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19458074?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19458074?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Angiogenesis is an important therapeutic target in cancer, and to fully exploit its therapeutic potential, combination chemotherapeutic/antiangiogenic regimens should be optimized and delivered earlier to more patients. Ideally, this could be done by a single potent oral agent with established safety. Rifampicin, a semisynthetic antibiotic derived from the rifamycins, is one of the most commonly used pharmaceutical compounds worldwide in the treatment of tuberculosis. Here, we present the effects of oral rifampicin on human cancer progression and its antiangiogenic properties, which were comparable to the angiogenesis inhibitor endostatin. Clinically, low-dose p.o. administration of rifampicin to six high-risk patients with hepatitis C virus-related liver cirrhosis resulted in a single occurrence of hepatocellular carcinoma during the follow-up period of 97.3 +/- 29.1 (mean +/- SD) months. Experimentally, rifampicin rapidly and markedly down-regulated the expression of a wide spectrum of angiogenesis-associated genes in growing human microvascular endothelial cells, thereby suppressing endothelial cell proliferation and migration. Rifampicin, at higher concentrations, also directly inhibited the growth of a variety of human cancer cells. P.o.

administration of rifampicin significantly inhibited in vivo growth and metastases of subcutaneous human cancer xenografts. Thus, the potent antiangiogenic properties of oral rifampicin therapy were effective in suppressing cancer progression. It provides a promising new addition to antiangiogenic strategies for designing human cancer therapies. Considering the clinical pharmacokinetics of rifampicin, which enters the enterohepatic circulation and undergoes subsequent hepatic accumulation, it may be especially beneficial as an antitumor agent targeting hepatobiliary tumors.

**Toward the back-up of boceprevir (SCH 503034): discovery of new extended P(4)-capped ketoamide inhibitors of hepatitis C virus NS3 serine protease with improved potency and pharmacokinetic profiles.** Bogen SL, Pan W, Ruan S, Nair LG, Arasappan A, et al. J Med Chem. 2009 May 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19456105?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19456105?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Hepatitis C is the most prevalent liver disease. Viral hepatitis C (HCV), a small (+)-RNA virus, infects chronically an estimated 300 million people worldwide. Results of Phase I clinical studies with our first generation HCV inhibitor Boceprevir, SCH 503034 (1), presented at the 56th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) were encouraging, and thus, additional human clinical studies are underway. In view of the positive data from our first generation compound, further work aimed at optimizing its overall profile was undertaken. Herein, we report that extension of our earlier inhibitor to the P(4) pocket and optimization of the P(1)' capping led to the discovery of new ketoamide inhibitors of the HCV NS3 serine protease with improved in vitro potency. In addition to being potent inhibitors of HCV subgenomic RNA replication, some of the new P(4)-capped inhibitors were also found to have improved PK profile.

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## HIV/HCV COINFECTION

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**Characteristics of hepatitis C virus co-infection in a human immunodeficiency virus-infected population with lower reported rates of injection drug use.** Burton MJ, Olivier J, Mena L. Am J Med Sci. 2009 May 26. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19474656?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19474656?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Injection drug use (IDU) is considered the major risk factor for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection. We examined risk factors for HIV/HCV coinfection in a region with a low reported rate of IDU. **METHODS:** We identified 146 HIV/HCV coinfecting patients in Jackson, Mississippi. Medical records were reviewed for demographics, social history, and risk factors for HIV and HCV acquisition. A randomly selected group of HIV-monoinfected patients from the same clinic served as a control group. **RESULTS:** History of IDU ( $P < 0.0001$ ), crack cocaine use ( $P < 0.0001$ ), incarceration ( $P < 0.0001$ ), and syphilis ( $P < 0.0001$ ) were significantly associated with HCV infection in this cohort of HIV patients. However, the reported rate of IDU (32.5%) is lower than other published HIV/HCV-infected cohorts. **CONCLUSIONS:** HIV/HCV patients in Mississippi are less likely to report a history of IDU than other coinfecting populations, suggesting an alternative means of HCV transmission. Further studies are needed to examine the role of syphilis, crack cocaine use, and incarceration as risk factors for HCV infection in this population of HIV patients.

**HAART is associated with lower hepatic necroinflammatory activity in HIV-hepatitis C virus-coinfected patients with CD4 cell count of more than 350 cells/microl at the time of liver biopsy.** Pascual-Pareja JF, Caminoa A, Larrauri C, González-García J, Montes ML, Díez J, Grande M, Arribas JR. AIDS. 2009 May 15;23(8):971-5.

[http://www.ncbi.nlm.nih.gov/pubmed/19425223?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19425223?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVE:** To evaluate the impact of HAART on the liver damage of HIV-hepatitis C virus (HCV)-coinfected patients with relatively preserved immune status. **DESIGN:** Cross-sectional study of liver biopsies. **METHODS:** HIV-HCV-coinfected patients who underwent liver biopsies and had a CD4 cell count of at least 350 cells/microl at the time of liver biopsy were included. Exclusion criteria included positive hepatitis B surface antigen and prior anti-HCV therapy.

Necroinflammatory activity and fibrosis was scored by the Scheuer fibrosis staging system. Steatosis was scored according to the percentage of hepatocytes affected. Logistic regression analysis was used to assess determinants of necroinflammatory activity of at least 3. **RESULTS:** One hundred and nineteen HIV-HCV coinfecting patients were included. In the univariate analysis, alcohol abuse, serum alanine aminotransferase levels, steatosis and a high fibrosis score were significantly associated with higher necroinflammatory activity. In the multivariate analysis, a high level of alanine aminotransferase, advanced fibrosis and absence of HAART were associated with higher necroinflammatory activity. **CONCLUSION:** Use of HAART was associated with lower levels of necroinflammatory activity. Necroinflammatory activity was strongly associated with higher fibrosis scores. These results suggest that HAART might decrease hepatitis C activity in HIV-HCV-coinfected patients with CD4 cell count of more than 350 cells/microl.

**Effect of antiviral treatment on serum markers of liver fibrosis in HIV-hepatitis C virus-coinfected patients: the Fibrovic 2 Study - ANRS HC02.** Halfon P, Carrat F, Bédossa P, Lambert J, Pénaranda G, Perronne C, Pol S, Cacoub P. Antivir Ther. 2009;14(2):211-9.

[http://www.ncbi.nlm.nih.gov/pubmed/19430096?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19430096?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Non-invasive liver fibrosis scores have been proposed as alternatives to liver biopsy (LB) in hepatitis C virus (HCV)-infected patients. Here, we aimed to assess the effect of antiviral treatment on non-invasive serological markers of liver fibrosis in HIV-HCV-coinfected patients. **METHODS:** We included 114 HIV-HCV-coinfected patients with LBs performed before and 6 months after the end of treatment (week 72; W72). Fibrotest, the Forn's index, age-platelet ratio index, SHASTA, FIB-4, Hepa-score and Fibrometer scores were assessed. There were 29 (25%) patients who achieved sustained virological response (SVR). **RESULTS:** At baseline (BL), all non-invasive fibrosis scores except the Forn's index did not show significantly lower values in SVR patients. At W72, all non-invasive scores, except Hepascore, showed a significant decrease in SVR patients ( $P < 0.01$ ). There was a significant difference in fibrosis stages on LBs between BL and W72 in SVR and non-SVR patients. **CONCLUSIONS:** In HIV-HCV-coinfected patients, HCV clearance is associated with a significant reduction in non-invasive fibrosis serological markers, which most likely reflect the histological improvement associated with SVR. If confirmed, such results will reinforce the reliability of these markers in the follow-up after HCV treatment.

**Psychiatric and substance use disorders comorbidities in veterans with hepatitis C virus and HIV coinfection.** Fuller BE, Loftis JM, Rodriguez VL, McQuesten MJ, Hauser P. Curr Opin Psychiatry. 2009 May 11. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19436202?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19436202?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**PURPOSE OF REVIEW:** A growing number of veterans in the Veterans Health Administration are coinfecting with HIV and hepatitis C virus. This review covers timely research relative to comorbid conditions that are common in this population including psychiatric diagnoses, substance use disorders and neurocognitive problems. **RECENT FINDINGS:** Current literature on the psychiatric, substance use disorders and cognitive problems of the coinfecting population show that not only are rates of morbidity higher in the coinfecting population but that this affects antiviral treatments as well. There is new evidence that brain injuries and infiltration of the virus into the central nervous system may be responsible for cognitive dysfunction. Cotesting, particularly in hepatitis C infected individuals, is not done routinely despite shared risk factors. **SUMMARY:** With this understanding of the comorbidities of the coinfecting population, integrated healthcare models involving mental health, internal medicine, substance abuse treatment and internal medicine are crucial to work with these medically and psychologically complex patients.

**Chronic hepatitis C in patients coinfecting with human immunodeficiency virus in Japan: a retrospective multicenter analysis.** Yotsuyanagi H, Kikuchi Y, Tsukada K, Nishida K, et al. *Hepato Res.* 2009 Apr 3. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19473427?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19473427?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**AIM:** A nationwide survey in Japan revealed that nearly one-fifth of human immunodeficiency virus (HIV)-positive patients are co-infected with hepatitis C virus (HCV). We conducted a study to further analyze the features of liver disease in HIV-HCV co-infected patients. **METHODS:** We analyzed 297 patients from eight hospitals belonging to the HIV/AIDS Network of Japan.

**RESULTS:** HCV genotypes 1, 2, 3, 4 and mixed genotypes were detected in 55.2, 13.7, 18.9, 0.9 and 11.3% of patients, respectively, in contrast to the fact that only genotypes 1 and 2 are detected in HCV mono-infected patients in Japan. This is compatible with the transmission of HCV through imported blood products contaminated by HCV. Sixteen of 297 HIV-HCV co-infected patients had advanced liver disease accompanied by ascites, hepatic encephalopathy or hepatocellular carcinoma. The average age of such patients was 41.1 +/- 14.0 years, which was much younger than that of HCV mono-infected patients with the same complications. The progression speed of liver disease estimated from the changes in the levels of serum albumin, bilirubin, or platelet was slower in patients who achieved sustained virological response with interferon treatment than in those who did not receive it. The overall sustained virological response rate to interferon treatment was 43.3%.

**CONCLUSIONS:** Our findings suggest that liver disease is more advanced in HIV-HCV co-infected patients than in HCV mono-infected patients, and interferon treatment may retard the progression of liver disease in such patients.

**HCV treatment decision-making substance use experiences and hepatitis C treatment decision-making among HIV/HCV coinfecting adults.** Fink Ogawa LM, Bova C. *Subst Use Misuse.* 2009 May 13:1. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Fink%20Ogawa%20LM%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Fink%20Ogawa%20LM%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Hepatitis C virus (HCV) infection is a major source of morbidity and mortality among substance users and persons living with human immunodeficiency virus (HIV) infection. Treatment for chronic HCV infection involves complex decision-making. These decisions are even more complicated in persons with HIV and substance use related problems. A secondary analyses of qualitative data collected in the United States (2004-2005) with 31 HIV/HCV coinfecting adults (48% women; mean age 44.7 years) revealed three themes related to substance use (substance use

evolution, revolving door: going back out and reconstructing life) and two HCV treatment decision-making themes (HCV infection treatment issues: not a priority, fear, misinformation and get clean and try it). Study limitations and implications are discussed.

**Kidney diseases in HIV/HCV-coinfected patients.** Izzedine H, Sene D, Cacoub P, Jansen H, Camous L, Brocheriou I, Bourry E, Deray G. *AIDS*. 2009 May 12. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19440143?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19440143?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Hepatitis C virus (HCV) co-infection occurs in 25% of HIV-infected persons. The impact of HIV/HCV coinfection on renal and patient outcomes is unclear. **METHODS:** The main objective of the study is the comparison of outcomes (progression to advanced renal failure, initiation of dialysis, and death) in patients with HIV (n = 40), HCV (n = 30) or coinfection (n = 30) during the period between January 1999 and December 2007. **RESULTS:** Patients were predominantly white men with a mean creatinine clearance of 50.6 +/- 32.2 ml per min per 1.73 m. Membranoproliferative glomerulonephritis (MPGN) and HIV-associated nephropathy were found in 34 and 9%, respectively. Seventeen patients needed transitory or definitive hemodialysis after 2, 2.5, and 12 months in HIV/HCV (n = 5), HIV (n = 6) and HCV (n = 6) infections, respectively. In multivariate analysis, variables found to independently predict outcome in HIV/HCV coinfecting patients were younger age, a longer delay to kidney biopsy, cryoglobulinemia and MPGN. Twenty-one patients died, mostly in the HCV (n = 8) and/or HIV/HCV coinfecting (n = 12) groups. The relative risk of death for HIV/HCV co-infected patients was 2.1 times more than for HCV-infected patients and 7.5 times more than for HIV-infected patients. HIV/HCV co-infection [odds ratio (OR), = 4; 95% confidence interval (CI), 1.3-12.9; P = 0.015] and MPGN (OR, 6; 95% CI, 2-18.8; P = 0.0018) were independently associated with death. **CONCLUSION:** Kidney disease is a relatively frequent complication in HIV or HCV mono-infected individuals. The impact of kidney disease on survival of HIV/HCV coinfecting patients seems deleterious but remains largely unknown.

**Long-term outcomes after treatment with interferon and ribavirin in HCV patients.**

Aronsohn A, Reau N. *J Clin Gastroenterol*. 2009 May 14. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19448563?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19448563?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Hepatitis C is a leading indication for transplantation and a common cause of liver-related death worldwide. Treatment for hepatitis C has evolved from interferon therapy alone, which yielded relatively poor response rates compared with the currently recommended and more effective combination of pegylated interferon and ribavirin. Factors such as hepatitis C viral genotype, pretreatment viral load, race, renal function, degree of hepatic fibrosis, and comorbid conditions such as HIV coinfection have clinical importance in that they influence viral kinetics, which play a large role in determining a sustained response to therapy or virologic "cure." However, the goal of therapy is to reduce liver-related morbidity and mortality by decreasing rates of progression or improvement of fibrosis, reducing risk of hepatocellular carcinoma, improving posttransplant graft and patient survival, and resolving or improving some of the extrahepatic manifestations of hepatitis C. Studies generally infer long-term success from the more tangible goal of sustained viral suppression; however, increasing data suggest that effective therapy does result in decreased morbidity and mortality. Given the heterogeneity of patients who are infected with hepatitis C, treatment decisions should be specifically tailored to each individual patient on the basis of their predisposing conditions and anticipated clinical outcomes.

**Plasma HCV-RNA decline in the first 48 h identifies hepatitis C virus mono-infected but not HCV/HIV coinfecting patients with an undetectable HCV viral load at week 4 of peginterferon-alfa-2a/ribavirin therapy.**

Arends JE, Stuart JC, Baak LC, van der Ende ME, et al. J Viral Hepat. 2009 May 11. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19457139?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19457139?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**SUMMARY:** During peginterferon-alfa-2a/ribavirin therapy, plasma hepatitis C virus (HCV)-RNA decreases with a rapid first phase and a slower second phase. We compared the viral load decrease and slope in the first 48 h in patients with a rapid viral response (RVR, i.e. HCV-RNA < 50 IU/mL at week 4) with patients not achieving an RVR. From 23 HCV-infected (14 mono-infected and nine HCV/HIV-coinfecting) genotype 1 or 4 positive peginterferon-alfa-2a/ribavirin-treated patients, plasma HCV-RNA was determined at baseline, 48 h, weeks 1, 2, 4, 8, 12, 48 and 72. The HCV viral load decrease ( $\Delta_{0-48}$ ), the slope ( $\lambda(1)$ ) and the efficiency factor ( $\epsilon$ ) were determined in the first 48 h after the start of therapy. Five (36%) HCV mono-infected patients and three (33%) HIV/HCV-coinfecting patients achieved an RVR whereas six (43%) HCV mono-infected patients and five (56%) HIV/HCV-coinfecting patients reached a sustained viral response (SVR). In contrast to HIV/HCV-coinfecting patients, five HCV mono-infected patients with an RVR showed both a larger  $\Delta_{0-48}$  and steeper  $\lambda(1)$  ( $-1.77\log(10)$  IU/mL  $\pm$  0.66 and  $-2.04/\text{day}$   $\pm$  0.76) compared to nine non-RVR patients ( $-0.66\log(10)$  IU/mL  $\pm$  0.39;  $P = 0.019$  and  $-0.76/\text{day}$   $\pm$  0.41;  $P = 0.019$ ). When divided by SVR, a greater  $\Delta_{0-48}$  and steeper  $\lambda(1)$  were also seen in both HCV mono-infected and HIV/HCV-coinfecting patients. Thus, in the first 48 h after the start of therapy, HCV mono-infected patients with an RVR have a larger viral load decrease, steeper viral slope and a higher efficiency factor as compared with non-RVR patients.

**Systematic review of HIV and HCV infection among drug users in China.** Bao YP, Liu ZM. Int J STD AIDS. 2009 Jun;20(6):399-405.

[http://www.ncbi.nlm.nih.gov/pubmed/19451325?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19451325?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

To determine the HIV and hepatitis C virus (HCV) geographical distribution among drug users in China, a systematic literature review of 40 peer-reviewed publications (comprising 15,565 drug users) was conducted. Of the total drug users, 10,724 were found to be injection drug users (IDUs) and 4841 were non-injection drug users (non-IDUs). Various studies identified that among IDUs and non-IDUs, the overall HIV prevalence rates were 12.55% and 1.05%, and the HCV prevalence rates were 66.97% and 18.30%, respectively. The HIV prevalence rate ranged from 0% (Anhui and Inner Mongolia) to 52.51% (Yunnan) among IDUs, and from 0% to 19.80% among non-IDUs correspondingly. The HCV prevalence rate ranged from 11.43% (Shannxi) to 90.77% (Hubei) among IDUs, and from 0% (Anhui) to 40.00% (Fujian) among non-IDUs. Based on the high prevalence of HIV and HCV among drug users, scaling-up harm reduction was required from 'heroin trafficking areas' to other areas in China.

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**EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS**

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**Donor livers with steatosis are safe to use in hepatitis C virus-positive recipients.** Burra P, Lorenzo M, Russo FP, Germani G, et al. Liver Transpl. 2009 May 28;15(6):619-628. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19479805?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19479805?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Whether donor graft steatosis affects liver function and influences survival after liver transplantation is still open to debate. The aim of this study was to assess the impact of donor graft steatosis on long-term liver histology after liver transplantation. One hundred sixteen consecutive liver transplants were performed in 56 hepatitis C virus-positive (HCV+) patients and 60 HCV- patients who had protocol liver biopsies at 6, 12, 24, and 36 months after liver transplantation. Liver biopsies were obtained from all grafts. No steatosis was seen in 50.9% of the biopsies taken at the back table before implantation, whereas steatosis was mild in 39.6% of the samples and moderate/severe in 9.5% of the samples. In the 56 HCV+ recipients, fibrosis stage 3 was seen in 22.2% and stage 4 was seen in 2.2% of 45 biopsies at 36 months after liver transplantation. There was no correlation between donor graft steatosis and fibrosis after liver transplantation, regardless of the etiology of liver disease. No difference in 36-month survival after liver transplantation was seen, regardless of whether the etiology of the patient's liver disease was HCV-related or non-HCV-related (80.3% versus 75%;  $P = 0.4$ ) and whether the steatosis in the graft was reportedly absent, mild, or moderate/severe (79.7% versus 73.9% versus 81.1%;  $P = 0.7$ ). In conclusion, nearly one-quarter of HCV+ recipients have precirrhosis/cirrhosis 3 years after liver transplantation. Steatotic grafts do not seem to exacerbate the progression of fibrosis in HCV+ recipients, nor do they seem to negatively affect 3-year patient survival.

**Impact of the donor risk index on the outcome of hepatitis C virus-positive liver transplant recipients.** Maluf DG, Edwards EB, Stravitz RT, Kauffman HM. *Liver Transpl.* 2009 May 28;15(6):592-599. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19479802?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19479802?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

We have investigated the impact of the donor risk index (DRI) on the outcome of hepatitis C virus (HCV)-infected patients undergoing liver transplantation (LTx). Retrospective analysis was performed from the Organ Procurement and Transplantation Network database (January 1, 2000 to June, 2006). The DRI was calculated as described by Feng et al. (*Am J Transplant* 2006;6:783-790). Model for End-Stage Liver Disease (MELD) exceptions were excluded from the analysis. Relative risk (RR) estimates of patient and graft loss were derived from Cox regression models. The Wald test was used to test the effect of the MELD score at transplant on the HCV-DRI interaction. Of the LTx recipients (16,678), 76.1% were Caucasian, and 66.7% were male; the median age was 52 (range, 18-80 years), and the mean follow-up time was 1148 days (range, 0-2959 days). Forty-six percent ( $n = 7675$ ) of LTx recipients were HCV(+). The median DRI was 1.3 (range, 0.77-4.27). Increasing DRI was associated with a statistically significant increase in the RR of graft failure and patient death for both HCV(+) and HCV(-) recipients. However, HCV(+) recipients demonstrated a significantly higher increase in the RR of patient and graft loss as a function of the DRI than HCV(-) subjects, even after adjustments for several recipient factors, including MELD. In conclusion, a synergistic interaction between donor DRI and recipient HCV status exists, such that an allograft from a high-DRI donor more adversely affects the outcome of an HCV(+) recipient than that of an HCV(-) recipient.

**Surveillance for acute viral hepatitis --- United States, 2007.** Daniels D, Grytdal S, Wasley A; Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC. *MMWR Surveill Summ.* 2009 May 22;58(3):1-27.

[http://www.ncbi.nlm.nih.gov/pubmed/19478727?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19478727?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**PROBLEM:** In the United States, acute viral hepatitis most frequently is caused by infection with any of three distinct viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), or hepatitis C virus

(HCV). These unrelated viruses are transmitted through different routes and have different epidemiologic profiles. Safe and effective vaccines have been available for hepatitis B since 1981 and for hepatitis A since 1995. No vaccine exists against hepatitis C. HBV and HCV can persist as chronic infections and represent a leading cause of chronic liver disease and hepatocellular carcinoma in the United States. Reporting Period Covered: Cases in 2007, the most recent year for which data are available, are compared with those from previous years. Description of System: Cases of acute viral hepatitis are reported voluntarily to CDC by state and territorial health departments via CDC's National Notifiable Disease Surveillance System (NNDSS). Reports are received electronically via CDC's National Electronic Telecommunications System for Surveillance (NETSS). Results: Acute hepatitis A incidence has declined 92%, from 12.0 cases per 100,000 population in 1995 to 1.0 case per 100,000 population in 2007, the lowest rate ever recorded. Declines were greatest among children and in those states where routine vaccination of children was recommended beginning in 1999. Acute hepatitis B incidence has declined 82%, from 8.5 cases per 100,000 population in 1990 to 1.5 cases per 100,000 population in 2007, the lowest rate ever recorded. Declines occurred among all age groups but were greatest among children aged <15 years. Following a peak in 1992, incidence of acute hepatitis C declined; however, since 2003, rates have plateaued. In 2007, as in previous years, the majority of these cases occurred among adults, and injection-drug use was the most common risk factor. Interpretation: The results documented in this report suggest that implementation of the 1999 recommendations for routine childhood hepatitis A vaccination in areas of the United States with consistently elevated hepatitis A rates has reduced rates of infection. In addition, universal vaccination of children against hepatitis B beginning in 1991 has reduced disease incidence substantially among younger age groups. Higher rates of hepatitis B continue among adults, particularly among males aged 30--44 years, reflecting the need to vaccinate adults at risk for HBV infection. The decline in hepatitis C incidence after 1992 was attributable primarily to a decrease in incidence among injection-drug users. The reasons for this decrease were unknown but probably reflected changes in behavior and practices among injection-drug users. Public Health Actions: The expansion in 2006 of recommendations for routine hepatitis A vaccination to include all children in the United States aged 12--23 months is expected to reduce hepatitis A rates further. Ongoing hepatitis B vaccination programs ultimately will eliminate domestic HBV transmission, and increased vaccination of adults with risk factors will accelerate progress toward elimination. Further prevention of hepatitis B and hepatitis C relies on identifying and preventing transmission of HBV or HCV in hospital and nonhospital health-care associated settings. In addition, prevention of hepatitis C relies on identifying and counseling uninfected persons at risk for hepatitis C (e.g., injection-drug users) regarding ways they can protect themselves from infection. Public health management of persons with chronic HBV or HCV infection will help to interrupt the transmission to susceptible persons, and their medical management will help to reduce the development of the sequelae from chronic liver disease.

**Effects of smoking on survival for patients with end-stage liver disease.** Lee DS, Mathur AK, Acker WB 2nd, et al. [J]6: J Am Coll Surg. 2009 Jun;208(6):1077-84. Epub 2009 Apr 24.  
[http://www.ncbi.nlm.nih.gov/pubmed/19476895?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19476895?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Smokers with chronic liver disease can become eligible for transplantation, but some insurers refuse reimbursement pending smoking cessation. **STUDY DESIGN:** Our hypothesis is that liver transplantation candidates and recipients who smoke have inferior survival compared with nonsmokers. Using a retrospective cohort study design, three Cox proportional hazards models were constructed to determine covariate-adjusted mortality from transplantation evaluation and transplantation based on smoking status at evaluation, transplantation, and

posttransplantation followup. **RESULTS:** From 1999 to 2007, 2,260 patients were evaluated. Seven hundred sixty were active smokers, and 1,500 were nonsmokers. Smokers at evaluation were younger (49.3 versus 51.7 years), were more likely to be men (65.9% versus 58.7%), have hepatitis C (54.2% versus 30.1%), have a lower Model for End-Stage Liver Disease score (10.5 versus 12.3), and less likely to receive transplant (12.2% versus 18.6%) (all  $p < 0.05$ ). The postevaluation multivariate model indicated that substance use, higher Model for End-Stage Liver Disease score, hepatitis C, and older age increased mortality risk (all  $p < 0.05$ ), and liver transplantation (hazards ratio = 0.986; 95% CI, 0.977 to 0.994) was associated with lower mortality. Smoking was not associated with increased mortality risk at any time point in those evaluated or receiving transplants.

**CONCLUSIONS:** Providers should continue encouraging potential liver transplantation candidates to stop smoking, but insurer-driven mandated smoking cessation might not improve survival.

### **Epidemic spread of hepatitis C virus genotype 3a and relation to high incidence of**

**hepatocellular carcinoma in Pakistan.** Khan A, Tanaka Y, Azam Z, et al. *J Med Virol.* 2009 May 27;81(7):1189-1197. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19475617?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19475617?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Studies conducted in different populations worldwide revealed an association between HCV genotype 1 and the development of hepatocellular carcinoma (HCC) than in infection with other HCV genotypes. There are reports which reveal the association of HCV genotype 3a (HCV-3a) with hepatic steatosis and fibrosis but its relation with the development of HCC has not been investigated. In Pakistan, where the incidence of HCC is increasing, 189 patients with chronic liver disease including 82 with HCC were enrolled. HCV genotypes were determined by phylogeny in the NS5B region and the epidemic history of HCV-3a was examined using coalescent theory based methods. HCV-3a was the predominant genotype (81.4%) in the cohort studied, followed by 3b (9.3%), 3k (2.3%), 1a (1.5%), 1c (1.5%), 1b (0.8%), and 2a (0.8%) where 76% of HCC and 86% of non-HCC were infected with HCV-3a. The significant factors associated with HCC were older age (mean  $\pm$  SD) 55.8 ( $\pm$ 9.9) ( $P < 0.0001$ ), and male gender ( $P < 0.001$ ). HCV RNA was significantly higher in patients with HCC and chronic hepatitis than in liver cirrhosis ( $P < 0.0001$ ). Molecular evolutionary analysis revealed a distinct phylogenetic cluster of HCV-3a in Pakistan and an estimation of the effective number of HCV infections indicated the appearance of HCV-3a in this region around 1920s and a rapid exponential growth in the 1950s. This indicates that the epidemic spread of HCV-3a occurred earlier in Pakistan than in other countries in which this genotype has been reported. HCV-3a which spread earlier in Pakistan may be associated with an increasing incidence of HCC.

### **A neuropsychological study comparing patients infected with HCV and HBV without**

**psychiatric comorbidities.** Quarantini LC, Miranda-Scippa A, Batista-Neves S, et al. *J Med Virol.* 2009 May 27;81(7):1184-1188. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19475611?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19475611?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Hepatitis C is one of the most common chronic infectious diseases worldwide, with well-documented extra-hepatic manifestations, such as a broad number of cognitive deficits. These impairments may be explained by psychiatric comorbidities, which have not been investigated properly in the literature. In order to elucidate a specific hepatitis C virus (HCV) induced cognitive impairment not related to mental disorders, neuropsychological performance of patients infected with HCV was compared with that of patients infected with hepatitis B virus cognitive impairment,

especially psychiatric comorbidities. A total of 33 patients infected with HCV and 22 patients infected with HBV were included in the study. There were no significant differences between the two groups with regard to age or years of education. The group of patients infected with HCV performed significantly worse on visuo-spatial memory tasks after adjusting for years of education and age. There were no significant differences between patients infected with HCV and patients infected with HBV with regards to other neuropsychological functions. The data indicate that patients infected with HCV patients have poorer visuo-spatial memory performance than patients infected with HBV, suggesting that the cognitive deficit may be specific to HCV infection and not to secondary comorbid psychiatric disorders.

**Hepatitis C virus infection in the family setting of patients with occult hepatitis C.** Castillo I, Bartolomé J, Quiroga JA, Barril G, Carreño V. *J Med Virol.* 2009 May 27;81(7):1198-1203. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19475603?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19475603?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Family members of patients with chronic hepatitis C virus (HCV) infection are at increased risk of HCV infection but the prevalence of HCV among family members of patients with occult HCV infection is not known. Anti-HCV, serum HCV RNA and levels of liver enzymes were determined in 102 family members of 50 index patients with occult HCV infection and in 118 family members of 59 chronic hepatitis C index patients. HCV RNA and/or anti-HCV were detected in 10/102 (9.8%) relatives of patients with occult HCV infection and in 4/118 (3.4%) of patients with chronic hepatitis C. Fourteen additional family members (seven were relatives of index patients with occult HCV infection) had abnormal values of liver enzymes without serological markers of HCV infection. Two of these patients (who were relatives of two index patients with occult HCV infection) underwent a liver biopsy and were diagnosed with an occult HCV infection because HCV RNA was detected in the liver cells in the absence of serological HCV markers. In conclusion, the prevalence of HCV infection among family members of patients with occult HCV infection was similar to that found among family members of patients with chronic hepatitis C. This stresses the need to adopt strategies to prevent the transmission of HCV in the family setting of patients with occult HCV infection.

**Future directions for investigation of fatigue in chronic hepatitis C viral infection.** Seaman K, Paterson BL, Vallis M, Hirsch G, Peltekian KM. [*Chronic Illn.* 2009 Jun;5(2):115-28.

[http://www.ncbi.nlm.nih.gov/pubmed/19474234?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19474234?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Fatigue is a common and often debilitating symptom for people living with chronic hepatitis C viral infection. Numerous published reports in the past decade have attempted to address the nature and aetiology of fatigue in chronic hepatitis C; however, this field is plagued with lack of clarity about how hepatitis C virus (HCV)-related fatigue occurs and when it is experienced by the infected person. Consequently, both patients and clinicians alike are unclear about how to mediate or prevent the negative consequences of HCV-related fatigue. In the following article, the authors identify areas of ambiguity and incongruity that have evolved primarily from the underlying assumptions and methodological decisions of researchers in the field of HCV-related fatigue. Research related to fatigue in chronic illness is drawn upon to suggest future directions for investigations and interventions in the field of HCV-related fatigue. Future research needs to move beyond the subjective symptomatology of HCV-related fatigue and begin to account for the multidimensional and contextualised nature of the fatigue experience.

**Undiagnosed hepatitis C on the general medicine and trauma services of two urban hospitals.**

Brady KA, Weiner M, Turner BJ. J Infect. 2009 May 3. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19473706?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19473706?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

The inpatient medical service may be an important location to identify undiagnosed hepatitis C virus (HCV) infection. We conducted a cross-sectional HCV prevalence study in consecutive patients aged 18-65 admitted in a three-month period to two urban hospitals' general internal medicine and trauma services. Patient sera were anonymously screened for anti-HCV antibody with an enzyme-linked immunoassay and, when anti-HCV positive (+), for HIV. Health system records were examined for prior HCV testing or diagnosis or an HIV diagnosis then linked anonymously to test results. Multivariate logistic regression was used to examine associations of patient and health care factors with unknown HCV+ status. Of 786 unique patients tested (60.3% of all admitted patients), 62 (7.9%) were HCV+ without a prior HCV+ test or diagnosis while 61 patients (7.8%) tested HCV+ but had prior HCV+ test or diagnosis. Of 62 patients with unknown HCV+, 6 (9.7%) were HIV+ but only 3 had a prior HIV diagnosis; of 61 patients with known HCV+, all 9 (14.8%) HIV+ had been diagnosed. Among the 640 patients with prior unknown HCV status, an HCV+ test was strongly associated with age: 50-65 (adjusted odds ratio [AOR] 5.44, CI 2.20-13.48) and age 36-49 (AOR 4.65, CI 1.91-11.32) versus. 18-35. In this anonymous study, we could not obtain HCV risk factor data but the positive and negative predictive values of HCV testing all in-patients with an unknown HCV status were 99.3% and 99.0%, respectively. In similar urban general medicine and trauma services, broader efforts to test for HCV in inpatients aged 36-65 may be warranted.

**Transplantation of high-risk donor organs: a survey of US solid organ transplant center practices as reported by transplant infectious diseases physicians.**

Ison MG, Stosor V. Clin Transplant. 2009 May 18. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19473202?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19473202?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Public Health Service (PHS) guidelines developed in 1994 provide guidance to minimize the risk of HIV transmission and to monitor recipients following the transplantation of "high-risk" organs. There are no data on current practices or opinions of these policies by transplant infectious diseases (TID) physicians. An electronic survey was sent to all US solid organ transplantation centers with identified TID expertise as self-reported to the American Society of Transplantation and Infectious Diseases Society of America. A total of 108 surveys were sent in December 2007 and 32 responses were received (30%). Thirty-three percent of centers obtain only verbal, 52% verbal and written, and 14% do not obtain any special consent from recipients of organs from high-risk donors (ROHRD). Post-solid organ transplantation serologies for HIV, hepatitis B (HBV), and hepatitis C virus (HCV) are obtained at 40% of centers in ROHRD only, 20% in all recipients, and not performed in 40%; post-solid organ transplantation nucleic acid testing (NAT) testing is carried out in 36-45% of centers in ROHRD, 11% in all recipients, and not performed in approximately 50% of centers. Only 22.7% of respondents believed current guidelines accurately represent what they consider to be high-risk donors. There is significant variability in the acceptance and management of ROHRD in the US. Most TID experts do not feel that the current PHS guidelines accurately define high-risk donors.

**Antiviral resistance and specifically targeted therapy for HCV (STAT-C).**

Thompson AJ, McHutchison JG. J Viral Hepat. 2009 Jun;16(6):377-87.  
[http://www.ncbi.nlm.nih.gov/pubmed/19472445?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19472445?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

As health care providers, we find ourselves on the verge of a new era in the treatment of chronic hepatitis C virus (HCV) infection. A number of directly acting antiviral agents are now in the latter stages of clinical development. The more promising candidates include direct inhibitors of the HCV nonstructural 3 protease, as well as both nucleoside and non-nucleoside inhibitors of the NS5B RNA-dependent RNA polymerase. Although these agents have demonstrated potent antiviral effect, monotherapy has been complicated by rapid virological breakthrough due to the selection of drug-resistant mutants. As for HIV and HBV, combination therapy will therefore be necessary. This brief review summarizes the current literature concerning resistance and directly acting antiviral agents, and identifies key challenges facing this emerging field.

**Access to care of patients with chronic hepatitis C virus infection in a university hospital: Is opioid dependence a limiting condition?** Perut V, Labalette C, Sogni P, Ferrand I, Salmon-Céron D, Vidal-Trecan G. *Drug Alcohol Depend.* 2009 May 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Perut%20V%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Perut%20V%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** We aimed to examine access to care of opioid-dependent patients with chronic hepatitis C. **METHODS:** A standardized form was used to conduct a retrospective survey from 1999 to 2003 in a French university hospital. All HCV RNA positive in- or outpatients who had not had a liver biopsy or anti-HCV treatment were included. Opioid-dependence was defined as active opioid drug use or being on opioid substitution treatment. **RESULTS:** The survey included 580 patients; 137 (23.6%) were opioid-dependent. Fewer patients with than without current opioid dependence had had genotyping (40.1% versus 67.7%,  $p < 0.001$ ), liver biopsy (51.8% versus 62.8%,  $p = 0.022$ ), and anti-HCV treatment (8.8% versus 18.3%,  $p = 0.008$ ). Genotyping was independently, negatively, associated with: (1) current opioid-dependence (OR=0.3, 95%CI=0.2-0.5), (2) former opioid-dependence (OR=0.5, 95%CI=0.3-0.9), (3) unemployment (OR=0.5, 95%CI=0.3-0.7), and (4) HCV infection discovered by screening (OR=0.5, 95%CI=0.3-0.7). Access to liver biopsy was independently, negatively associated with current opioid-dependence (OR=0.6, 95%CI=0.4-0.9), but positively associated with alcohol consumption (OR=2.0, 95%CI=1.2-3.4) and abnormal ALT level (OR=2.2, 95%CI=1.5-3.2). Access to anti-HCV treatment was independently, negatively associated with HCV infection discovered by screening (OR=0.5, 95%CI=0.3-0.9), but positively associated with moderate hepatitis (OR=6.8, 95%CI=2.8-16.8), extensive fibrosis or cirrhosis (OR=12.3, 95%CI=5.5-27.5), abnormal ALT level (OR=2.1, 95%CI=1.3-3.6) and age (40-64 years) (OR=1.9, 95%CI=1.0-3.4). **CONCLUSIONS:** Genotyping and liver biopsies were performed less frequently on current opioid dependent patients. Absence of genotyping was also independently associated with unemployment and former opioid-dependence. Alcohol consumption or abnormal ALT levels favored access to biopsy. Histological grade strongly conditioned access to anti-HCV treatment.

**Insulin resistance, serum adipokines and risk of fibrosis progression in patients**

**transplanted for hepatitis C.** Veldt BJ, Poterucha JJ, Watt KD, Wiesner RH, Hay JE, et al. *Am J*  
[http://www.ncbi.nlm.nih.gov/pubmed/19459812?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19459812?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

In the nontransplant setting diabetes mellitus is a risk factor for disease progression in patients with chronic hepatitis C virus (HCV) infection. The impact of early insulin resistance on the development of advanced fibrosis, even in the absence of clinically apparent diabetes mellitus, is not known. Our aim was to determine whether the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) can be used to identify insulin-resistant patients at risk for rapid fibrosis progression. Cohort study including patients transplanted for chronic HCV between January 1, 1995 and January 1, 2005. One hundred sixty patients were included; 25 patients (16%) were treated for diabetes mellitus and

36 patients (23%) were prediabetic, defined as HOMA-IR >2.5. Multivariate Cox regression analysis showed that insulin resistance (hazard ratio (HR) 2.07; confidence interval (CI) 1.10-3.91,  $p = 0.024$ ), donor age (HR 1.33;CI 1.08-1.63,  $p = 0.007$ ) and aspartate aminotransferase (HR 1.03;CI 1.01-1.05,  $p < 0.001$ ) were significantly associated with a higher probability of developing advanced fibrosis, i.e. Knodell fibrosis stage 3 or 4, whereas steatosis (HR 0.94;CI 0.46-1.92,  $p = 0.87$ ) and acute cellular rejection (HR 1.72;CI 0.88-3.36,  $p = 0.111$ ) were not. In conclusion, posttransplant insulin resistance is strongly associated with more severe recurrence of HCV infection. HOMA-IR is an important tool for the identification of insulin resistance among patients at risk for rapid fibrosis progression after liver transplantation for HCV.

### **Hepatitis C virus compartmentalization and infection recurrence after liver transplantation.**

Ramirez S, Perez-Del-Pulgar S, Carrion JA, et al. Am J Transplant. 2009 May 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19459796?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19459796?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Hepatitis C virus (HCV) compartmentalization may have important implications in the pathogenesis of HCV infection. The aim of this study was to investigate the presence and relevance of HCV compartmentalization in the setting of liver transplantation (LT). We collected samples of serum, peripheral blood mononuclear cells (PBMC), perihepatic lymph nodes (PLN) and liver explant at the time of LT, and serum and PBMC after transplantation from 57 HCV-infected cirrhotic patients undergoing LT: 38 individuals received antiviral treatment before LT and 19 were untreated controls. HCV-RNA levels were determined by real-time PCR and the hypervariable region 1 (HVR-1) was sequenced. HCV-RNA was detected in all samples from control patients. In virological responders, recurrence after LT was associated with residual HCV-RNA in the liver explant. Within the entire cohort, 47% of patients harbored differences in direct sequences from distinct compartments. Quasispecies analysis revealed that in most cases, HVR-1 sequences recovered after infection recurrence were identical or closely related to those isolated from the liver explant and serum at the time of LT. Our study shows that a significant proportion of HCV-infected cirrhotic patients exhibit compartmentalization. Viral variants originating within the liver appear to be the main cause of HCV recurrence after LT.

### **Management and treatment of patients with cirrhosis and portal hypertension:**

#### **Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center**

#### **Program and the National Hepatitis C Program.** Garcia-Tsao G, Lim J. Am J Gastroenterol.

2009 May 19. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19455106?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19455106?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Cirrhosis represents the end stage of any chronic liver disease. Hepatitis C and alcohol are currently the main causes of cirrhosis in the United States. Although initially cirrhosis is compensated, it eventually becomes decompensated, as defined by the presence of ascites, variceal hemorrhage, encephalopathy, and/or jaundice. These management recommendations are divided according to the status, compensated or decompensated, of the cirrhotic patient, with a separate section for the screening, diagnosis, and management of hepatocellular carcinoma (HCC), as this applies to patients with both compensated and decompensated cirrhosis. In the compensated patient, the main objective is to prevent variceal hemorrhage and any practice that could lead to decompensation. In the decompensated patient, acute variceal hemorrhage and spontaneous bacterial peritonitis are severe complications that require hospitalization. Hepatorenal syndrome is also a severe complication of cirrhosis but one that usually occurs in patients who are already in the hospital and,

as it represents an extreme of the hemodynamic alterations that lead to ascites formation, it is placed under treatment of ascites. Recent advances in the pathophysiology of the complications of cirrhosis have allowed for a more rational management of cirrhosis and also for the stratification of patients into different risk groups that require different management. These recommendations are based on evidence in the literature, mainly from randomized clinical trials and meta-analyses of these trials. When few or no data exist from well-designed prospective trials, emphasis is given to results from large series and consensus conferences with involvement of recognized experts. A rational management of cirrhosis will result in improvements in quality of life, treatment adherence, and, ultimately, in outcomes.

**Factors associated with awareness of infection status among chronic hepatitis B and C carriers in Korea.** Shin A, Cho ER, Kim J, Sung J, Park KW, Lim MK, Shin HR. *Cancer Epidemiol Biomarkers Prev.* 2009 May 19. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19454614?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19454614?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Hepatitis B (HBV) and hepatitis C (HCV) viral infections are the most important risk factors for hepatocellular carcinoma (HCC), which is responsible for 17.5% of cancer deaths in Korea. The objectives of this study were to identify demographic characteristics that may affect hepatitis carriers' awareness of their infection status, and to assess whether health-related behaviors differed by awareness of the infection. Among 18,636 persons who were recruited from a cancer screening cohort, 904 were HBV carriers and 146 were HCV carriers. Among the HBV carriers, 74.2% were aware of their infection status. Higher education (odds ratio, 1.8; college versus middle school or less), family history of liver cancer or disease, and marriage were associated with awareness of HBV infection status. Participants who were aware of their HBV carrier status were more likely to be former smokers or drinkers than those who were not aware of their status. Only 34.9% of HCV carriers were aware of their HCV infection status. No demographic characteristics were related to awareness of HCV infection status among HCV carriers. However, HCV carriers who were aware of their infection status were more likely to be former drinkers (odds ratio, 9.2; 95% confidence interval, 1.8-47.2). In conclusion, two thirds of HCV carriers and one fourth of HBV carriers in this study population were not aware of their infection status, and awareness of hepatitis infection status was significantly associated with other risk behaviors, such as alcohol consumption and cigarette smoking.

**Holiday haemodialysis and imported hepatitis C virus infection: A series of sixteen cases in two large haemodialysis units.** Bhattacharya S, Price N, Boxall E, Adu D, Lipkin G, Smith S, Osman H. *J Clin Virol.* 2009 May 16. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19451020?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19451020?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Patients in haemodialysis units are at an increased risk of blood borne virus infections. Birmingham city (West Midlands, UK) has a large number of its population from an ethnic origin other than white (30%). Recently due to the increase in number of haemodialysis centres abroad and particularly in the Indian Subcontinent, a large number of haemodialysis patients from these ethnic minorities are encouraged to take holidays in their countries of origin.

**OBJECTIVES:** To present the data on a series of cases of holiday haemodialysis acquired hepatitis C virus (HCV) infections from two large dialysis units in Birmingham. **STUDY DESIGN:** In this retrospective study we have reviewed the case records of all patients in two large dialysis units who had holiday dialysis abroad and developed HCV infection after returning to the UK. **RESULTS:** A total of 16 patients from two large dialysis units in Birmingham who developed HCV infection after

haemodialysing abroad mainly in the Indian Subcontinent are being described. This constituted 44% of the total HCV positive patients in the two haemodialysis units (16/36). The cases occurred over a period of 9 years between 2000 and 2008. The last twelve of these fifteen cases had been diagnosed in the past 17 months. There were 10 male patients with a mean age 62.8 years (range 26-84 years) and 6 female patients with a mean age of 57 years (range 44-68 years). HCV genotypes 1, 3 and 4 were found in 9, 4 and 3 patients, respectively. **CONCLUSION:** These cases underline the importance of enhanced surveillance and infection control procedures in haemodialysis units for patients who return after dialysing in resource poor countries. To the best of our knowledge this represents the largest series of imported HCV infection after holiday haemodialysis, and demonstrates clearly the significance of the perceived risk with increasing number of incident infections.

**Thoracic complications of liver cirrhosis: radiologic findings.** Kim YK, Kim Y, Shim SS.

Radiographics. 2009 May-Jun;29(3):825-37.

[http://www.ncbi.nlm.nih.gov/pubmed/19448118?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19448118?ordinalpos=8&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Patients with chronic liver disease exhibit various cardiovascular and pulmonary complications. Hepatopulmonary syndrome results in dyspnea due to intrapulmonary arteriovenous shunting and ventilation-perfusion mismatch. Portopulmonary hypertension occurs in patients with portal hypertension. Intrathoracic portosystemic collateral vascular pathways develop in patients with portal hypertension to allow decompression of the portal vein into the systemic circulation. Hepatic hydrothorax may develop in patients with cirrhosis and ascites. Massive necrosis of the liver from any cause may be associated with acute hypoxic respiratory failure, necessitating ventilatory support. Bacterial infection is common in cirrhotic patients because of a compromised host defense system. Hepatocellular carcinoma may produce hematogenous lung metastases, intrathoracic lymph node metastases, direct intracardiac extension, and pulmonary embolism. Interferon therapy for treatment of chronic active hepatitis C may disturb cellular immune activation in some patients and contribute to the onset and progression of sarcoidosis. Awareness of the various thoracic manifestations in chronic liver disease can be helpful for making a differential diagnosis and planning proper management.

**Efficacy of chronic hepatitis C therapy in community-based trials.** Marotta P, Hueppe D, Zehnter E, Kwo P, Jacobson I. Clin Gastroenterol Hepatol. 2009 May 14. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19447199?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19447199?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Prospective, randomized, controlled, phase 3 clinical trials establish pegylated interferon (PEG-IFN) alfa plus ribavirin as the standard of care for patients with chronic hepatitis C. Such clinical trials are conducted in a highly regimented manner; patients must meet strict inclusion/exclusion criteria, and treatment is administered under rigid protocols with close monitoring by study personnel. Whether the results of phase 3 trials can be generalized or achieved in everyday clinical practice is questioned in several therapeutic areas. The efficacy of PEG-IFN alfa plus ribavirin therapy observed in pivotal phase 3 trials has been confirmed in several community-based trials conducted in North America and Europe, demonstrating consistent overall rates of sustained virologic response across a wide range of patient populations. Sustained virologic response rates stratified by genotype, viral load, fibrosis score, age, and ethnicity-factors known to impact treatment outcome-are consistent between these trials and comparable to those reported in clinical trials. The United Statesbased WIN-R trial confirmed the value of combining weight-based ribavirin dosing with weight-based PEG-IFN alfa-2b dosing across a spectrum of patient body weights. Large Canadian trials (POWeR and EAP), a

German trial (AWB), a French study (Hepatys), and an Italian study demonstrated that PEG-IFN alfa plus ribavirin produces excellent efficacy in difficult-to-treat patient populations. Collectively, these results confirm the efficacy of current standard treatment regimens in a wide range of community-based settings, affording clinicians confidence that they can attain results similar to those of rigidly controlled randomized trials.

**Glucose abnormalities in non-alcoholic fatty liver disease and chronic hepatitis C virus infection: the role of iron overload.** Lecube A, Hernández C, Simó R. *Diabetes Metab Res Rev.* 2009 May 14. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19444865?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19444865?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus (HCV) infection are major causes of liver disease frequently described in outpatient patients with glucose abnormalities. Hyperferritinemia, which suggests that iron overload plays a decisive role in the pathophysiology of insulin resistance and hyperglycemia, is a common finding in both disorders. However, the role of the hepatic iron deposition differs from one to the other. In NAFLD, a moderate liver iron accumulation has been observed and molecular mechanisms, including the downregulation of the liver iron exporter ferroportin-1, have been described. Iron overload will enhance intrahepatic oxidative stress that promotes hepatic fibrosis, interfere with insulin signalling at various levels and may hamper hepatic insulin extraction. Therefore, liver fibrosis, hyperglycemia and hyperinsulinemia will lead to increased levels of insulin resistance and the development of glucose abnormalities. Furthermore, iron depletion by phlebotomy removes liver iron content and reduces serum glucose and insulin resistance in NAFLD patients. Therefore, it seems that iron overload participates in those glucose abnormalities associated with NAFLD. Concerning chronic HCV infection, it has been classically assumed that iron overload contributes to insulin resistance associated with virus infection. However, recent evidence argues against the presence of iron overload in these patients and points to inflammation associated with diabetes as the main contributor to the elevated ferritin levels. Therefore, glucose abnormalities, and specially type 2 diabetes, should be taken into account when evaluating serum ferritin levels in patients with HCV infection.

**Relative and combined effects of chronic alcohol consumption and HCV infection on serum zinc, copper, and Selenium.** González-Reimers E, Martín-González MC, Alemán-Valls MR, et al. *Biol Trace Elem Res.* 2009 May 15. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19444388?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19444388?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

In alcoholic hepatitis, Kupffer cells are activated by intestinal gram-bacteria, leading to cytokine production and free radicals release, which, enhancing cytokine secretion, create a positive feedback loop which contributes to liver inflammation. Free radicals also damage the liver in chronic hepatitis C virus (HCV) infection, a condition frequently associated to alcohol consumption. In both situations, activity of antioxidant enzymes and of its cofactors zinc (Zn), selenium (Se), and copper (Cu) is important. This study was performed to assess the relative and combined effects of chronic alcoholism and HCV infection on serum Se, Zn, and Cu, and its relation with serum malondialdehyde (MDA) and tumor necrosis factor-alpha, interferon-gamma, and interleukins (IL) 4, 6, and 8, in 19 HCV- alcoholic patients, 12 HCV+ alcoholic patients, nine HCV+ non-alcoholic patients, and 20 controls. Serum Zn and Se were lower in both HCV+ and HCV- alcoholic patients, whereas serum Cu was lower in HCV+ individuals. Serum Zn and Se were related to liver function derangement. MDA levels were higher in alcoholics, but no relation was observed between trace

elements and MDA or cytokines, so that our results do not support a relevant role of the analyzed trace elements in the pathogenesis of chronic liver disease.

### **HCV-related mortality among male prison inmates in Texas, 1994-2003.**

Harzke AJ, Baillargeon JG, Kelley MF, Diamond PM, Goodman KJ, Paar DP. *Ann Epidemiol.* 2009 May 12. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19443239?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19443239?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**PURPOSE:** The prevalence of hepatitis C virus (HCV) infection is high among adult incarcerated populations, but HCV-related mortality data are lacking. The study purpose was to assess HCV-related mortality over time and across racial/ethnic categories from 1994 through 2003 among male prisoners in the Texas Department of Criminal Justice (TDCJ). **METHODS:** TDCJ decedent data were linked with Texas Vital Statistics multiple-cause-of-death data. Crude annual HCV death rates, age- and race-adjusted summary rates, and average annual percent changes were estimated. The proportion of deaths due to chronic liver disease/cirrhosis, liver cancer, hepatitis B, and HIV for which HCV was identified as an intervening or contributing cause of death was calculated.

**RESULTS:** Among Texas male prisoners, HCV death rates were high and increased over the 10-year study period by an average 21% annually, with the largest increase occurring among Hispanic prisoners. HCV was identified as an intervening or contributing cause of death in 15% of chronic liver disease/cirrhosis deaths, 33% of liver cancer deaths, 81% of hepatitis B deaths, and 7% of HIV deaths. **CONCLUSIONS:** Because HCV-related deaths among Texas male prisoners are high and increasing, particularly among Hispanics, targeted prevention, screening, and treatment of HCV infections should be among the priorities of U.S. correctional healthcare systems.

### **Hepatitis B virus and hepatitis C virus in medical waste handlers in Tripoli, Libya.**

Franka E, El-Zoka AH, Hussein AH, Elbakosh MM, Arafa AK, Ghenghesh KS. *J Hosp Infect.* 2009 May 12. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Franka%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Franka%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Medical waste handlers (MWHs) are at risk of exposure to serious viral infections. No data are available on the prevalence of hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) among MWHs in Libya. During a one-year period (January to December 2004) blood samples from 300 (59 females) MWHs employed by a local contractor in Tripoli and 300 blood samples from non-medical waste handlers (NMWHs) who had no direct or indirect contact with medical waste were examined for HBV, HCV and HIV using enzyme-linked immunosorbent assays. HBV was detected in 7 (2.3%) and 1 (0.3%) and HCV in 8 (2.7%) and 0 (0.0%) of MWHs and NMWHs, respectively. Significant differences were observed in the detection rates of HBV (OR: 7.14; P<0.04) and HCV (OR: undefined; P<0.005) in MWHs when compared with NMWHs. HIV was not detected in both groups. Of the MWHs studied, 21% were immunised against HBV and 7% were trained to handle medical waste. In addition, 99.7% wore overalls, 57.7% thick disposable gloves, 55% boots and 17.7% masks while handling medical waste. In conclusion, prevalence rates of HBV and HCV were significantly higher in MWHs than those in NMWHs examined. Training, immunisation, and post-exposure protection of MWHs, in addition to proper management of medical waste by the health authorities, may significantly reduce the risk of acquiring infectious agents by MWHs in Libya.

**CXCL10 and CCL2 chemokine serum levels in patients with hepatitis C associated with autoimmune thyroiditis.** Antonelli A, Ferri C, Fallahi P, et al. *J Interferon Cytokine Res.* 2009 Jun;29(6):345-51.

[http://www.ncbi.nlm.nih.gov/pubmed/19441886?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19441886?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

To evaluate CXCL10 and CCL2 in patients with hepatitis C virus chronic infection in presence/absence of autoimmune thyroiditis (AT). CXCL10 was significantly higher in: (1) patients with AT than controls without AT (control 1) ( $P < 0.001$ ; ANOVA); (2) patients with hepatitis C infection than control 1 and patients with AT ( $P < 0.001$ ); (3) patients with hepatitis C virus chronic infection and AT (HCV+AT) than control 1 and patients with AT ( $P < 0.001$ ) and hepatitis C ( $P = 0.004$ ). By defining a high CXCL10 level as a value  $>218$  pg/mL, 2% of control 1, 14% of patients with AT, 68% of patients with hepatitis C infection, 81% of HCV+AT had high CXCL10 ( $P < 0.0001$ ; chi-square). CCL2 was similar in control 1 and patients with AT. CCL2 was significantly higher in: (1) patients with hepatitis C infection than control 1 ( $P = 0.04$ ; ANOVA); (2) HCV+AT than patients with AT ( $P = 0.03$ ) and control 1 ( $P = 0.02$ ); no difference was observed between HCV with or without AT. Our study demonstrates: (1) higher circulating CXCL10 and CCL2 in patients with hepatitis C virus chronic infection than in controls; (2) higher CXCL10 in HCV+AT than in patients with hepatitis C infection, suggesting a stronger Th1 immune response in these patients.

**Specialty care and education associated with greater disease-specific knowledge but not satisfaction with care for chronic hepatitis C.** Beste LA, Straits-Troster K, Zickmund S, Larson M, Chapko M, Dominitz JA. *Aliment Pharmacol Ther.* 2009 May 6. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19438425?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19438425?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Little is known about differences among hepatitis C virus (HCV) patients managed by generalists versus specialists with respect to patient-centered outcomes, such as disease-specific knowledge, health-related quality of life (HRQoL), and satisfaction with care. **AIM:** To examine selected patient-centered outcomes of HCV-related care provided in primary care, specialty care, or both. **METHODS:** 629 chronic HCV patients completed a survey including an HCV knowledge assessment and validated instruments for satisfaction and HRQoL. Multivariable linear regression was used to compare outcomes between groups. **RESULTS:** Adjusted total HCV knowledge score was lower among patients who did not attend specialty care ( $p < .01$ ). Primary care and specialty patients did not differ in adjusted general HRQoL or satisfaction. Sixty percent of specialty patients underwent formal HCV education, which was associated with 5% higher knowledge score ( $p = 0.01$ ). General HRQoL and patient satisfaction did not differ between primary care and specialty groups. Disease-specific knowledge and care satisfaction were independent of mental illness, substance abuse, socio-economic variables, history of antiviral treatment, formal HCV education, and duration of time between last visit and survey completion. **CONCLUSIONS:** Primary care patients with chronic HCV have lower adjusted disease-specific knowledge than specialty patients, but no difference in general HRQoL or patient satisfaction.

**Health-related quality of life in patients with different stages of liver disease induced by hepatitis C.** Bjornsson E, Verbaan H, Oksanen A, et al. *J Gastroenterol.* 2009 May 12:1-10. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19437190?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19437190?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVE:** Patients with hepatitis C have been shown to have impaired health-related quality of life (HRQoL). The aim of this study was to determine HRQoL in patients in different stages of hepatitis C virus (HCV) and to compare HRQoL in HCV cirrhosis with non-HCV-induced cirrhosis. **MATERIAL AND METHODS:** Out of 489 consecutive patients who fulfilled the inclusion criteria, 472 (96%) agreed to participate in the study: 158 patients with mild/moderate fibrosis with chronic hepatitis C (CHC group), 76 patients with HCV compensated cirrhosis (CC), 53 patients with HCV decompensated (DC) cirrhosis, 52 non-cirrhotic patients with sustained viral response (SVR), and a control group consisting of 32 patients with non-HCV CC and 101 with non-HCV DC who completed the Short Form-36 (SF-36) and EQ-5D questionnaire. **RESULTS:** The CHC group had significantly lower SF-36 scores than healthy controls, with the exception of scores for the dimensions physical function and bodily pain. HCV patients with DC had lower scores in all SF-36 dimensions in comparison with those of the CHC group, as well as in physical and mental component summaries ( $p < 0.001$ ). In comparison with the CHC group, the HCV CC group had lower scores on the SF-36 general health dimension ( $p < 0.05$ ) and lower SF-36 physical component summary (PCS) scores ( $p < 0.05$ ). No major differences were seen in patients with HCV- and non-HCV-induced cirrhosis. **CONCLUSIONS:** Impairment in HRQoL in patients with HCV was associated with the severity of liver disease, patients with decompensated cirrhosis exhibiting the highest impairment in HRQoL. The etiology of liver disease does not seem to be important in determining HRQoL in cirrhosis.

**Quality of life in hemodialysis patients: hepatitis C virus infection makes sense.** Afsar B, Elsurer R, Sezer S, Ozdemir NF. *Int Urol Nephrol.* 2009 May 9. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19430922?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19430922?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**PURPOSE:** Hepatitis C virus (HCV) infection impairs quality of life (QOL) in patients who are not on dialysis therapy. In dialysis patients, how HCV infection affects QOL is unknown. In our study, we investigated the independent relationship between HCV infection and QOL. **METHODS:** Sociodemographic and laboratory variables were recorded. Severity of depressive symptoms and QOL were assessed by Beck Depression Inventory (BDI) and Short Form-36 (SF-36), respectively. **RESULTS:** Among 165 patients, 83 were anti-HCV antibody positive and 82 were anti-HCV antibody negative. Anti-HCV antibody positive patients had higher BDI scores than anti-HCV antibody negative patients ( $P = 0.011$ ). Other than the social functioning subscale, all SF-36 subscales were lower in anti-HCV antibody positive patients when compared with anti-HCV negative patients. Anti-HCV antibody positive patients had lower physical ( $P = 0.003$ ) and mental component summary scores ( $P = 0.018$ ) than negative patients. Physical component summary score was independently associated with hemodialysis duration ( $P = 0.003$ ), sleep disturbance ( $P = 0.046$ ), BDI score ( $P = 0.027$ ), albumin ( $P = 0.002$ ), and serum hemoglobin ( $P < 0.0001$ ). Physical component summary score was not associated with anti-HCV antibody positivity. Mental component summary score was independently associated with BDI score ( $P = 0.001$ ), anti-HCV antibody positivity ( $P = 0.016$ ), and serum hemoglobin ( $P < 0.0001$ ). **CONCLUSION:** HCV infection impairs QOL, especially in mental aspects, in hemodialysis patients.