



# Caring Ambassadors Hepatitis C Program Newsletter

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## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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**Ketoprofen, peginterferon 2a and ribavirin for genotype 1 chronic hepatitis C: a phase II study.** Gramenzi A, Cursaro C, Margotti M, et al. World J Gastroenterol. 2009 Dec 21;15(47):5946-52.

[http://www.ncbi.nlm.nih.gov/pubmed/20014458?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20014458?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**AIM:** To evaluate the safety of adding ketoprofen to pegylated-interferon (PEG-IFN) with or without ribavirin and the effect on viral kinetics, STAT1 activity and expression of 2'-5'-oligoadenylate synthetase (2'-5'OAS) in genotype 1 chronic hepatitis C in a phase II study.

**METHODS:** Forty-five patients were studied: fifteen were randomized to PEG-IFN plus ribavirin (PR), 16 to PEG-IFN plus ketoprofen and 14 to PR and ketoprofen. The molecular study of IFN-dependent signal transduction was conducted in 9 patients from each group.

**RESULTS:** The combination of ketoprofen and PEG-IFN with or without ribavirin was safe and well tolerated. An early activation of STAT1 was observed in ketoprofen-treated patients, but this activation was less sustained over time. Conversely, ketoprofen plus PEG-IFN and ribavirin induced an early and sustained increase of 2'-5'OAS transcription starting 24 h after the first dose until the 36th wk. These data are consistent with the clinical results, showing a better sustained virological response and a lower relapse rate in patients receiving ketoprofen plus PEG-IFN and ribavirin. **CONCLUSION:** The addition of ketoprofen to the standard therapy of chronic hepatitis C should be explored in larger randomized clinical studies.

**Interferon alpha receptor 2 expression by peripheral blood monocytes in patients with a high viral load of hepatitis c virus genotype 1 showing substitution of amino acid 70 in the core region.** Ishii K, Shinohara M, Sawa M, et al. Kogame. Intervirology. 2009 Dec 3;53(2):105-110. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19955815?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19955815?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND/AIM:** When patients with chronic hepatitis C (CHC) are treated with interferon (IFN)-based therapy, achieving serum HCV-RNA negativity by week 12 (early viral response, EVR) is an important predictor of a sustained virologic response. The aim of this study was to clarify whether changes in IFN-alpha receptor 2 (IFNAR-2) expression by peripheral blood monocytes (Mo) and the EVR rate differed between patients with genotype 1b and a high viral load showing substitution of amino acid 70 in the core region of HCV (mutant, n = 20) and

patients without this substitution (wild, n = 23). **PATIENTS AND METHODS:** Forty-three CHC patients were studied, and received pegylated IFN plus ribavirin. IFNAR-2 expression by Mo was determined using flow cytometry to measure the mean fluorescence intensity (MFI) before and up to 28 days after starting therapy. **RESULTS:** The EVR rate of the mutant group was significantly lower than that of the wild group (35 vs.70%). The MFI of Mo was significantly higher in the wild group than in the mutant group before and also 3, 7, and 28 days after starting therapy. **CONCLUSIONS:** Mutation of HCV was related to lower IFNAR-2 expression by Mo before and after starting therapy.

### **Circulating fibronectin isoforms predict the degree of fibrosis in chronic hepatitis C.**

Hackl NJ, Bersch C, Feick P, et al. Scand J Gastroenterol. 2009 Dec 17. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed?term=%22Hackl%20NJ%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Hackl%20NJ%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract)

**OBJECTIVE:** Hepatic stellate cells only produce fibronectin isoforms in disease states. The isoform-defining domains can be detected in the blood circulation. This study examines whether circulating levels of fibronectin isoforms show a relationship with liver fibrosis on histology in patients with chronic hepatitis C. **MATERIAL AND METHODS:** In a prospective study, 50 patients with chronic hepatitis C who underwent a liver biopsy were compared to 50 matched controls and 35 patients with other liver conditions. **RESULTS:** Circulating levels of the fibronectin isoforms were significantly higher in patients with chronic hepatitis C compared to healthy controls [oncofetal fibronectin (oFN) 2.45 +/- 0.17 versus 1.76 +/- 0.16 mg/l, P < 0.005; extra domain-A (EDA) 1.05 +/- 0.06 versus 0.86 +/- 0.06 mg/l, P < 0.05; and extra domain-B (EDB) 14.55 +/- 0.74 versus 9.31 +/- 0.58 mg/l, P < 0.001], even though total fibronectin was lower (198.9 +/- 3.5 versus 343.6 +/- 14.5 mg/l, P < 0.001). A correlation with the fibrosis score was found for both oFN (r = 0.46, P < 0.005) and EDA (r = 0.51, P < 0.001). The combination of an elevation in both markers (oFN and EDA) in the upper quartile was associated with a specificity of > 99% for predicting significant fibrosis (stages 2-4) and 95% for predicting advanced fibrosis (stages 3-4). A combination of decreased values in the lowest tertile for both markers had a specificity of 94% for excluding significant fibrosis. Based on these findings, 30% of the patients scheduled for a liver biopsy could be correctly classified as having or not having significant fibrosis. The remainder would have to proceed with a biopsy. **CONCLUSION:** Circulating fibronectin isoforms produced by activated stellate cells represent a viable marker for the presence of significant fibrosis or a lack thereof.

### **Peginterferon/ribavirin treatment achieves a higher compliance rate than interferon /ribavirin combination in patients chronically infected with HCV on methadone maintenance.**

Dimitroulopoulos D, Petroulaki E, Manolakopoulos S, et al. Eur J Gastroenterol Hepatol. 2009 Dec;21(12):1407-12.

[http://www.ncbi.nlm.nih.gov/pubmed/19916203?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19916203?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**INTRODUCTION:** Chronic hepatitis C virus infection (HCV) is the most common infectious disease among intravenous drug users. **AIMS:** To determine and compare compliance rates between two groups of chronic HCV patients from the methadone substitution program of the National Greek Organization Against Drugs treated with either pegylated interferon alpha-2b/ribavirin or with interferon alpha-2b/ribavirin during 48 weeks of therapy and 24 weeks of follow-up. Furthermore, to evaluate the efficacy of each treatment modality. **METHODS:** Forty-

five consecutive methadone maintenance (MM) patients (group A, 36 males, nine females) were treated with pegylated interferon alpha-2b (weight-based dosing 1.5 microg/kg/week) and ribavirin 1000-1200 mg/day orally. Sixty-five consecutive MM patients (group B, 52 males, 13 females) were treated with interferon alpha-2b (6 MIU, three times/week) and ribavirin with the doses reported above. During the study, all patients were followed up periodically by hepatologists, internists, and psychiatrists. **RESULTS:** Baseline characteristics were similar between the two groups. Thirty-four out of 45 patients (75.6%) from group A and 31 of 65 patients (47.7%) from group B completed therapy ( $P = 0.006$ ). Thirty-two (71.1%) patients from group A and 27 patients (41.5%) from group B were followed-up until the end of week 72 ( $P = 0.004$ ). At the end of the follow-up, sustained virologic response was achieved in 23 of 45 (51.1%) patients from group A and 21 of 65 patients (32.3%) from group B ( $P = 0.075$ ). **CONCLUSION:** Pegylated interferon alpha-2b/ribavirin treatment achieved a significantly higher compliance rate than interferon alpha-2b/ribavirin in MM patients with chronic HCV infection. After 24 weeks of follow-up, response rates were similar for patients who were compliant to treatment for both groups.

**A randomized controlled trial of double versus triple therapy with amantadine for genotype 1 chronic hepatitis c in Latino patients.** Méndez-Navarro J, Chirino RA, Corey KE, et al. Dig Dis Sci. 2009 Dec 4. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19960257?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19960257?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** With only a third of Latinos achieving sustained virologic response (SVR), there is a need for enhanced HCV treatment. Amantadine has been proposed to improve response rates in addition to standard therapy with peginterferon alpha and ribavirin. Our objective is to evaluate whether triple therapy with amantadine improves SVR rates in this special population. **METHOD:** Treatment-naïve Latino subjects with HCV genotype 1 infection were randomized to receive peginterferon alpha-2a plus weight-based ribavirin for 48 weeks (double therapy) or the same regimen plus amantadine 200 mg daily (triple therapy). The primary endpoint was SVR. Predictors of liver fibrosis using APRI and Forns indices were also evaluated. **RESULTS:** We enrolled 124 patients with chronic hepatitis C genotype 1. Sixty-three received conventional therapy and 61 patients had triple therapy with amantadine. SVR at week 72 was achieved in 25 patients (39.7%) vs. 26 patients (42.6%) in the double and triple regimen, respectively ( $p = 0.561$ ). After multivariate analysis, advanced fibrosis, obesity, and low pretreatment ALT levels were associated with non-response in both groups ( $p = 0.0234$ ,  $p = 0.0012$ ,  $p = 0.0249$ , respectively). APRI values delimited an area under the ROC curve (AUROC) of 0.724 and Forns index with AUROC of 0.733. There was no difference between both indices in predicting significant fibrosis (Knodell index: F3-F4). **CONCLUSION:** Our study demonstrates that the addition of amantadine to standard treatment of chronic HCV does not improve SVR rates in Latino patients with genotype 1. Further research to improve response rates in this special population is needed.

**Treatment persistence in and cost of therapy for patients with chronic hepatitis C: Peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin.**

Brixner DI, Ye X, Chu TC, Blumentals WA, Hassanein TI. *J Health Syst Pharm.* 2009 Dec 15;66(24):2171-8.

[http://www.ncbi.nlm.nih.gov/pubmed/19966085?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19966085?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**PURPOSE:** Treatment persistence and cost of therapy for patients with chronic hepatitis C (CHC) treated with peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin were evaluated. **METHODS:** This retrospective database analysis used eligibility, pharmacy, and medical claims data from a large U.S. health plan for patients with CHC treated with peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin from January 2002 through June 2006. For the purposes of this analysis, the study population included all hepatitis C virus (HCV) genotypes. Comparable groups for assessment of outcomes were constructed using propensity score matching to reduce the effect of known sources of bias. Outcome variables included treatment persistence and annualized overall and HCV-attributable health care costs. **RESULTS:** A total of 1783 matched pairs were analyzed. Compared with patients receiving peginterferon alfa-2a plus ribavirin, patients receiving peginterferon alfa-2b plus ribavirin were 18% less likely to be persistent with therapy at week 48 ( $p = 0.013$ ). During the first six months of follow-up, mean all-cause costs ( $p = 0.0368$ ) and HCV-attributable costs ( $p < 0.0001$ ) were significantly lower for peginterferon alfa-2a plus ribavirin than for peginterferon alfa-2b plus ribavirin. Mean annualized all-cause costs ( $p = 0.0060$ ) and HCV-attributable costs ( $p = 0.0167$ ) over the entire follow-up period were significantly lower for patients treated with peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin. **CONCLUSION:** Analysis of information from a health care claims database suggests that treating CHC with peginterferon alfa-2a plus ribavirin may improve treatment persistence and help reduce the health care costs imposed by CHC compared with treatment with peginterferon alfa-2b plus ribavirin.

**Merimepodib, pegylated interferon, and ribavirin in genotype 1 chronic hepatitis C pegylated interferon and ribavirin nonresponders.**

Rustgi VK, Lee WM, Lawitz E, et al. *Hepatology.* 2009 Dec;50(6):1719-26.

[http://www.ncbi.nlm.nih.gov/pubmed/19852040?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19852040?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Merimepodib (MMPD) is an orally administered, inosine monophosphate dehydrogenase inhibitor that has shown antiviral activity in nonresponders with chronic hepatitis C (CHC) when combined with pegylated interferon alfa 2a (Peg-IFN-alfa-2a) and ribavirin (RBV). We conducted a randomized, double-blind, multicenter, phase 2b study to evaluate the antiviral activity, safety, and tolerability of MMPD in combination with Peg-IFN-alfa-2a and RBV in patients with genotype 1 CHC who were nonresponders to prior therapy with Peg-IFN and RBV. Patients received 50 mg MMPD, 100 mg MMPD, or placebo every 12 hours, in addition to Peg-IFN-alfa-2a and RBV, for 24 weeks. Patients with a 2-log or more decrease from baseline or undetectable hepatitis C virus (HCV) RNA levels at week 24 were then eligible to continue Peg-IFN-alfa-2a and RBV for a further 24 weeks, followed by 24 weeks of follow-up. The primary efficacy endpoint was sustained virological response (SVR) rate at week 72 in all randomized patients who received at least one dose of study drug and had a history of nonresponse to standard therapy. A total of 354 patients were randomized to treatment (117 to placebo; 119 to

50 mg MMPD; 118 to 100 mg MMPD), and 286 completed the core study. The proportion of patients who achieved SVR was similar among the treatment groups: 6% (6/107) for 50 mg MMPD, 4% (5/112) for 100 mg MMPD, and 5% (5/104) for placebo (P = 0.8431). Adverse-event profiles for the MMPD combination groups were similar to that for Peg-IFN-alfa and RBV alone. Nausea, arthralgia, cough, dyspnea, neutropenia, and anemia were more common in patients taking MMPD. **CONCLUSION:** The addition of MMPD to Peg-IFN-alfa-2a and RBV combination therapy did not increase the proportion of nonresponder patients with genotype 1 CHC achieving an SVR.

**Long-term outcome of hepatitis B and hepatitis C virus co-infection and single HBV infection acquired in youth.** Zampino R, Marrone A, Merola A, et al. J Med Virol. 2009 Dec;81(12):2012-20.

[http://www.ncbi.nlm.nih.gov/pubmed/19856471?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19856471?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Co-infection with HBV and HCV seems to be associated with more severe liver disease in retrospective and cross-sectional studies in adults, but no data are available when co-infection is acquired in youth. The long-term outcome of infection acquired in youth was assessed in patients co-infected with HBV and HCV and in patients with HBV infection only. Twenty-seven patients with HBV and HCV co-infection and 27 patients infected with HBV only were enrolled. Seventy-six per cent of the patients were treated with alpha-interferon for 1 year. After a median follow-up of 23 years, the annual progression rate of fibrosis was 0.07 in patients co-infected with HBV and HCV, and in those infected with HBV it was 0.07 and 0.11 (P < 0.004) for HBe and anti-HBe-positive patients, respectively. In co-infected patients, the development of cirrhosis was observed in 2 (7.4%) and of hepatocellular carcinoma (HCC) in 1 (3.7%), while in those with HBV, cirrhosis appeared in one patient (3.7%). Alcohol intake (OR = 9.5 +/- 1.2; 95% CI = 6.6-13.9; P < 0.0001) was independently associated with cirrhosis and HCC. alpha-interferon showed no efficacy during treatment, but the treated group showed higher HCV RNA clearance during post-treatment follow-up. Co-infection with HBV and HCV and single HBV infection acquired in youth showed a low rate of progression to liver fibrosis, no liver failure, and low development of HCC during a median follow-up of 23 years (range 17-40).

**Management of chronic hepatitis C patients who have relapsed or not responded to pegylated interferon alfa plus ribavirin.** Dieterich DT, Rizzetto M, Manns MP. J Viral Hepat. 2009 Dec;16(12):833-43.

[http://www.ncbi.nlm.nih.gov/pubmed/19889142?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19889142?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

Development of therapeutic strategies for patients with chronic hepatitis C who experience virological breakthrough, relapse or nonresponse lag behind those for treatment-naïve patients. The probability of a previously treated patient responding to re-treatment depends on the nature of the previous regimen, the magnitude of the response to previous treatment and the patient's characteristics. Relapsers have higher sustained virological response rates than nonresponders when re-treated with pegylated interferon plus ribavirin. Re-treatment of nonresponders to pegylated interferon plus ribavirin with the standard 48-week regimen resulted in an approximate 6% sustained response rate in the EPIC-3 program. In the REPEAT trial, the sustained response rate was significantly higher in nonresponders to pegylated interferon alfa-2b (12 kD) plus ribavirin randomized to 72 weeks of peginterferon alfa-2a (40 kD) plus ribavirin, compared with

a 48-week regimen (16% vs 8%,  $P = 0.0006$ ). Based on available data, extended treatment is the best option for these individuals. Undetectable viral RNA at week 12 is an important criterion for re-treatment in the REPEAT and EPIC studies. Maintenance therapy with pegylated interferon is generally ineffective in nonresponders and cannot be recommended. Directly acting antivirals may increase response rates and the burden of adverse events when combined with the standard of care, but will not be available for some years. **In conclusion**, after careful evaluation of an individual's benefit-risk ratio, a 72-week regimen is the preferred strategy for optimizing sustained response rates in patients who have not responded to the standard of care, provided that viral RNA is undetectable at week 12 of re-treatment.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**A Time-Resolved Fluorescence-Resonance Energy Transfer Assay for Identifying Inhibitors of Hepatitis C Virus Core Dimerization.** Kota S, Scampavia L, Spicer T, et al. Assay Drug Dev Technol. 2009 Dec 28. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20035614?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20035614?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Binding of hepatitis C virus (HCV) RNA to core, the capsid protein, results in the formation of the nucleocapsid, the first step in the assembly of the viral particle. A novel assay was developed to discover small molecule inhibitors of core dimerization. This assay is based on time-resolved fluorescence resonance energy transfer (TR-FRET) between anti-tag antibodies labeled with either europium cryptate (Eu) or allophycocyanin (XL-665). The N-terminal 106-residue portion of core protein (core106) was tagged with either glutathione-S-transferase (GST) or a Flag peptide. Tag-free core106 was selected as the reference inhibitor. The assay was used to screen the library of pharmacologically active compounds (LOPAC) consisting of 1,280 compounds and a 2,240-compound library from the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU). Ten of the 28 hits from the primary TR-FRET run were confirmed in a secondary amplified luminescent proximity homogeneous assay (ALPHA screen). One hit was further characterized by dose-response analysis yielding an IC(50) of 9.3 microM. This 513 Da compound was shown to inhibit HCV production in cultured hepatoma cells.

**Phospholipase A2 and Cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels.** Su KP, Huang SY, Peng CY, et al. Biol Psychiatry. 2009 Dec 23. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20034614?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20034614?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** Phospholipase A2 (PLA2) and cyclooxygenase 2 (COX2) are the two key enzymes in the metabolism of polyunsaturated fatty acids, which in turn play an important role in cytokine-induced depression and sickness behavior. **METHODS:** Patients with chronic hepatitis C viral infection ( $n = 132$ ) were assessed to examine the effects of seven single nucleotide polymorphisms in COX2 and PLA2 genes on the development of depression during interferon (IFN)-alpha treatment; a subsample ( $n = 63$ ) was assessed for the erythrocyte levels of the three main polyunsaturated fatty acids, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid. An independent "replication" sample of patients with major depression unrelated to cytokine treatment ( $n = 82$ ) was also examined. **RESULTS:** Twenty-eight percent

of participants developed INF-alpha-induced depression. Participants with the PLA2 BanI GG or the COX2 rs4648308 AG genotypes had a higher risk of IFN-alpha-induced depression (odds ratio = 3.1 and 3.5, respectively). The "at risk" PLA2 genotype was associated with lower EPA levels, and the "at risk" COX2 genotype was associated with lower DHA levels, during IFN-alpha treatment. The PLA2 BanI GG polymorphism was also associated with more somatic symptoms of depression, both in patients with INF-alpha-induced depression and in the replication sample of patients with major depression. **CONCLUSIONS:** Genetic variations in the COX2 and PLA2 genes increase the risk of IFN-alpha-induced depression, possibly by affecting the levels of EPA and DHA. Moreover, PLA2 genotype is associated with somatic symptoms in depression. Our study confirms the role of inflammatory mechanisms in major depression.

**Generation of cellular immune responses to HCV NS5 protein through in vivo activation of dendritic cells.** Wintermeyer P, Gehring S, Eken A, Wands JR. J Viral Hepat.. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20002303?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20002303?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Chronic hepatitis C (HCV) infection is a substantial medical problem that leads to progressive liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The aim of this study was to achieve sustained cellular immune responses in vivo to a HCV nonstructural protein using dendritic cell (DC)-based immunization approach. We targeted the HCV NS5 protein to DCs in vivo by injecting microparticles loaded with this antigen. The DC population was expanded in BALB/C mice (H-2(d)) by hydrodynamic injection of a plasmid pUMVC3-hFLex expressing the secreted portion of the human Fms-like tyrosine kinase receptor-3 ligand (hFlt3). Mice were subsequently injected with microparticles coated with HCV NS5 protein via the tail vein. Cellular immune responses were determined with respect to secretion of INFgamma and IL2 by CD4(+) cells and cytotoxic T-lymphocyte (CTL) assays in vitro; inhibition of tumour cell growth was employed for the assessment of CD8(+) generated activity in vivo. We found that Flt3L treatment expanded the DC population in the spleen to 43%, and such cells displayed a striking upregulation of CD86 as well as CD80 and CD40 co-stimulating molecules. Viral antigen-specific T(H)1 cytokine secretion by splenocytes was generated, and CTL activity against syngeneic NS5 expressing myeloma target cells was observed. In addition, these cells inhibited tumour growth indicating that NS5-specific robust CTL activity was operative in vivo. Thus, the capability of activating DCs in vivo using the methods described is valuable as a therapeutic vaccine strategy for chronic HCV infection.

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## HIV/HCV COINFECTION

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**Hepatitis C viral kinetics during treatment with peg IFN-alpha-2b in HIV/HCV co-infected patients as a function of baseline CD4+ T-cell counts.** Avidan NU, Goldstein D, Rozenberg L, et al. J Acquir Immune Defic Syndr. 2009 Dec 1;52(4):452-8.

[http://www.ncbi.nlm.nih.gov/pubmed?term=%22Avidan%20NU%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Avidan%20NU%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** HIV/hepatitis C virus (HCV) coinfecting patients are known to have lower sustained viral response (SVR) rates than HCV mono-infected patients. However, the role of CD4+ T-cell counts on viral kinetics and outcome is not fully understood. **METHODS:** HCV

RNA kinetics (bDNA v3, lower limit of detection [LD] = 615 IU/mL) was analyzed in 32 HIV/HCV coinfecting persons treated with Pegylated-interferon-alpha2b (1.5 microg/kg weekly) and ribavirin (1-1.2 g daily) for 48 weeks and compared with results obtained from 12 HCV monoinfected patients treated with the same regimen. **RESULTS:** Baseline CD4+ T-cell counts  $\geq$  450 cells/mm<sup>3</sup> were significantly ( $P < 0.002$ ) associated with SVR in coinfecting genotype 1 patients. First phase decline was significantly lower among patients with low as compared with high CD4 counts ( $P < 0.03$ ) and among coinfecting compared with monoinfected patients ( $P < 0.002$ ). Second phase decline slope showed a similar trend for coinfecting patients.

**CONCLUSIONS:** Low baseline CD4+ T-cell count is associated with slower HCV viral kinetics and worse response to treatment among HIV coinfecting patients, suggesting HCV treatment response depends on immune status. HCV genotype 1 coinfecting patients have slower first phase viral kinetics than HCV monoinfected patients. First phase viral decline ( $>1.0$  log) and second phase viral decline slope ( $>0.3$  log/wk) are excellent predictors of SVR for coinfecting patients.

**Risk factors for thrombocytopenia in HIV-infected persons in the era of potent anti-retroviral therapy.** Marks KM, Clarke RM, Bussel JB, Talal AH, Glesby MJ. J Acquir Immune Defic Syndr. 2009 Dec;52(5):595-9.

[http://www.ncbi.nlm.nih.gov/pubmed/19734800?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19734800?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**OBJECTIVE:** Before potent antiretroviral therapy, thrombocytopenia was observed frequently. Little is known about risk factors for or severity and consequences of thrombocytopenia since establishment of highly effective therapy for HIV. **METHODS:** We conducted a retrospective-matched case-control study of HIV-infected adult outpatients with and without thrombocytopenia to elucidate the contribution of HIV viremia, hepatitis C infection, and other potential risk factors for thrombocytopenia. Seventy-three cases with thrombocytopenia (platelet count  $<100 \times 10^9/L$  persistent for  $>3$  months) were matched by age, sex, and first clinic visit with 73 nonthrombocytopenic controls. Risk factors and outcomes were assessed using conditional logistic regression. **RESULTS:** Nadir platelet counts in cases were  $\leq 50 \times 10^9/L$  in 58% and  $\leq 30 \times 10^9/L$  in 38%. In multivariate modeling, HIV RNA  $>400$  copies/ml, hepatitis C virus infection, and cirrhosis were significantly associated with thrombocytopenia with adjusted odds ratios of 5.3 [confidence interval (CI) 1.6-17.1,  $P = 0.006$ ], 6.1 (CI 1.6-22.6,  $P = 0.007$ ), and 24.0 (CI 1.7-338,  $P = 0.019$ ), respectively. Thrombocytopenia was significantly associated with major bleeding events and nonbleeding-related death. **CONCLUSIONS:** Thrombocytopenia in the era of potent antiretroviral therapy is associated with hepatitis C virus infection, cirrhosis, and uncontrolled HIV replication, and serious complications including major bleeding and death.

**Hepatitis B and hepatitis C seroprevalence in children receiving antiretroviral therapy for human immunodeficiency virus-1 infection in China, 2005-2009.** Zhou S, Zhao Y, He Y, et al. J Acquir Immune Defic Syndr. 2009 Dec 23. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20032784?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20032784?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** Coinfection of hepatitis B virus (HBV) or hepatitis C virus (HCV) may compromise pediatric antiretroviral therapy (ART) in China. In this study, we evaluated the seroprevalence of HBV and HCV in children receiving ART and associated factors.

**METHODS:** Patients were selected from HIV-1-infected children under age 16 enrolled in China National Pediatric ART Cohort since July 2005. Medical assessments, hepatitis B surface antigen (HBsAg), and anti-HCV antibody serologies, and transaminase levels were obtained for analysis. **RESULTS:** A total of 53 of 1082 children tested were HBsAg seropositive [4.9%; 95% confidence interval (CI): 3.6% to 6.2%], and 90 of 938 children tested were anti-HCV antibody positive (9.6%; 95% CI: 7.7% to 11.5%). No other serologic assays were performed for HBV detection. Age was associated with HBV coinfection in univariate analysis; older children were more likely to be HBsAg positive. Multivariate analysis revealed that children infected with HIV through transfusion of contaminated blood or blood products were more likely to be anti-HCV antibody positive than those infected with HIV through other routes (adjusted odds ratio = 6.2; 95% CI: 3.3% to 11.7%). **CONCLUSIONS:** The high prevalence of HBV and HCV coinfection in HIV-infected children in China receiving ART demands routine screening for viral hepatitis coinfection, intensive prevention of childhood HBV and HCV transmission, and modification of the management of pediatric HIV infection.

**Factors associated with the progression of hepatic fibrosis in end-stage kidney disease patients with hepatitis C virus infection.** Becker VR, Badiani RG, Lemos LB, et al. Eur J Gastroenterol Hepatol. 2009 Dec;21(12):1395-9.

[http://www.ncbi.nlm.nih.gov/pubmed/19525852?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19525852?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**BACKGROUND:** Few studies have evaluated the histological aspects of hepatitis C virus (HCV) infection in hemodialysis patients and the factors related to the progression of hepatic fibrosis in this population have not been defined. AIM: To evaluate the influence of host-related factors on the fibrosis progression in end-stage renal disease (ESRD) patients with HCV infection. **METHODS:** HCV-infected ESRD patients who submitted to liver biopsy were included. The fibrosis stages were classified according to METAVIR scoring system. For the identification of factors associated with more advanced liver fibrosis, the patients were classified into two groups: group 1, absence of septal fibrosis (F0-1) and group 2, presence of septal fibrosis (F2-4). Groups 1 and 2 were compared regarding demographic, epidemiological, and laboratory variables and logistic regression analysis was used to identify the variables that were independently associated with the presence of septal fibrosis. **RESULTS:** A total of 216 ESRD patients (63% men, 44+/-11 years) were included. In the histological analysis, the fibrosis stages were as follows: F0=36%, F1=41%, F2=12%, F3=7, and 4% had cirrhosis (F4). In the logistic regression model, the variables that were independently associated with the presence of septal fibrosis were duration of infection, estimated age at infection, coinfection with HBV and aspartate aminotransferase levels. **CONCLUSION:** These findings support the importance of obtaining an adequate immune response to HBV vaccination and careful monitoring of liver disease in patients who become infected at an advanced age and/or those presenting elevated aspartate aminotransferase levels, as these are the main factors associated with the presence of septal fibrosis in ESRD patients.

**Factors that influence an HIV coinfecting patient's decision to start hepatitis C treatment.** Osilla KC, Ryan G, Bhatti L, Goetz M, Witt M, Wagner G. AIDS Patient Care STDS. 2009 Dec;23(12):993-9.

[http://www.ncbi.nlm.nih.gov/pubmed/19929229?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19929229?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Liver disease is a leading cause of morbidity and mortality among patients coinfecting with HIV and hepatitis C (HCV), yet few HIV coinfecting patients actually receive HCV treatment. Providers must first be willing to prescribe treatment, but the patient ultimately makes the decision to accept or decline a treatment recommendation. We used a process model framework to explore the factors influencing patients' treatment decision-making. We conducted semistructured interviews with 35 HIV coinfecting patients and 11 primary care providers at three HIV clinics in Los Angeles, California. Patients reported that stability of HIV disease, perceived need for HCV treatment, treatment readiness, willingness to deal with side effects, absence of substance abuse, and stability of mental health and overall life circumstances are key factors influencing treatment decision-making. Patients also spoke of the influence of the trusting relationship that many had with their provider, and providers acknowledged an awareness of the influence of how they present the risks and benefits of HCV treatment and the overall tone of their recommendation (encouraging, dissuasive, or neutral). These results speak to a social decision-making process between the patient and provider—a partnership that involves sequential interactions whereby both the patient and provider may influence the other's evaluation of the patient's readiness for treatment, with treatment initiation dependent on both agreeing on the need for treatment and the patient's readiness for treatment.

**Association between plasma levels of eotaxin (CCL-11) and treatment response to interferon- $\alpha$  and ribavirin in HIV/HCV co-infected patients.** Vargas A, Berenguer J, Catalán P, et al. J Antimicrob Chemother. 2009 Dec 16. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20016018?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/20016018?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**OBJECTIVES:** To analyse the association between plasma chemokine levels at baseline and virological response to interferon- $\alpha$  (IFN- $\alpha$ ) + ribavirin in human immunodeficiency virus (HIV)/hepatitis C virus (HCV) co-infected patients. **METHODS:** We carried out a retrospective study in 109 patients. Chemokines were measured using Multiplex kits using a Luminex 100 Analyzer. Logistic regression was used to evaluate the association between plasma chemokine levels before HCV therapy and virological response at weeks 48 and 72 after starting HCV therapy. **Results:** Fifty-seven patients out of 103 achieved end of treatment virological response (ETR). In patients achieving ETR, the baseline levels of eotaxin, MCP-1 and MCP-3 were higher than non-responder (NR) patients. Similarly, 51 patients out of 106 achieved sustained virological response (SVR). In patients achieving SVR, the baseline levels of eotaxin and MCP-1 were higher than in NR patients. Plasma levels of eotaxin, MCP-1 and MCP-3 had a significant positive association with ETR, as well as eotaxin and MCP-1 with SVR. However, after stepwise multivariate logistic regression, eotaxin was the only chemokine selected capable of predicting ETR and SVR with odds ratio (OR) of 1.016 (95% CI: 1.004-1.029) and 1.015 (95% CI: 1.002-1.027) for ETR and SVR, respectively. **CONCLUSIONS:** Our preliminary data suggest that plasma eotaxin levels prior to HCV antiviral therapy may be useful in predicting virological response to HCV treatment with IFN- $\alpha$  + ribavirin in HIV/HCV co-infected patients. Further experimental research is necessary to corroborate this hypothesis.

**Curcumin inhibits hepatitis C virus replication via suppressing the Akt-SREBP-1 pathway.**

Kim K, Kim KH, Kim HY, et al. FEBS Lett. 2009 Dec 17. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20026048?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=4](http://www.ncbi.nlm.nih.gov/pubmed/20026048?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=4)

A polyphenolic compound from the curry spice turmeric, curcumin, is known to show anti-viral activity against the influenza virus, adenovirus, coxsackievirus, and the human immunodeficiency virus. However, it remains to be determined whether curcumin can inhibit the replication of hepatitis C virus (HCV). In this study, we showed that curcumin decreases HCV gene expression via suppression of the Akt-SREBP-1 activation, not by NF-kappaB pathway. The combination of curcumin and IFNalpha exerted profound inhibitory effects on HCV replication. Collectively, our results indicate that curcumin can suppress HCV replication in vitro and may be potentially useful as novel anti-HCV reagents.

**Lamiridosins, hepatitis C virus entry inhibitors from *Lamium album*.**

Zhang H, Rothwangl K, Mesecar AD, et al. J Nat Prod. 2009 Dec 28;72(12):2158-2162.

[http://www.ncbi.nlm.nih.gov/pubmed/19904996?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=8](http://www.ncbi.nlm.nih.gov/pubmed/19904996?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=8)

Phytochemical study of the aqueous extract of the flowering tops of *Lamium album* led to identification of the antiviral iridoid isomers lamiridosins A and B (1, 2). These compounds were found to significantly inhibit hepatitis C virus entry (IC<sub>50</sub>) 2.31 μM) in vitro. Studies of 14 iridoid analogues showed that, while the parent iridoid glucosides demonstrated no anti-HCV entry activity, the aglycones of shanzhiside methyl ester (4), loganin (5), loganic acid (6), geniposide (10), verbenalin (12), eurostoside (15), and picroside II (17) exhibited significant anti-HCV entry and anti-infectivity activities.

**Silibinin and related compounds are direct inhibitors of hepatitis c virus RNA-dependent RNA polymerase.**

Ahmed-Belkacem A, Ahnou N, Barbotte L, et al. Gastroenterology. 2009

Dec 4. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19962982?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19962982?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND & AIMS:** Silymarin is a mixture of flavonolignans extracted from the milk thistle. Silymarin contains several molecules, including silibinin A, silibinin B, isosilibinin A, isosilibinin B, silicristin, and silidianin. Intravenous infusion of silibinin induces dose-dependent reduction of hepatitis C virus (HCV) RNA levels. The aim of this study was to test the principal isomers contained in silymarin preparations for their ability to inhibit HCV enzymatic functions and replication in different models. **METHODS:** The inhibitory activity of silymarin components was tested in HCV RNA-dependent RNA polymerase and NS3/4A protease enzyme assays. Their ability to inhibit replication of an HCV genotype 1b replicon model and the JFH1 infectious HCV model in cell culture was also studied. **RESULTS:** Silibinin A, silibinin B, their water-soluble dihydrogen succinate forms and Legalon SIL, a commercially available intravenous preparation of silibinin, inhibited HCV RNA-dependent RNA polymerase function, with inhibitory concentrations 50% of the order of 75-100 μM. Silibinin A and silibinin B also inhibited HCV genotype 1b replicon replication and HCV genotype 2a strain JFH1 replication in

cell culture. None of these compounds inhibited HCV protease function. **CONCLUSIONS:** Silibinin A and silibinin B, as well as Legalon SIL, inhibit HCV replicon and JFH1 replication in cell culture. This effect is at least partly explained by the ability of these compounds to inhibit HCV RNA-dependent RNA polymerase activity. Our results provide a basis for the optimization and subsequent development of members of the Flavonoid family as specific HCV antivirals.

**Prevalence of vitamin d deficiency in chronic liver disease.** Arteh J, Narra S, Nair S. Dig Dis Sci. 2009 Dec 4. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19960254?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19960254?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Vitamin D deficiency has been associated with cholestatic liver disease such as primary biliary cirrhosis. Some studies have suggested that cirrhosis can predispose patients to development of osteoporosis because of altered calcium and vitamin D homeostasis. The aim of this study was to determine the prevalence of vitamin D deficiency in patients with chronic liver disease.

**METHODS:** One hundred and eighteen consecutive patients (43 with hepatitis C cirrhosis, 57 with hepatitis C but no cirrhosis, 18 with nonhepatitis C-related cirrhosis) attending the University of Tennessee Hepatology Clinic had their 25-hydroxyvitamin D level measured. Severity of vitamin D deficiency was graded as mild (20-32 ng/ml), moderate (7-19 ng/ml) or severe (<7 ng/ml), normal being >32 ng/ml. **RESULTS:** Of patients, 109/118 (92.4%) had some degree of vitamin D deficiency. In the hepatitis C cirrhosis group, 16.3% (7/43) had mild, 48.8% (21/43) had moderate, and 30.2% (13/43) had severe vitamin D deficiency. In the hepatitis C noncirrhotic group, 22.8% (19/57) had mild, 52.6% (30/57) had moderate, and 14% (8/57) had severe vitamin D deficiency. In the nonhepatitis C-related cirrhosis group, 38.9% (7/18) had mild, 27.8% (5/18) had moderate, and 27.8% (5/18) had severe vitamin D deficiency. Severe vitamin D deficiency (<7 ng/ml) was more common among patients with cirrhosis compared with noncirrhotics (29.5% versus 14.1%, P value = 0.05). Female gender, African American race, and cirrhosis were independent predictors of severe vitamin D deficiency in chronic liver disease. **CONCLUSION:** Vitamin D deficiency is universal (92%) among patients with chronic liver disease, and at least one-third of them suffer from severe vitamin D deficiency. African American females are at highest risk of vitamin D deficiency.

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Frequency of alcohol and smoking cessation counseling in hepatitis C patients among internists and gastroenterologists.** Chandra T, Reyes M, Nguyen H, Borum M. World J Gastroenterol. 2009 Dec 21;15(47):6010-1.

[http://www.ncbi.nlm.nih.gov/pubmed/20014469?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20014469?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Given the overwhelming evidence that both alcohol consumption and smoking accelerate the progression of hepatitis C virus (HCV)-induced liver disease, we evaluated the frequency of alcohol and smoking counseling of patients with HCV-induced liver disease by their primary care internists and gastroenterologists. One hundred and twenty-three medical records of consecutive patients with HCV-induced liver disease referred by an internist to a gastroenterologist for its management were reviewed. Patient gender, race, history of and counseling against alcohol and tobacco use by a physician and a gastroenterologist were obtained. A database was created using Microsoft Excel. There were 105 African-Americans, 12

Caucasians and six patients of other races/ethnicities. Forty-six (37%) patients were daily tobacco users and 34 (28%) patients were daily alcohol consumers. There was a statistically significant difference in the frequencies of alcohol ( $P = 0.0002$ ) and smoking cessation ( $P = 0.0022$ ) between gastroenterologists and internists. This study reveals that internists and gastroenterologists, alike, inadequately counsel patients with hepatitis C about tobacco and alcohol use.

**Real-time quantitative assay for routine testing of HCV RNA in formalin-fixed, paraffin-embedded liver samples.** Gruppioni E, Vasuri F, Fiorentino M, et al. *Diagn Mol Pathol*. 2009 Dec;18(4):232-8.

[http://www.ncbi.nlm.nih.gov/pubmed/19861893?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=5](http://www.ncbi.nlm.nih.gov/pubmed/19861893?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=5)

The assessment of hepatitis C virus (HCV) RNA in liver tissues is clinically relevant in cases where histology, liver function tests, and HCV serology are not sufficient for a definitive diagnosis of HCV-related hepatitis. We analyzed 215 formalin-fixed, paraffin-embedded liver needle biopsies from patients infected with HCV genotypes 1b and 2. HCV RNA extracted from paraffin sections were quantified by means of a TaqMan real-time reverse transcription-polymerase chain reaction method. The quantification of HCV RNA in liver tissue was correlated with the amount of HCV detected by immunohistochemistry (IHC) on paired frozen biopsies, the HCV RNA load in the serum, and the main serum tests of liver function and cholestasis. HCV RNA was detected by real-time reverse transcription-polymerase chain reaction in 169 liver biopsies (78.6%) with a mean value of  $13.59 \pm 37.25$  IU/ng. Tissue HCV RNA levels strongly correlated with the IHC results ( $P < 0.001$ , Spearman test), HCV serum load ( $P < 0.001$ ), aspartate aminotransferase ( $P = 0.001$ ), gamma-glutamyl transpeptidase ( $P = 0.012$ ), and aspartate aminotransferase/alanine aminotransferase ratio ( $P = 0.029$ ). HCV RNA was amplified in up to 7-year-old archival tissue samples. Real-time HCV RNA quantification on archival liver tissue may be clinically relevant in case of "occult" HCV infection or for the diagnosis of patients with known HCV infection and hepatic dysfunction but seronegative for HCV RNA. The assessment of the levels of HCV RNA in the liver might also be important for monitoring the effectiveness of antiviral therapy and the progression of disease in patients with chronic HCV hepatitis.

**Public health impact of antiviral therapy for hepatitis C in the United States.** Volk ML, Tocco R, Saini S, Lok AS. *Hepatology*. 2009 Dec;50(6):1750-5.

[http://www.ncbi.nlm.nih.gov/pubmed/19824079?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=4](http://www.ncbi.nlm.nih.gov/pubmed/19824079?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=4)

Despite dramatic improvements in antiviral therapy for hepatitis C, there is reason to believe that the uptake of antiviral therapy remains limited. The aims of this study were to determine the number of patients being treated with antiviral therapy in the U.S., to estimate the public health impact of these treatment patterns, and to identify barriers to treatment for patients with hepatitis C. Data on the number of new patient pegylated interferon prescriptions each year, from 2002-2007, was obtained from Wolters Kluwer Inc., which maintains an electronic audit of pharmacies nationwide. A Markov model was created of the population with chronic hepatitis C in the U.S. from 2002 to 2030, and was used to estimate the number of liver-related deaths caused by hepatitis C that will be prevented by current treatment patterns. The National Health and Nutrition Evaluation Survey (NHANES) Hepatitis C Follow-Up Questionnaire was used to

investigate reasons for lack of treatment and to identify strategies for improving access. Approximately 663,000 patients received antiviral therapy between 2002 and 2007, and treatment rates appear to be declining. If this trend continues, only 14.5% of liver-related deaths caused by hepatitis C from 2002-2030 will be prevented by antiviral therapy. Results from the NHANES questionnaire suggest that the primary barrier to treatment is lack of diagnosis, with 69/133 (adjusted proportion 49%) of respondents previously unaware that they had hepatitis C. **CONCLUSION:** Efforts to improve rates of diagnosis and treatment will be required if the future public health burden of hepatitis C is to be ameliorated.

**Europe's hepatitis challenge: defusing the "viral time bomb".** Piorkowsky NY. J Hepatol. 2009 Dec;51(6):1068-73.

[http://www.ncbi.nlm.nih.gov/pubmed?term=%22Piorkowsky%20NY%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Piorkowsky%20NY%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Since its foundation in 2005, the European Liver Patients' Association (ELPA) - a not-for-profit-organisation with 21 members across Europe - has been at the forefront of raising awareness of liver diseases, in particular hepatitis, throughout the EU. In line with the main challenge for hepatitis carriers, which is to "become a patient", ELPA calls for targeted screening of risk groups in order to facilitate early diagnosis and, if appropriate, treatment. To this end, ELPA and its members have embarked on a multi-level lobbying campaign, involving EU and national policymakers, liver specialist associations and public health experts. First successes include the adoption of the European Parliament's Written Declaration on Hepatitis C and the European Centre for Disease Prevention and Control's (ECDC) decision to include viral hepatitis in its annual work plan as of 2008, as well as a compilation of expert recommendations on screening, which were endorsed by the European Association for the Study of the Liver (EASL). For a sustainable change in the perception of liver diseases by the public and decision-makers in public health and a subsequent improvement of the situation for patients and specialists, it will be important for both to move beyond the immediate doctor-patient relationship and address jointly a wider audience. Essential in this context is the link to cancer. Policymakers have to know that by taking preventative measures (primary and secondary) against liver disease they prevent liver cancer, one of the few cancers on the rise in Europe.

**Peripheral CXCR3-associated chemokines as biomarkers of fibrosis in chronic hepatitis C virus infection.** Zeremski M, Dimova R, Brown Q, et al. J Infect Dis. 2009 Dec 1;200(11):1774-80.

[http://www.ncbi.nlm.nih.gov/pubmed/19848607?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19848607?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** CXCR3-associated chemokines CXCL9-CXCL11 promote histologic progression in chronic hepatitis C virus (HCV) infection, as indicated by elevated intrahepatic levels of messenger RNA in patients with advanced inflammation and fibrosis. We evaluated the potential of peripheral chemokine levels to discriminate among patients with chronic HCV infection who had different stages of fibrosis. **METHODS:** Peripheral levels of CXCR3-associated chemokines were measured by enzyme-linked immunosorbent assay of plasma samples obtained from 93 patients with chronic HCV infection. Of the subjects, 79 (85%) were white, and 68 (73%) were infected with HCV genotype 1. **RESULTS:** Expression of all 3 chemokines, when analyzed as a group, was significantly associated with intrahepatic inflammation and fibrosis. Plasma levels of CXCL10 were significantly elevated in patients with

advanced fibrosis, whereas CXCL9 levels were significantly elevated in patients with advanced inflammation. By proportional odds multivariate modeling, we observed an association between fibrosis and CXCL10 ( $P < .002$ ) as well as between fibrosis and inflammation ( $P < .001$ ). Of the individual parameters, the CXCL10 level was most useful in identifying patients with more-severe (stage 3-4) fibrosis. Discriminatory ability was improved by the combination of CXCL10 and CXCL9. **CONCLUSIONS:** The strong association between CXCR3-associated chemokines and fibrosis suggests that they may have promise as noninvasive markers of hepatic fibrosis in a predominantly white HCV genotype 1-infected population.

**The complement component C3a fragment is a potential biomarker for hepatitis C virus-related hepatocellular carcinoma.** Kanmura S, Uto H, Sato Y, et al. J Gastroenterol.. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/20012107?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/20012107?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** Hepatocellular carcinoma (HCC) has a high mortality rate, and early detection of HCC improves patient survival. However, the molecular diagnostic markers for early HCC have not been fully elucidated. The aim of this study was to identify novel diagnostic markers for HCC. **METHODS:** Serum protein profiles of 45 hepatitis C virus infection (HCV)-related HCC patients (HCV-HCC) were compared to 42 HCV-related chronic liver disease patients without HCC (HCV-CLD) and 21 healthy volunteers using the ProteinChip SELDI system. One of the identified proteins was evaluated as a diagnostic marker for HCC in patients with HCV. **RESULTS:** Five protein peaks (4067, 4470, 7564, 7929, and 8130 m/z) had p-values less than  $1 \times 10^{-7}$  and were significantly increased in the sera of HCV-HCC patients compared to HCV-CLD patients and healthy volunteers. Among these proteins, an 8130 m/z peak was the most differentially expressed and identified as the complement component 3a (C3a) fragment. For HCV-HCC and HCV-CLD, the relative intensity of this C3a fragment had the best area under the ROC curve [0.70], followed by des-gamma-carboxy prothrombin (DCP) [0.68], lectin-bound alpha fetoprotein (AFP-L3) [0.58] and AFP [0.53] for HCC. A combined analysis of the C3a fragment, AFP and DCP led to a 98% positive identification rate. In addition, the measurable C3a fragment in some HCC patients was not only significantly higher in the year of HCC onset compared to the pre-onset year, but also decreased after treatment. **CONCLUSIONS:** The 8130 m/z C3a fragment is a potential marker for the early detection of HCV-related HCC.