

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

Coffee Consumption is Associated with Response to Peginterferon and Ribavirin Therapy in Patients with Chronic Hepatitis C. Freedman ND, Curto TM, Lindsay KL, et al.

Gastroenterology. 2011 Mar 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21376050>

BACKGROUND & AIMS: High level coffee consumption has been associated with reduced progression of pre-existing liver diseases and lower risk of hepatocellular carcinoma. However, its relationship with therapy for Hepatitis C virus (HCV) infection has not been evaluated.

METHODS: Patients (n=885) from the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial recorded coffee intake before re-treatment with peginterferon alfa-2a (180 µg/wk) and ribavirin (1000-1200 mg/day). We assessed patients for early virologic response (EVR, 2 log(10) reduction in level of HCV RNA at week 12; n=466) and undetectable HCV RNA at week 20 (W20VR; n=320), week 48 (end of treatment, EOT; n=284), and week 72 (sustained virologic response, SVR; n=157). **RESULTS:** The median log(10) drop from baseline to week 20 was 2.0 (interquartile range: 0.6-3.9) among non-drinkers and 4.0 (2.1-4.7) among patients that drank ≥3 cup/day of coffee (P-trend <0.0001). In unadjusted models, the odds ratios (OR) and 95% confidence intervals (CI) for drinking ≥3 cups/day vs non-drinking were 3.2 (1.9-5.3) for EVR, 3.1 (1.8-5.1) for W20VR, 3.5 (2.0-5.9) for EOT, and 2.7 (1.4-5.3) for SVR (P-trend<0.0001 for all). After adjustment for age, race/ethnicity, sex, alcohol, cirrhosis, ratio of aspartate aminotransferase: alanine aminotransferase, the IL28B polymorphism rs12979860, dose reduction of peginterferon, and other covariates, the OR (95% CI) for EVR was 2.0 (1.1-3.6; P-trend = 0.004); for W20VR was 2.1 (1.1-3.9; p-trend=0.005); for EOT was 2.4 (1.3-4.6; P-trend=0.001), and for SVR was 1.8 (0.8-3.9; P-trend=0.034). **CONCLUSION:** High-level consumption of coffee (more than 3 cups per day) is an independent predictor of improved virologic response to peginterferon plus ribavirin in patients with Hepatitis C.

Insulin Resistance Is Independently Associated With Significant Hepatic Fibrosis in Asian Chronic Hepatitis C Genotype 2 Or 3 Patients. Patel K, Thompson A, Chuang W, et al. *J Gastroenterol Hepatol.* 2011 Mar 16. doi: 10.1111/j.1440-1746.2011.06722.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21410752>

BACKGROUND: The role of insulin resistance (IR) and hepatic steatosis in fibrogenesis in chronic hepatitis C infection (CHC) has yielded conflicting data and few studies have been performed in Asian-region populations. We retrospectively investigated the relationship between host metabolic variables, including IR and hepatic steatosis, to hepatic fibrosis in Asian-region CHC genotype 2/3 patients. **METHODS:** 303 treatment-naïve Asian-region patients with CHC Genotype 2/3 were enrolled in a multicenter phase 3, study of albinterferon alfa-2b plus ribavirin for 24 weeks. IR was defined as HOMA-IR > 2. Baseline liver biopsy was evaluated by a single expert histopathologist. Post hoc subgroup logistic regression modeling selected for independent variables associated with significant fibrosis (METAVIR stage F2-F4) **RESULTS:** IR was available in 263 non-diabetic Asian-region patients (HCV-2 = 171, HCV-3 = 92), and 433 non-Asian region patients (407 "Caucasian"); METAVIR fibrosis prevalence F0-F1 (minimal fibrosis) = 201(77%) and F2-F4 (significant fibrosis) = 59 (23%), and steatosis prevalence of grade 0 = 169 (65%), grade 1 = 64 (25%), grade 2/3 = 27 (10%). Median HOMA-IR was 1.8 (Interquartile range: 1.2 - 2.7); 100 (38%) of patients had HOMA-IR > 2. Factors independently associated with significant fibrosis included HOMA-IR (OR = 8.42), necro-inflammatory grade (OR = 3.17), age (OR = 1.07) and serum total cholesterol levels (OR = 0.008). This was similar to non-Asian region patients, but steatosis was not associated with significant fibrosis in either cohort. **CONCLUSIONS:** In this subgroup study of Asian-region HCV Genotype-2 or -3 patients, insulin resistance, along with age, cholesterol levels and necro-inflammation, but not steatosis may be associated with significant hepatic fibrosis.

Genetic variation in IL28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV infected children. Ruiz-Extremera A, Muñoz-Gómez J, Salmerón-Ruiz MA, et al. *Hepatology.* 2011 Mar 16. doi: 10.1002/hep.24298. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21413051>

The vertical transmission of Hepatitis C Virus (HCV-VT) is a major route of HCV infection in children, but the risk factors remain incompletely understood. This study analyses the role of IL28B in HCV-VT and in the spontaneous clearance of HCV among infected infants. Between 1991 and 2009, 145 mothers were recruited to this study: 100 were HCV-RNA+ve/HIV-ve, with 128 children, and 33 were HCV-RNA-ve/HCV antibody+ve, with 43 children. The infants were tested for HCV-RNA at birth and at regular intervals until the age of 6 years. IL28B (single nucleotide polymorphism rs12979860) was determined in the mothers and children. HCV-VT was assumed when children presented HCV-RNA+ve in two subsequent blood samples. HCV-VT infected infants were categorized as: (A) transient viremia with posterior HCV-RNA-ve and without serum-conversion; (B) persistent infection with serum-conversion. Of the 31 mothers with CC polymorphism, 19(61%) were HCV-RNA+ve whereas among the 68 mothers with non-CC polymorphism, 56(82%) were HCV-RNA+ve. 26 of 128(20%) infants born to the HCV-RNA+ve mothers acquired HCV infection, but only 9(7%) were chronically infected. The rate of HCV-VT was higher among the mothers with higher HCV viremia. No HCV-VT was detected in the HCV-RNA-ve women. Neither the mothers' nor the children's IL-28 status was associated

with an increased risk of HCV-VT. The factors influencing viral clearance among the infected children were genotype non-1 and genotype CC of the IL28B. In logistic regression, child CC polymorphism was the only predictor of HCV-clearance in HCV genotype-1. **CONCLUSIONS:** High maternal viral load is the only predictive factor of HCV-VT. IL28B plays no role in HCV-VT, but IL28B CC child polymorphism is associated independently with the spontaneous clearance of HCV genotype-1 among infected children.

No increase in depression with low-dose maintenance peginterferon in prior non-responders with chronic hepatitis C. Kronfol Z, Litman HJ, Back-Madruga C, et al. *J Affect Disord.* 2011 Mar;129(1-3):205-12.

<http://www.ncbi.nlm.nih.gov/pubmed/20889211>

BACKGROUND: Peginterferon and ribavirin treatment of chronic hepatitis C (CHC) is frequently associated with dose-limiting neuropsychiatric toxicity. The purpose of this study is to determine whether prolonged administration of low-dose peginterferon- α 2a is associated with an increase in the rate and severity of depression compared to untreated controls. **METHODS:** 129 non-responders to full-dose peginterferon and ribavirin treatment were randomized to low-dose maintenance treatment with peginterferon- α 2a 90 μ g/week or no treatment for 3.5 years. Depression was assessed using the Beck Depression Inventory (BDI-II) and the Composite International Diagnostic Interview (CIDI) at baseline and at 12, 24, 36, and 48 months. "Clinical depression" was defined as BDI-II \geq 11 and/or meeting DSM-IV criteria for major depression on the CIDI. Serial cortisol and serotonin plasma concentrations were obtained in a subgroup of patients. **RESULTS:** Rates of clinical depression did not significantly differ over time or between treatment groups. Baseline clinical depression was the only significant predictor of clinical depression over time ($p < 0.001$). Rates of clinical depression were also significantly higher in patients experiencing liver disease progression ($p = 0.016$). Antidepressant use did not significantly differ between groups. Adjusted whole blood serotonin levels dropped significantly over time ($p = 0.04$), but there was no group by time effect. **LIMITATIONS:** Lack of significant group differences in antidepressant use does not completely preclude significant mood changes masked by antidepressants. Results may differ in treatment naïve CHC patients or in those receiving full-dose peginterferon. **CONCLUSIONS:** Prolonged low-dose peginterferon- α 2a treatment is not associated with an increase in the frequency or severity of clinical depression in prior non-responder patients with chronic hepatitis C.

Seizures during pegylated interferon and ribavirin therapy for chronic Hepatitis C: observations from the WIN-R trial. Ahmed F, Jacobson IM, Herrera JL, et al. *J Clin Gastroenterol.* 2011 Mar;45(3):286-92.

<http://www.ncbi.nlm.nih.gov/pubmed/20930643>

BACKGROUND: Seizures are reported as an uncommon side effect of interferon therapy. **AIM:** To determine the frequency and presentation of seizures occurring during pegylated interferon- α (PEG-IFN α) and ribavirin therapy for chronic hepatitis C. **METHODS:** Patients were identified using data from the WIN-R trial database, a US multicenter study comparing fixed (800 mg) versus weight-based (800 to 1400 mg) daily dosing of ribavirin in combination with PEG-IFN α -2b (1.5 μ g/kg/wk). **RESULTS:** Of the 4913 enrolled patients, 8 (0.16%) had a seizure. Three patients had a grand mal seizure and the seizure type was unknown in 5 patients. At the time of seizure, 6 patients were taking antidepressants (including 3 on bupropion), 1 was hyponatremic, and 1 had consumed a significant amount of alcohol. One patient had a history of

seizures. Neuroimaging and electroencephalographic studies were negative. Antiepileptic medications were continued in the patient with a history of seizures and initiated in 1 patient. PEG-IFN α -2b plus ribavirin therapy was continued in 2 patients following seizure and neither experienced a recurrent seizure. **CONCLUSIONS:** Seizures occur infrequently in patients receiving PEG-IFN α -2b plus ribavirin, and appear to be associated with other risk factors including antidepressant use.

Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Kamal SM, Ahmed A, Mahmoud S, et al. *Liver Int.* 2011 Mar;31(3):401-11. doi: 10.1111/j.1478-3231.2010.02435.x. Epub 2011 Jan 11.

<http://www.ncbi.nlm.nih.gov/pubmed/21281434>

AIM: The therapy of chronic hepatitis C genotype 4 (HCV-4) has not been optimized yet. This randomized, prospective, parallel-group clinical trial compared the efficacy and safety of pegylated interferon α -2a (PEG-IFN α -2a) plus ribavirin and PEG-IFN α -2b plus ribavirin and assessed the health-related quality of life (HRQOL) in patients with chronic HCV-4.

METHODS: Eligible patients with proven chronic HCV-4 were randomized to receive either a weekly dose of PEG-IFN α -2a (180 μ g) or PEG-IFN α -2b (1.5 μ g/kg) and a daily dose of ribavirin (1000-1200 mg) for 48 weeks with 24 weeks post-treatment follow-up. The primary end point was sustained virological response (SVR) defined by undetectable HCV RNA 24 weeks after treatment. The Short form-36 Health Survey version 2 (SF-36v2) and the Chronic Liver Disease questionnaires (CLDQ) were assessed before, during and after therapy.

RESULTS: The overall SVR rate of the entire cohort was 59.9%. The SVR rates were significantly higher in patients treated with PEG-IFN α -2a and ribavirin (Group A; n=109) compared with those treated with PEG-IFN α -2b and ribavirin (Group B; n=108, 70.6 vs. 54.6%, respectively; P=0.017). The relapse rates were 5.1% for PEG-IFN α -2a and 15.7% for PEG-IFN α -2b (P=0.0019). The SF-36v2 and CLDQ were low during therapy and improved significantly after therapy successful therapy. **CONCLUSION:** Pegylated interferon α -2a plus ribavirin was significantly more effective than PEG-IFN α -2b and ribavirin therapy in the treatment of chronic HCV-4 patients. The tolerability and adverse events were comparable between the two regimens. The HRQOL improved significantly after successful PEG-IFN α -2a plus ribavirin therapy.

Changes in hepatitis C viral load during first 14 days can predict the undetectable time point of serum viral load by pegylated interferon and ribavirin therapy. Itakura J, Asahina Y, Tamaki N, et al. *Hepato Res.* 2011 Mar;41(3):217-24. doi: 10.1111/j.1872-034X.2010.00768.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21338453>

AIM: In the treatment of chronic hepatitis C, pegylated interferon (PEG-IFN) and ribavirin combination therapy must be continued for an adequate duration to improve the rate of sustained virological response. We attempted to predict the time point at which serum hepatitis C virus (HCV) RNA are undetectable during combination therapy. **METHODS:** Patients with HCV genotype 1b were enrolled in a model preparation (n = 35) and a validation group (n = 70). All patients received PEG-IFN- α -2b/ribavirin combination therapy for at least 48 weeks, and serological samples were screened a minimum of 17 times during the therapy. Serum HCV RNA were measured by the Abbott RealTime HCV assay. Using the HCV dynamics model described by Neumann et al., we used multiple linear regression analysis to select factors that

affected the undetectable time point. **RESULTS:** Difference in viral load between weeks 1 and 2 was the only predictive factor for the undetectable time point of serum HCV RNA ($r(2) = 0.67, P < 0.0005$), and we derived the following prediction equation: undetectable time point (week) = $13.495 \times (\text{viral load at day 14} [\log \text{ IU/mL}] - \text{viral load at day 7} [\log \text{ IU/mL}]) + 25.456$. The equation was applicable to the validation group. **CONCLUSION:** We created a formula for predicting the undetectable time point from viral load measurements early in PEG-IFN- α -2b/ribavirin combination therapy. An early response reflects sensitivity to therapy, and the estimation of an undetectable time point would be useful for determining the optimal duration of treatment for chronic hepatitis C patients.

Efficacy and safety in sitagliptin therapy for diabetes complicated by chronic liver disease caused by hepatitis C virus. Arase Y, Suzuki F, Kobayashi M, et al. *Hepatol Res.* 2011 Mar 24. doi: 10.1111/j.1872-034X.2011.00798.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21435130>

AIM: Diabetes is present in patients with chronic liver disease caused by hepatitis C virus (HCV). The aim of this case-control study is to assess the efficacy and safety of dipeptidyl peptidase-4 inhibitor (sitagliptin) for type 2 diabetes mellitus (T2DM) with chronic liver disease caused by HCV. **METHODS:** Sixteen HCV positive patients with T2DM treated by sitagliptin were retrospectively enrolled. These patients were given sitagliptin between December 2009 and January 2010. Another 16 HCV patients with T2DM treated only with diet and exercise for 48 weeks were selected as the control group. Serum levels of fasting plasma glucose (FPG), hemoglobin A1C (HbA1C), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured before and 12, 24, 36 and 48 weeks after the initiation of treatment. **RESULTS:** In the sitagliptin group, the average HbA1C level decreased approximately 0.8% at 48 weeks after the initiation of sitagliptin. Next, the average FPG level decreased approximately 20 mg/dL during follow up after the initiation of sitagliptin. All the patients were able to take sitagliptin of 50 mg/day without reduction because of sitagliptin-related side-effects. On the other hand, in the control group, the average HbA1C and FPG level did not change with statistical significance during follow up of 48 weeks. Regarding aminotransferase, there were no significant changes of average AST and ALT level during follow up of 48 weeks in both the sitagliptin group and control group. **CONCLUSION:** Our results indicate that sitagliptin is effective and safe for the treatment of T2DM complicated with HCV positive chronic liver disease.

Chronic Hepatitis C Virus Infection is Associated with More Severe Asthma. Nakashima T, Yokoyama A, Ohnishi H, et al. *Allergol Int.* 2011 Mar 25. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21430435>

BACKGROUND: Chronic hepatitis C virus (HCV) infection causes intra- and extra-hepatic complications. The elimination of HCV has been reported to be beneficial for asthmatic patients with HCV infection. Therefore, we hypothesized that chronic HCV infection might be associated with the severity of asthma. **METHODS:** Asthmatic patients were prospectively enrolled from 13 outpatient settings. Hepatitis B surface (HBs) antigen and HCV-RNA were measured at the time of enrollment and evaluated along with the clinical characteristics of the patients including the age, sex, duration of asthma, atopic status, smoking history, and treatment step according to the Global Initiative for Asthma guideline. **RESULTS:** Of 1327 asthmatic patients, 1258 patients (94.8%) were treated with inhaled corticosteroids, 18 patients were positive for HBs

antigen (1.4%), and 32 patients (2.4%) were positive for HCV-RNA. When compared with HCV-RNA-negative patients, HCV-RNA-positive patients required significantly more drugs for the treatment of asthma. No such relationship was observed in patients with positive HBs antigen. A multivariate logistic regression analysis showed that the male sex, a long duration of asthma, status as a current smoker, and HCV-RNA positivity were independently associated with more severe asthma. **CONCLUSIONS:** These results suggest that chronic HCV infection is an independent factor that predisposes asthmatic patients to more severe asthma. The evaluation of chronic HCV infection may be helpful for the management of severe asthmatic patients without obvious factors associated with severe asthma.

Depression in patients with nonalcoholic Fatty liver disease and chronic viral hepatitis B

and C. Weinstein AA, Kallman Price J, Stepanova M, et al. *Psychosomatics*. 2011 Mar-Apr;52(2):127-32.

<http://www.ncbi.nlm.nih.gov/pubmed/21397104>

BACKGROUND: Patients with chronic liver disease (CLD) and depression may be at a higher risk for various complications, including impaired quality of life and more advanced liver disease. The purpose of this study was to determine the prevalence of depression in CLD patients (non-alcoholic fatty liver disease (NAFLD), Hepatitis B (HBV), and Hepatitis C (HCV)) and to identify potential clinical and laboratory correlates of depression in these patients. **METHODS:** We used a database of CLD patients that contains extensive clinical (including self-reported depression) and laboratory data for each patient. We compared the prevalence of depression in patients with HBV, HCV, and NAFLD. We also used regression models to find independent predictors of depression in these patients. **RESULTS:** Of 878 CLD patients, 207 (23.6%) had a diagnosis of depression (NAFLD 27.2%, HCV 29.8%, and HBV 3.7%). Examination of predictors of depression differed by the type of chronic liver disease. For NAFLD, independent predictors of depression were the presence of hypertension, smoking, history of lung disease, being female, and non-African-American. For HBV patients, the only independent predictor of depression was excessive alcohol consumption (defined as >10 g/d), while for HCV patients, independent predictors were being female and non-Asian, presence of fatigue, and excessive alcohol intake. **CONCLUSIONS:** This study demonstrates that individuals with NAFLD and HCV have a higher prevalence of depression than HBV patients and the rates of depression reported for the general population. The most consistent correlates of depression status in CLD patients are being female and excessive alcohol consumption.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

The CD8+ T-Cell Response Promotes Evolution of Hepatitis C Virus Nonstructural

Proteins. Ruhl M, Knuschke T, Schewior K, et al. *Gastroenterology*. 2011 Mar 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21376049>

BACKGROUND & AIMS: Hepatitis C virus (HCV) acquires mutations that allow it to escape the CD8+ T cell response, although the extent to which this process contributes to viral evolution, at the population level, is not clear. We studied viral adaptation using data from a large outbreak of HCV genotype 1b infection that occurred among women immunized with contaminated immunoglobulin from 1977 to 1978. **METHODS:** The HCV nonstructural protein

coding regions NS3-NS5B were sequenced from 78 patients and mutations were mapped according to their location, inside or outside previously described CD8+ T-cell epitopes. A statistical approach was developed to identify sites/regions under reproducible selection pressure associated with HLA class I. **RESULTS:** The frequency of non-synonymous mutations was significantly higher inside previously described CD8+ T-cell epitopes than outside-particularly in NS3/4A and NS5B. We identified new regions that are under selection pressure, indicating that not all CD8+ T-cell epitopes have been identified; 6 new epitopes that interact with CD8+ T cells were identified and confirmed in vitro. In some CD8+ T-cell epitopes mutations were reproducibly identified in patients that shared the relevant HLA allele, indicating immune pressure at the population level. There was statistical support for selection of mutations in 18 individual epitopes. Interestingly, 14 of these were restricted by HLA-B allele. **CONCLUSION:** HLA class I-associated selection pressure on the nonstructural proteins and here predominantly on NS3/4A and NS5B promotes evolution of HCV. HLA-B alleles have a dominant effect in this selection process. Adaptation of HCV to the CD8+ T-cell response, at the population level, creates challenges for vaccine design.

Strong CD8(+) T cell antigenicity and immunogenicity of large foreign proteins incorporated in HIV-1 VLPs able to induce a Nef-dependent activation/maturation of dendritic cells. Sistigu A, Bracci L, Valentini M, et al. *Vaccine*. 2011 Mar 5. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21382480>

Virus-like particles (VLPs) are excellent tools for vaccines against pathogens and tumors. They can accommodate foreign polypeptides whose incorporation efficiency and immunogenicity however decrease strongly with the increase of their size. We recently described the CD8(+) T cell immune response against a small foreign antigen (i.e., the 98 amino acid long human papilloma virus E7 protein) incorporated in human immunodeficiency virus (HIV)-1 based VLPs as product of fusion with an HIV-1 Nef mutant (Nef(mut)). Here, we extended our previous investigations by testing the antigenic/immunogenic properties of Nef(mut)-based VLPs incorporating much larger heterologous products, i.e., human hepatitis C virus (HCV) NS3 and influenza virus NP proteins, which are composed of 630 and 498 amino acids, respectively. We observed a remarkable cross-presentation of HCV NS3 in dendritic cells challenged with Nef(mut)-NS3 VLPs, as detected using a NS3 specific CD8(+) T cell clone as well as PBMCs from HCV infected patients. On the other hand, when injected in mice, Nef(mut)-NP VLPs elicited strong anti-NP CD8(+) T cell and CTL immune responses. In addition, we revealed the ability of Nef(mut) incorporated in VLPs to activate and mature primary human immature dendritic cells (iDCs). This phenomenon correlated with the activation of Src tyrosine kinase-related intracellular signaling, and can be transmitted from VLP-challenged to bystander iDCs. Overall, these results prove that Nef(mut)-based VLPs represent a rather flexible platform for the design of innovative CD8(+) T cell vaccines.

Association of Serum Cytokine Levels with Treatment Response to Pegylated Interferon and Ribavirin Therapy in Genotype 1 Chronic Hepatitis C Patients. Yoneda S, Umemura T, Katsuyama Y, et al. *J Infect Dis*. 2011 Mar 11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21398397>

BACKGROUND: We sought to clarify the associations among serum cytokines, amino acid substitutions in the interferon sensitivity-determining region (ISDR) and core region, and

treatment outcome of pegylated interferon and ribavirin therapy in genotype 1 hepatitis C virus (HCV)-infected patients. **METHODS:** We quantified a total of 8 serum cytokines before, during, and after treatment in 79 genotype 1 chronic HCV patients. Viral ISDR and core region variants were determined by direct sequencing. **RESULTS:** High levels of interleukin (IL)-12 and IL-18 and more than 2 mutations in the ISDR were associated with a sustained virological response (SVR). Conversely, high baseline IL-10 levels and glutamine at amino acid 70 of the HCV core protein (Gln70) were significantly associated with a nonresponse to treatment, and patients with Gln70 had significantly higher IL-10 levels. In multivariate analysis, low IL-10, high IL-12, and high IL-18 levels were independently associated with an SVR. These 3 cytokine levels were decreased from baseline levels 4 weeks into treatment and remained low in patients with an SVR. **CONCLUSION:** Serum IL-10, IL-12, and IL-18 levels are predictive of the response to HCV treatment with pegylated interferon and ribavirin and are associated with amino acid substitutions in the ISDR and core region.

Antiviral Stilbene 1,2-Diamines Prevent Initiation Of Hepatitis C Viral RNA Replication At The Outset of Infection. Gastaminza P, Pitram SM, Dreux M, et al. J Virol. 2011 Mar 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21430055>

The recent development of a cell culture model of HCV infection based on the JFH-1 molecular clone has enabled discovery of new antiviral agents. Using a cell-based colorimetric screening assay to interrogate a 1,200 compound chemical library for anti-HCV activity, we identified a family of 1,2-diamines derived from trans-stilbene oxide that prevent HCV infection at nontoxic, low micromolar concentrations in cell culture. Structure-activity relationship analysis of ~300 derivatives synthesized using click chemistry yielded compounds with greatly enhanced low nanomolar potency and a >1000:1 therapeutic ratio. Using surrogate models of HCV infection we showed that the compounds selectively block the initiation of replication of incoming HCV RNA but have no impact on viral entry, primary translation, or ongoing HCV RNA replication, nor do they suppress persistent HCV infection. Selection of an escape variant revealed that NS5A is directly or indirectly targeted by this compound. **In summary,** we have identified a family of HCV inhibitors that target a critical step in the establishment of HCV infection in which NS5A translated de novo from an incoming genomic HCV RNA template is required to initiate the replication of this important human pathogen.

Serum visfatin is correlated with disease severity and metabolic syndrome in chronic hepatitis C infection. Huang JF, Huang CF, Yu ML, et al. J Gastroenterol Hepatol. 2011 Mar;26(3):530-5. doi: 10.1111/j.1440-1746.2010.06438.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21332548>

BACKGROUND AND AIM: Cytokines activation is a common feature in chronic hepatitis C (CHC) infection. Visfatin, as a recently-recognized adipocytokine, may correlate with metabolic abnormalities. We aimed to elucidate the characteristics of visfatin in CHC patients.

METHODS: This retrospective study included 102 treatment-naïve CHC patients and 97 sex-/age-matched healthy adults. Serum visfatin levels were examined by an enzyme linked immunosorbent assay test. The correlation between visfatin and hepatitis C virus (HCV) infection in terms of virological, metabolic, and histopathological profiles was analyzed. The impact of visfatin on the treatment response to pegylated interferon plus ribavirin (PEGIFN/RBV) therapy was also assessed. **RESULTS:** The visfatin level was correlated

significantly with fibrosis scores ($r = 0.23$, $P = 0.02$) in CHC patients. A significant higher visfatin level was observed in CHC patients with histological activity index scores of mild and more ($P = 0.01$) and advanced fibrosis ($P = 0.04$). The mean visfatin level (0.81 ± 0.28 log ng/mL) of 26 CHC patients with metabolic syndrome was significantly lower than their counterparts (0.95 ± 0.30 log ng/mL) ($P = 0.03$). There was no significant correlation between visfatin and HCV genotypes, viral load, and treatment response to PEGIFN/RBV therapy. Multiple logistic regression analyses demonstrated that metabolic syndrome was the leading negative variable (odds ratio = 0.09, 95% confidence interval = 0.02-0.46, $P = 0.004$) associated with high visfatin level, followed by advanced fibrosis (odds ratio = 2.88, 95% confidence interval = 1.06-6.78, $P = 0.03$). **CONCLUSIONS:** Serum visfatin was correlated with disease severity and metabolic syndrome in CHC patients.

Sequence heterogeneity of NS5A and core proteins of hepatitis C virus and virological responses to pegylated-interferon/ribavirin combination therapy. El-Shamy A, Shoji I, Saito T, Watanabe H, Ide YH, Deng L, Kawata S, Hotta H. *Microbiol Immunol.* 2011 Mar 4. doi: 10.1111/j.1348-0421.2011.00331.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21371092>

Both host and viral factors have been implicated in influencing the response to pegylated-interferon/ribavirin (PEG-IFN/RBV) therapy for hepatitis C virus (HCV) infection. Among the viral factors, sequence heterogeneity within NS5A and core regions has been proposed. This study aimed to clarify the relationship between virological responses to PEG-IFN/RBV therapy and sequence heterogeneity within NS5A, including the IFN/RBV resistance-determining region (IRRDR) and the IFN sensitivity-determining region (ISDR), and the core regions. Pretreatment sequences of NS5A and the core regions were analyzed in 57 HCV-1b-infected patients who were treated with PEG-IFN/RBV. Of 40 patients infected with HCV having an IRRDR with 4 or more mutations ($IRRDR \geq 4$), 28 (70%) patients achieved sustained virological response (SVR). On the other hand, only 4 (24%) of 17 patients infected with HCV having an IRRDR with 3 or fewer mutations ($IRRDR \leq 3$) achieved SVR ($P = 0.001$). Similarly, 22 (71%) of 31 patients infected with HCV having an ISDR with one or more mutations ($ISDR \geq 1$) achieved SVR while 10 (38%) of 26 patients infected with HCV having an ISDR without any mutation ($ISDR = 0$) achieved SVR ($P = 0.014$). As for the core region, there was significant correlation between a single mutation at position 70 (Gln(70)) and non-SVR ($P = 0.02$). Notably, Gln(70) was more prominently associated with the null response ($P = 0.0007$). **In conclusion**, sequence heterogeneity within the IRRDR and ISDR, and a single point mutation at position 70 of the core region of HCV-1b are likely to be correlated with virological responses to PEG-IFN/RBV therapy.

IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. Moghaddam A, Melum E, Reinton N, et al. *Hepatology.* 2011 Mar;53(3):746-54. doi: 10.1002/hep.24154.

<http://www.ncbi.nlm.nih.gov/pubmed/21374656>

Polymorphisms near the IL28B gene, which code for interferon (IFN)- $\lambda 3$, predict response to pegylated interferon- α (PEG-IFN) and ribavirin treatment in hepatitis C virus (HCV) genotype 1 infected patients. Follow-up studies of the effect of IL28B gene in HCV non-genotype 1 infected patients have almost always used predominantly HCV genotype 2-infected or mixed genotype 2/3-infected cohorts with results partly conflicting with HCV genotype 1. We performed a

retrospective analysis of 281 patients infected with HCV genotype 3 for association of response to therapy with IL28B polymorphisms. We found that the HCV genotype 1 responder genotypes at rs12979860 and rs8099917 did not associate with sustained virological response to PEG-IFN/ribavirin therapy. However, the responder genotypes of both SNPs showed association with rapid viral response measured at 4 weeks (rs12979860, $P = 3 \times 10^{-5}$; rs8099917, $P = 3 \times 10^{-4}$). In multivariate analysis, age (<40 years), baseline viral load (< 4×10^5 IU/mL) and the responder genotypes of SNPs rs12979860 or rs8099917 remained significant independent predictors of rapid viral response to therapy. Furthermore, we show that IL28B polymorphisms are associated with relapse in patients who achieve rapid viral response to PEG-IFN/ribavirin therapy. The responder genotypes also showed association with markers of stage and activity of liver disease, namely high aspartate aminotransferase platelet ratio index (APRI, rs12979860, $P = 0.018$; rs8099917, not significant) and high alanine aminotransferase (ALT, rs12979860, $P = 0.002$; rs8099917, $P = 0.001$), in addition to a high baseline viral load (rs12979860, $P = 1.4 \times 10^{-5}$; rs8099917, $P = 7.3 \times 10^{-6}$). **CONCLUSION:** Polymorphisms near the IL28B gene show association with rapid viral response but not sustained viral response to PEG-IFN/ribavirin therapy in HCV genotype 3-infected patients.

HIV/HCV COINFECTION

HCV RNA decline in the first 24h exhibits high negative predictive value of sustained virologic response in HIV/HCV genotype 1 co-infected patients treated with peginterferon and ribavirin. Laufer N, Bolcic F, Rolón MJ, et al. Antiviral Res. 2011 Mar 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21376083>

BACKGROUND: Treatment with Peg-interferon and ribavirin (PEG-IFN/RBV) for HIV patients co-infected with hepatitis C virus (HCV) genotype 1 has suboptimal rates of response. Viral kinetics has emerged as one of the best prognostic factors of treatment outcome.

METHODS: Twenty HIV/HCV genotype 1 co-infected patients in treatment with PEG-IFN/RBV, had blood drawn at baseline, 24h, 4, 12, 24, 48, and 72 weeks. HCV-RNA levels were evaluated at each time point. ROC curves were used to evaluate the \log_{10} HCV-RNA decay at 24h that exhibits the best predictive value of achieving response. Genomic characterization of HCV NS5A at both interferon sensitivity-determining region (ISDR) and protein-kinase binding (PKRBD) domains were performed in order to evaluate its heterogeneity and association with 24h HCV-RNA decay and SVR. **RESULTS:** Non-responder patients exhibited a mean of $0.7\log_{10}$ (SD $0.74\log_{10}$) HCV-RNA decay at 24h, whereas responder-patients presented $1.6\log_{10}$ (SD $0.28\log_{10}$), $p=0.04$. A reduction in HCV viral load from baseline to 24h of <1.4 had a negative predictive value for achieving SVR of 100% and a positive predictive value of 50%. HCV genotype 1 isolates from patients with a decrease of HCV-RNA at 24h $>1.4\log_{10}$, exhibited 3.1(SD 1.5) amino acids substitutions in ISDR and 4.8(SD 2.3) in PKRBD regions and 1.6(SD 0.7) and 2.4(SD 1.3), respectively, in those patients presenting lower reduction in HCV-RNA. **CONCLUSIONS:** HIV/HCV genotype 1 co-infected patients with a decrease in HCV-VL at 24h $>1.4\log_{10}$ are more likely to achieve SVR when treated with PEG-IFN/RBV than those with lower levels of HCV-RNA decay. Along with other host-related and viral-related prognostic factors in HIV/HCV co-infected patients, this very early time point of evaluation could be of relevance in the management of HCV-specific treatment.

Association between IL28B gene polymorphisms and plasma HCV-RNA levels in HIV/HCV-co-infected patients. Labarga P, Soriano V, Caruz A, et al. AIDS. 2011 Mar 27;25(6):761-766.

<http://www.ncbi.nlm.nih.gov/pubmed/21378537>

BACKGROUND: IL28B polymorphisms influence both the rate of spontaneous hepatitis C virus (HCV) clearance and response to interferon α (IFN α)-based therapy. This observation has been reproduced in HIV-co-infected individuals. Controversy exists about the impact of IL28B alleles on HCV load. **METHODS:** CoRIS is a nationwide, open cohort of newly diagnosed HIV-1 adults in Spain. In the subset of HCV-co-infected individuals, the relationship between plasma HCV-RNA and IL28B (rs12979860) genotypes was evaluated. **RESULTS:** A total of 4670 HIV-1-infected patients had been included in CoRIS up to June 2010. All were naive for IFN α . HCV antibodies were reactive in 895 (19%). Of them, 289 specimens were available and tested positive for plasma HCV-RNA, with median values of 959 900 IU/ml. The rs12979860 genotype distribution in HCV viremic patients was CC 45%, CT 42.2% and TT 12.8%. The median plasma HCV-RNA according to IL28B genotypes was: CC 1 385 000, CT 848 939 and TT 251 189 IU/ml ($P = 0.006$). The percentage of patients with HCV-RNA more than 600 000 IU/ml was: CC 67.7%, CT 56.6% and TT 35.1% ($P = 0.001$). In multivariate analysis, IL28B CC/CT genotypes, infection with HCV genotypes 1/4 and prior intravenous drug users were independent predictors of HCV-RNA more than 600 000 IU/ml. **CONCLUSION:** HIV/HCV-co-infected patients with the C allele (CC/CT) at rs12979860 show significantly higher plasma HCV-RNA load than TT carriers. Notably, plasma HCV-RNA levels associated with poorer response to IFN α -based therapy are significantly more frequent in CC/CT than TT carriers. Hypothetically, patients harboring the rs12979860 allele C could display a lower activity of endogenous IFN α , allowing higher HCV replication while keeping an enhanced susceptibility to exogenous IFN α therapy.

Hepatitis C virus (HCV) protease variability and anti-HCV protease inhibitor resistance in HIV/HCV-coinfected patients. Trimoulet P, Belzunce C, Faure M, et al. HIV Med. 2011 Mar 16. doi: 10.1111/j.1468-1293.2011.00913.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21410862>

OBJECTIVES: Data on the natural selection of isolates harbouring mutations within the NS3 protease, conferring resistance to hepatitis C virus (HCV) protease inhibitors (PIs), are limited for HIV/HCV-coinfected patients. The aim of this study was to describe the natural prevalence of mutations conferring resistance to HCV PIs in HIV/HCV-coinfected patients compared with HCV-monoinfected patients. **METHODS:** The natural prevalences of HCV PI resistance mutations in 120 sequences from HIV/HCV-coinfected patients (58 genotype 1a, 18 genotype 1b and 44 genotype 4) and 501 sequences from HCV-monoinfected patients (476 genotype 1 and 25 genotype 4), retrieved from GenBank as a control group, were compared. **RESULTS:** Of 76 sequences from HIV/HCV genotype 1-coinfected patients, six (7.9%) showed amino acid substitutions associated with HCV PI resistance (V36L, n=1; V36M, n=2; T54S, n=2; R155K, n=1). In 31 of 476 (6.5%) HCV genotype 1 sequences retrieved from the GenBank database, HCV PI resistance mutations were found. The difference was not statistically significant ($P=0.6$). All of the sequences from HIV/HCV genotype 4-coinfected patients and those retrieved from the GenBank database had amino acid changes at position 36 (V36L). **CONCLUSION:** Our study suggests that the natural prevalence of strains resistant to HCV PIs does not differ between

HCV-monoinfected and HIV/HCV-coinfected patients. Further studies on larger cohorts are needed to confirm these findings and to evaluate the impact of these mutations in clinical practice.

Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. Nguyen LH, Ko S, Wong SS, et al. *Hepatology*. 2011 Mar 21. doi: 10.1002/hep.24308. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21425314>

BACKGROUND AND AIMS: Studies of HBV/HCV dual infection are limited. Most are small, conducted outside the U.S., and compare dual infection with HCV monoinfection. The goal of this study was to characterize HBV/HCV dual infection in a large multiethnic, matched, case-control study of dual infected and HBV-monoinfected patients at two U.S. centers. **METHODS:** Using ICD-9 electronic query and chart review, we identified 115 HBV/HCV dual infection patients with serial HBV DNA, HCV RNA, and ALT levels. As a control, 115 monoinfected HBV patients were chosen randomly and matched to cases by age \pm 10 years, gender, Asian vs. non-Asian ethnicity, and study site. **RESULTS:** Both groups had similar gender, ethnic, and age distributions: 68% male, 83% Asian, and age 52 \pm 14 years. Median follow-up was 33-38 months. More monoinfected patients received HBV antiviral therapy than dual infected patients (43% vs. 24%, $P=0.002$). No significant difference was detected between the proportion of monoinfected vs. dual infected patients with ALT above 40 U/L at presentation or during follow-up. Dual infection patients exhibited very little HBV/HCV codominance at baseline and throughout follow up: patients had either HBV viremia with low or absent HCV RNA or detectable HCV RNA with low or absent HBV DNA. Asian ethnicity was predictive of HBV dominance after adjusting for gender, age, and baseline ALT elevation (OR = 7.35, $P=0.01$). **CONCLUSION:** HBV/HCV dual infected and HBV monoinfected patients generally had similar clinical characteristics. Asian ethnicity is a major independent predictor of HBV-dominant disease, and HCV dominance with undetectable HBV DNA is more common in non-Asians. Larger studies are needed to further characterize the natural history of HBV/HCV dual infection in Asians and non-Asians.

Stronger hepatitis C virus-specific CD8+ T-cell responses in HIV coinfection. Barrett L, Gallant M, Howley C, et al. *J Viral Hepat*. 2011 Mar;18(3):170-80. doi: 10.1111/j.1365-2893.2010.01293.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20497309>

Hepatitis C virus (HCV) is a widespread chronic infection that shares routes of transmission with human immunodeficiency virus (HIV). Thus, coinfection with these viruses is a relatively common and growing problem. In general, liver disease develops over years with HIV coinfection, when compared to decades in HCV monoinfection. The role of the immune system in the accelerated pathogenesis of liver disease in HIV/HCV coinfection is not clear. In this study, we compared the frequency, magnitude, breadth and specificity of peripheral blood CD4+ and CD8+ T-cell responses between HCV-monoinfected and HCV/HIV-coinfected individuals and between HIV/HCV-coinfected subgroups distinguished by anti-HCV antibody and HCV RNA status. While HIV coinfection tended to reduce the frequency and breadth of anti-HCV CD8+ T-cell responses in general, responses that were present were substantially stronger than in monoinfection. In all groups, HCV-specific CD4+ T-cell responses were rare and weak, independent of either nadir or concurrent CD4+ T-cell counts of HIV-infected individuals.

Subgroup analysis demonstrated restricted breadth of CD8+ HCV-specific T-cell responses and lower B-cell counts in HIV/HCV-coinfected individuals without anti-HCV antibodies. The greatest difference between HIV/HCV-coinfected and HCV-monoinfected groups was substantially stronger HCV-specific CD8+ T-cell responses in the HIV-coinfected group, which may relate to accelerated liver disease in this setting.

Twelve week post-treatment follow-up predicts sustained virological response to pegylated interferon and ribavirin therapy in HIV/hepatitis C virus co-infected patients.

Rivero-Juárez A, Mira JA, Pérez-Camacho I, et al. J Antimicrob Chemother. 2011 Mar 17.

[Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21415037>

OBJECTIVES: The aim of this study was to evaluate whether the assessment of hepatitis C virus (HCV) RNA serum at 12 weeks after the end of treatment (W12) was as informative as after 24 weeks (W24) for determining sustained virological response (SVR) in HIV/HCV co-infected patients who received a combination of pegylated interferon (PEG-INF) plus ribavirin (PEG-INF/RBV) and had a virological response at the end of treatment. **METHODS:** Treatment-naïve HIV/HCV patients were included in this prospective study if they had completed a full course of therapy with PEG-INF/RBV, had an undetectable serum HCV RNA at the end of treatment and complied with the W12 and W24 schedule for determining HCV RNA. HCV RNA levels were measured using a quantitative PCR assay (detection limit=15 IU/mL). Positive predictive value (PPV) was defined as the probability of an undetectable serum HCV RNA at W12 and W24 after the end of treatment. **RESULTS:** Of 186 patients treated during the study period, 104 (55.9%) were included in the study. At W24, 83 (79.8%) patients had an SVR and 21 (20.2%) had a virological relapse. At W12, HCV RNA was undetectable in 83 (79.8%) patients and all of these had SVR. Undetectable HCV RNA at W12 had a 100% PPV [95% confidence interval (CI) 96.5%-100%] for SVR. **CONCLUSIONS:** Our results show that undetectable HCV RNA at W12 post-treatment has a high PPV for SVR. Testing for HCV RNA at this moment may therefore be considered an appropriate point in time for identifying SVR and relapse in HIV/HCV co-infected patients receiving treatment with PEG-INF/RBV.

Correlates of high hepatitis C virus RNA load in a cohort of HIV-negative and HIV-positive individuals with haemophilia. Gadalla SM, Preiss LR, Eyster ME, Goedert JJ. J Viral Hepat. 2011 Mar;18(3):161-9. doi: 10.1111/j.1365-2893.2010.01289.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20337924>

Hepatitis C virus (HCV) treatment failure and disease progression are more likely with high HCV-RNA load. Correlates of high HCV-RNA load in individuals with haemophilia are largely unknown. Among 1266 interferon naïve HCV-infected individuals with haemophilia, we compared those with high ($> 2 \times 10^6$ HCV-RNA copies/mL) to lower viral load, overall and stratifying on HIV co-infection status using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). Overall, high HCV load was independently associated with longer duration of HCV infection ($P(\text{trend})=0.0001$), body mass index ≥ 25 kg/m² (OR=1.4, 95% CI=1.1-1.9), and HIV co-infection (OR=1.4, 95% CI=1.0-1.8). Among 795 HIV-negative participants, high HCV-RNA load was associated with older age at HCV acquisition (OR=1.9 for > 15 years vs ≤ 2 years, $P(\text{trend})=0.008$), and lower AST/platelet ratio ($P(\text{trend})=0.01$), in addition to longer duration of HCV infection ($P(\text{trend})=0.0008$), and body mass index ≥ 25 kg/m² (OR=1.6, $P=0.005$). Among 471 HIV-positive individuals, anti-retroviral therapy (ART)

was the only variable associated with high HCV-RNA load (OR=1.8, CI=1.1-2.9 for combination ART; OR=1.8, CI=0.9-3.4, for other ART vs no treatment). High HCV-RNA load with haemophilia is more likely with longer duration of infection, older age at infection, higher body mass index, and antiretroviral therapy. These findings may help identify individuals at increased risk of HCV treatment failure and progression to end-stage liver disease.

A Comparison of Treatment Eligibility for Hepatitis C Virus in HCV-Monoinfected versus HCV/HIV-Coinfected Persons in Electronically Retrieved Cohort of HCV-Infected Veterans. Butt AA, McGinnis K, Skanderson M, Justice AC. *AIDS Res Hum Retroviruses*. 2011 Mar 18. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21338329>

Treatment rates for hepatitis C virus (HCV) are low in actual clinical settings. However, the proportion of patients eligible for treatment, especially among those coinfecting with HIV, is not well known. Our aim was to determine and compare the rates for HCV treatment eligibility among HCV and HCV-HIV-coinfected persons. We assembled a national cohort of HCV-infected veterans in care from 1998-2003, using the VA National Patient Care Database for demographic/clinical information, the Pharmacy Benefits Management database for pharmacy records, and the Decision Support Systems database for laboratory data. We compared the HCV-monoinfected and HCV-HIV-coinfected subjects for treatment indications and eligibility using current treatment guidelines. Of the 27,452 subjects with HCV and 1225 with HCV-HIV coinfection, 74.0% and 84.6% had indications for therapy and among these, 43.9% of HCV-monoinfected and 28.4% of HCV-HIV-coinfected subjects were eligible for treatment. Anemia, decompensated liver disease (DLD), chronic obstructive pulmonary disease (COPD), recent alcohol abuse, and coronary artery disease were the most common contraindications in the HCV, and anemia, DLD, renal failure, recent drug abuse, and COPD in the HCV-HIV-coinfected group. Among those eligible for treatment, only 23% of the HCV-monoinfected and 15% of the HCV-HIV-coinfected subjects received any treatment for HCV. Most veterans with HCV are not eligible for treatment according to the current guidelines. Even for those who are eligible for treatment, only a minority is prescribed treatment. Several contraindications are modifiable and aggressive management of those may improve treatment prescription rates.

Different distributions of hepatitis C virus genotypes among HIV-infected patients with acute and chronic hepatitis C according to interleukin-28B genotype. Neukam K, Nattermann J, Rallón N, et al. *HIV Med*. 2011 Mar 6. doi: 10.1111/j.1468-1293.2011.00912.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21375685>

OBJECTIVES: The C allele of the single nucleotide polymorphism rs12979860, located near the interleukin-28B (IL-28B) gene, has a strong impact on hepatitis C virus (HCV) treatment response, as well as on spontaneous viral clearance. In patients with chronic hepatitis C (CHC), genotype CC carriers harbour HCV genotype 3 more commonly than those with non-CC genotypes. The aim of this study was to compare the HCV genotype distributions, according to IL-28B genotype, in HIV-infected patients with CHC and those with acute hepatitis C (AHC). **METHODS:** The rs12979860 genotype was determined by polymerase chain reaction (PCR) in two subpopulations of HIV-infected patients. The first consisted of 80 German patients with AHC. The second consisted of 476 patients with CHC, belonging to one German and two Spanish cohorts. **RESULTS:** In the AHC group, 31 (81.6%) rs12979860 CC carriers were

infected with HCV genotype 1 or 4 vs. 32 (76.2%) among non-CC carriers (P=0.948). In patients with CHC, among those with the CC genotype, 119 (54.6%) were infected with HCV genotype 1 or 4 and 99 (45.4%) with genotype 2 or 3, whereas in the subset with non-CC genotypes, 200 (77.5%) harboured HCV genotype 1 or 4 and 58 (22.5%) genotype 2 or 3 (P<0.001).

CONCLUSIONS: Among HIV-infected patients with CHC, those bearing the IL-28B genotype CC were more commonly infected with genotype 3 than subjects with non-CC genotypes, whereas in HIV-infected subjects with AHC this finding was not obtained. These results strongly suggest that the protective effect of the CC genotype against evolution to CHC is mainly exerted in patients infected with HCV genotype 1 or 4.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Diosgenin, a Plant-Derived Sapogenin, Exhibits Antiviral Activity in Vitro against Hepatitis C Virus. Wang YJ, Pan KL, Hsieh TC, Chang TY, Lin WH, Hsu JT. *J Nat Prod.* 2011 Mar 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21391660>

Diosgenin (3 β -hydroxy-5-spirostene, 1), a plant-derived sapogenin, is used as a dietary supplement. However, the biological effects of 1 related to viral replication remain unexplored. In this study, the effects of 1 on hepatitis C virus (HCV) replication were evaluated. Based on a reporter-based HCV subgenomic replicon system, 1 was found to inhibit HCV replication at low micromolar concentrations. The EC(50) (concentration at which 50% of HCV replication is inhibited) of 1 was 3.8 μ M. No cellular toxicity was observed at this concentration. Diosgenin (1) also significantly reduced the levels of viral RNA and viral proteins as evaluated by quantitative real-time reverse transcriptase PCR and Western blot analysis, respectively. In addition, in an alternative HCV antiviral system more closely aligned to all steps involved in the HCV infection and life cycle, 1 totally abolished HCV replication at 20 μ M. Moreover, 1 reduced the phosphorylation of signal transducer and activator of transcription 3. A combination of 1 and interferon- α exerted an additive effect on the resultant anti-HCV activity.

Birch bark extract as therapy for chronic hepatitis C - A pilot study. Shikov AN, Djachuk GI, Sergeev DV, Pozharitskaya ON, Esaulenko EV, Kosman VM, Makarov VG. *Phytomedicine.* 2011 Mar 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21377854>

The hepatoprotective effect of birch bark extract (BBE) in patients with chronic hepatitis C (CHC) was studied. Forty-two patients with serologically confirmed chronic hepatitis C were treated for 12 weeks with 160mg standardized BBE per day. The primary outcome parameter measured was the rate of alanine aminotransferase (ALT) normalization after 12 weeks. Secondary parameters included the course of ALT, aspartate aminotransferase (AST) levels, quantitative HCV RNA levels, subjective symptoms associated with CHC (fatigue, abdominal discomfort, depression, and dyspepsia), safety and compliance. The qualitative-quantitative analysis of BBE was made using high performance liquid chromatography to confirm the presence of 75% betulin and 3.5% betulinic acid. Significant differences in the mean ALT and HCV RNA levels were observed after 12 weeks of treatment. The level of ALT was decreased in 54.0% and normalized (p=0.046). HCV RNA was reduced in 43.2% (p=0.016). After 12 weeks of treatment, reports of fatigue and abdominal discomfort were reduced by 6-fold (p=0.028) and

3-fold ($p=0.05$), respectively. Dyspepsia was no longer reported ($p=0.042$) and the effect was significantly different from baseline. Because this study lacks a control group clinical relevance of the data can only be estimated in future by following controlled clinical trials.

Preliminary results of ozone therapy as a possible treatment for patients with chronic hepatitis C. Zaky S, Kamel SE, Hassan MS, et al. *J Altern Complement Med.* 2011 Mar;17(3):259-63.

<http://www.ncbi.nlm.nih.gov/pubmed/21417811>

BACKGROUND: Medical ozone is more bactericidal, fungicidal, and virucidal than any other natural substance. Some studies proved that ozone infused into donated blood samples can kill viruses 100% of the time. Ozone, because of its special biologic properties, has theoretical and practical attributes to make it a potent hepatitis C virus (HCV) inactivator, which suggests an important role in the therapy for hepatitis C. **AIM:** The study aim is to evaluate the role of ozone therapy in decreasing HCV ribonucleic acid (HCV RNA) load and its effect on the liver enzymes among patients with chronic hepatitis C. **METHODS:** This study included 52 patients with chronic hepatitis C (positive polymerase chain reaction [PCR] for HCV RNA and raised serum alanine transaminase [ALT] for more than 6 months). All patients were subjected to meticulous history taking and clinical examination. Complete blood count, liver function tests, and abdominal ultrasonography were requested for all patients. The ozone group included 40 patients who received major autohemotherapy, minor autohemotherapy, and rectal ozone insufflation. The other 12 patients (conventional group) received silymarin and/or multivitamins. **RESULTS:** There were significant improvements of most of the presenting symptoms of the patients in the ozone group in comparison to the conventional group. ALT and aspartate transaminase (AST) levels normalized in 57.5% and 60% in the ozone group, respectively, in comparison to 16.7% and 8% in the conventional group, respectively. Polymerase chain reaction (PCR) for HCV RNA was negative among 25% and 44.4% after 30 and 60 sessions of ozone therapy, respectively, in comparison to 8% among the conventional group. **CONCLUSIONS:** Ozone therapy significantly improves the clinical symptoms associated with chronic hepatitis C and is associated with normalized ALT and AST levels among a significant number of patients. Ozone therapy is associated with disappearance of HCV RNA from the serum (-ve PCR for HCV RNA) in 25%-45% of patients with chronic hepatitis C.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Non-Invasive Tests for Fibrosis and Liver Stiffness Predict 5-Year Outcomes of Patients with Chronic Hepatitis C. Vergniol J, Foucher J, Terrebbonne E, et al. *Gastroenterology.* 2011 Mar 1. [Epub ahead of print] France.

<http://www.ncbi.nlm.nih.gov/pubmed/21376047>

BACKGROUND & AIMS: Liver stiffness can be measured, non-invasively, to assess liver fibrosis in patients with chronic hepatitis C. In patients with chronic liver diseases, level of fibrosis predicts liver-related complications and survival. We evaluated the abilities of liver stiffness, results from non-invasive tests for fibrosis, and liver biopsy analyses to predict overall survival or survival without liver-related death with a 5-year period. **METHODS:** In a consecutive cohort of 1457 patients with chronic hepatitis C, we assessed fibrosis, and on the

same day, liver stiffness, performed the non-invasive tests of fibrosis (FibroTest, the platelet ratio index, FIB-4), and analyzed liver biopsy samples. We analyzed data on death, liver-related death, and liver transplantation collected over a 5 year follow-up period. **RESULTS:** At 5 years, 77 patients had died (39 liver-related deaths) and 16 patients had undergone liver transplantation. Overall survival was 91.7% and survival without liver-related death was 94.4%. Survival was significantly decreased among patients diagnosed with severe fibrosis, regardless of the non-invasive method of analysis. All methods were able to predict shorter survival times in this large population; liver stiffness and results of the FibroTest had higher predictive values. Patient outcomes worsened as liver stiffness and FibroTest values increased. The prognostic values of stiffness ($P < 0.0001$) and FibroTest results ($P < 0.0001$) remained after they were adjusted for treatment response, patient age, and estimates of necroinflammatory grade. **CONCLUSION:** Non-invasive tests for liver fibrosis (measurement of liver stiffness or FibroTest) can predict 5-year survival of patients with chronic hepatitis C. These tools might help physicians to determine prognosis at earlier stages and discuss specific treatments, such as liver transplantation.

Autotaxin as a novel serum marker of liver fibrosis. Nakagawa H, Ikeda H, Nakamura K, et al. Clin Chim Acta. 2011 Mar 16. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21419756>

BACKGROUND: The clinical significance of autotaxin (ATX), a key enzyme for the production of the bioactive lysophospholipid lysophosphatidic acid remains unknown. Serum ATX enzymatic activity reportedly increases in parallel with liver fibrosis and exhibits a gender difference. **METHODS:** Serum ATX antigen level, measured easier than the activity, was evaluated as a marker of liver fibrosis in 2 cohorts of chronic liver disease caused by hepatitis C virus. **RESULTS:** In the first cohort, serum ATX level correlated significantly with liver fibrosis stage and was the best parameter for prediction of cirrhosis with an area under the receiver operating characteristic curve (AUROC) of 0.756 in male and 0.760 in female, when compared with serum hyaluronic acid and aminotransferase-to-platelet ratio index, an established marker of liver fibrosis. In another cohort, serum ATX level correlated significantly with liver stiffness, a novel reliable marker of liver fibrosis, being the second-best parameter in male (AUROC, 0.799) and in female (AUROC, 0.876) for prediction of significant fibrosis, and the best parameter in male (AUROC, 0.863) and the third-best parameter in female (AUROC, 0.872) for prediction of cirrhosis, both of which were judged by liver stiffness. **CONCLUSIONS:** Serum ATX level may be a novel marker of liver fibrosis.

The impact of hepatitis C on labor force participation, absenteeism, presenteeism and non-work activities. Dibonaventura MD, Wagner JS, Yuan Y, et al. J Med Econ. 2011;14(2):253-61. Epub 2011 Mar 9.

<http://www.ncbi.nlm.nih.gov/pubmed/21385147>

OBJECTIVE: Between 2.7 and 3.9 million people are currently infected with the hepatitis C virus (HCV) in the United States. Although many studies have investigated the impact of HCV on direct healthcare costs, few studies have estimated the indirect costs associated with the virus using a nationally-representative dataset. **METHODS:** Using data from the 2009 United States (US) National Health and Wellness Survey, patients who reported a hepatitis C diagnosis ($n = 695$) were compared to controls on labor force participation, productivity loss, and activity impairment after adjusting for demographics, health risk behaviors, and comorbidities. All analyses applied sampling weights to project to the population. **RESULTS:** Patients with HCV

were significantly less likely to be in the labor force than controls and reported significantly higher levels of absenteeism (4.88 vs. 3.03%), presenteeism (16.69 vs. 13.50%), overall work impairment (19.40 vs. 15.35%), and activity impairment (25.01 vs. 21.78%). A propensity score matching methodology replicated many of these findings. **CONCLUSIONS:** While much of the work on HCV has focused on direct costs, our results suggest indirect costs should not be ignored when quantifying the societal burden of HCV. To our knowledge, this is the first study which has utilized a large, nationally-representative data source for identifying the impact of HCV on labor force participation and work and activity impairment using both a propensity-score matching and a regression modeling framework. Limitations: All data were patient-reported (including HCV diagnosis and work productivity), which could have introduced some subjective biases.

Should patients with abnormal liver function tests in primary care be tested for chronic viral hepatitis: cost minimisation analysis based on a comprehensively tested cohort.

Arnold DT, Bentham LM, Jacob RP, Lilford RJ, Girling AJ. BMC Fam Pract. 2011 Mar 3;12:9. <http://www.ncbi.nlm.nih.gov/pubmed/21371303>

BACKGROUND: Liver function tests (LFTs) are ordered in large numbers in primary care, and the Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) study was set up to assess their usefulness in patients with no pre-existing or self-evident liver disease. All patients were tested for chronic viral hepatitis thereby providing an opportunity to compare various strategies for detection of this serious treatable disease. **METHODS:** This study uses data from the BALLETS cohort to compare various testing strategies for viral hepatitis in patients who had received an abnormal LFT result. The aim was to inform a strategy for identification of patients with chronic viral hepatitis. We used a cost-minimisation analysis to define a base case and then calculated the incremental cost per case detected to inform a strategy that could guide testing for chronic viral hepatitis. **RESULTS:** Of the 1,236 study patients with an abnormal LFT, 13 had chronic viral hepatitis (nine hepatitis B and four hepatitis C). The strategy advocated by the current guidelines (repeating the LFT with a view to testing for specific disease if it remained abnormal) was less efficient (more expensive per case detected) than a simple policy of testing all patients for viral hepatitis without repeating LFTs. A more selective strategy of viral testing all patients for viral hepatitis if they were born in countries where viral hepatitis was prevalent provided high efficiency with little loss of sensitivity. A notably high alanine aminotransferase (ALT) level (greater than twice the upper limit of normal) on the initial ALT test had high predictive value, but was insensitive, missing half the cases of viral infection. **CONCLUSIONS:** Based on this analysis and on widely accepted clinical principles, a "fast and frugal" heuristic was produced to guide general practitioners with respect to diagnosing cases of viral hepatitis in asymptomatic patients with abnormal LFTs. It recommends testing all patients where a clear clinical indication of infection is present (e.g. evidence of intravenous drug use), followed by testing all patients who originated from countries where viral hepatitis is prevalent, and finally testing those who have a notably raised ALT level (more than twice the upper limit of normal). Patients not picked up by this efficient algorithm had a risk of chronic viral hepatitis that is lower than the general population.

Using mass media and the Internet as tools to diagnose hepatitis C infections in the general population. Zuure FR, Davidovich U, Coutinho RA, et al. Am J Prev Med. 2011 Mar;40(3):345-52.

<http://www.ncbi.nlm.nih.gov/pubmed/21335268>

BACKGROUND: Many individuals with hepatitis C virus (HCV) infection are undiagnosed.

PURPOSE: This study describes the development and the use and outcomes of a mass media campaign, combined with an Internet risk assessment and an Internet-mediated blood-testing procedure for HCV to identify individuals infected with HCV in the general population.

METHODS: From April 2007 to December 2008, individuals in HCV risk groups were referred to an online, previously validated risk-assessment questionnaire at www.heptest.nl. Individuals at risk could download a referral letter for a free, anonymous HCV blood test in a nonclinical setting. Test results could be obtained online, 1 week later, using a personal log-in code. Anti-HCV-positive participants were requested to visit the Public Health Service for confirmation and RNA testing. Chronically HCV-infected individuals were referred for treatment. Data were analyzed in 2009-2010. **RESULTS:** The website attracted 40,902 visitors. Of the 9653 who completed the questionnaire, 2553 were at risk for HCV (26.4%). Main reported risk factors were a blood transfusion prior to 1992 and noninjecting drug use. Of the 1480 eligible for the blood test, 420 opted for testing (28%). HCV antibodies were detected in 3.6% (n=15, 95% CI=2.1%, 5.7%); of the 12 with a chronic HCV infection, six began treatment.

CONCLUSIONS: Internet-mediated risk-based testing for HCV has proved to be a feasible and effective strategy to identify undiagnosed HCV infection in the general population. All HCV-infected individuals belonged to hard-to-reach populations. Test uptake was 28%, which is high for an online project that includes blood testing. Because Internet-mediated testing is low-cost, this strategy holds promise for future screening.

Irritability: an underappreciated side effect of interferon treatment for chronic hepatitis C?

C? Blacklaws H, Gardner A, Usher K. J Clin Nurs. 2011 Mar 3. doi: 10.1111/j.1365-2702.2010.03494.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21371144>

AIM AND OBJECTIVES: The research literature was reviewed with the aim of answering the question 'is irritability an underappreciated side effect of interferon and ribavirin treatment for hepatitis C'.

BACKGROUND: The majority of information regarding interferon treatment identifies depression as the main psychological side effect. However, clinical observation and patient reports suggest that irritability, not depression, is the predominant side effect. Design.

The literature review included research and discussion papers. Data bases were searched using the keywords interferon and hepatitis C in combination with one of the following: side effects, depression, mood alteration/change, irritability, anger, impulse control, psychiatric side effects or neuropsychiatric side effects. **RESULTS:** The review revealed a gap in the literature regarding interferon-related irritability. Whereas depression was well researched and described, irritability was afforded little research time. However, where irritability was assessed, it was found to occur to a significant degree. Issues identified were difficulty defining and categorising irritability; lack of irritability-specific assessment tools and failure of depression rating scales to adequately discern irritable mood; and the confounding effect of physiological side effects on mood alteration. **RELEVANCE TO CLINICAL PRACTICE:** Under appreciation and under recognition of irritability have implications for clinical practice. Good research is the foundation for evidence-based practice; therefore, the possibility exists that, based on current research evidence, patients may not be receiving a standard care that adequately addresses the entirety of the side effect spectrum.

CONCLUSION: Irritability is an underappreciated psychological side effect of interferon therapy. Although irritability is recognised as a side effect of interferon, there

is considerable discordance between clinical observation, patient reports and research evidence as reported in the literature.

Population attributable fraction of infection-related cancers in Korea. Shin A, Park S, Shin HR, et al. *Ann Oncol.* 2011 Mar 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20974652>

BACKGROUND: A number of infectious agents have been classified as human carcinogens. The purpose of the current study was to provide an evidence-based assessment of the burden of infection-related cancers in the Korean population. **MATERIALS AND METHODS:** The population attributable fraction was calculated using infection prevalence data from 1990 or earlier, relative risk estimates from meta-analyses using mainly Korean studies and national data on cancer incidence and mortality for the year 2007. **RESULTS:** The fractions of all cancers attributable to infection were 25.1% and 16.8% for cancer incidence in men and women, and 25.8% and 22.7% of cancer mortality in men and women, respectively. Among infection-related cancers, *Helicobacter pylori* was responsible for 56.5% of cases and 45.1% of deaths, followed by hepatitis B virus (HBV) (23.9% of cases and 37.5% of deaths) and human papillomavirus (HPV) (11.3% of cases and 6% of deaths) and then by hepatitis C virus (HCV) (6% of cases and 9% of deaths). Over 97% of infection-related cancers were attributable to infection with *H. pylori*, HBV, HCV and HPV. **CONCLUSION:** Up to one-quarter of cancer cases and deaths would be preventable through appropriate control of infectious agents in Korea.

A Prospective Time Course Study on Serological Testing for Human Immunodeficiency Virus, Hepatitis B Virus and Hepatitis C Virus with Blood Samples Taken up to 48 Hours After Death. Edler C, Wulff B, Schroeder AS, et al. *J Med Microbiol.* 2011 Mar 24. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21436373>

The transmission of viral and non-viral infectious pathogens continues to be the most serious of the potential adverse effects of allogenic tissue transplantations. The EU directive 2006/17/EC stipulates that cadaveric blood specimens for serology testing in the context of post-mortem tissue donation must be taken not later than 24 hours post-mortem. An expanded time slot would significantly improve availability of tissue donations, but there are no significant data on the stability of infectious serology assays for anti-HIV, anti-HCV, HBsAg and anti-HBc in samples collected more than 24 hours post-mortem. In this prospective study, serum samples of 30 deceased persons were taken upon admission to the Institute of Forensic Medicine, and after a further 12, 24, 36 and 48 hours post-mortem. All samples were measured twice. First, using the Abbott AxSYM system, and on average, after 9-month storage at -70 degrees C using the BEP-III-System with Siemens and Ortho reagents. HIV: Six deceased persons with a pre-mortem HIV history were included. All samples (0, 12, 24, 36, 48 h) were reactive. Indeterminate or false negative results did not occur. HCV: Seventeen deceased persons with a pre-mortem HCV history were included. 16/17 samples were reactive up to 48 h and 1/17 samples was reactive 36 h post mortem (48 h sample was not available). Indeterminate or false negative results did not occur. HBV: Nine deceased persons were included. 5 samples were initially positive for HBsAg and remained positive up to 48 h. 8/9 samples were reactive for anti-HBc up to 48 h and 1/9 sample up to 36 h post mortem (48 h sample was not available). Indeterminate or false negative results did not occur. Our data suggest that infectious serological testing may be extended for blood

samples collected up to 48 hours post-mortem to detect antibodies or antigens for HIV, HBV and HCV of potential tissue donors.

LIVER CANCER

Occult and previous hepatitis B virus infection are not associated with hepatocellular carcinoma in us patients with chronic hepatitis C. Lok AS, Everhart JE, Di Bisceglie AM, et al. *Hepatology*. 2011 Mar 3. doi: 10.1002/hep.24257. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21374690>

BACKGROUND & AIM: Previous studies have suggested that prior exposure to hepatitis B virus (HBV) infection may increase the risk of development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C. The aim of this study was to compare the prevalence of previous or occult HBV infection in a cohort of HBsAg-negative patients with histologically advanced chronic hepatitis C in the United States who did or did not develop HCC. **METHODS:** Stored sera from 91 patients with HCC and 182 matched controls who participated in the HALTC Trial were tested for anti-HBc, anti-HBs and HBV DNA. Frozen liver samples from 28 HCC cases and 55 controls were tested for HBV DNA by real-time PCR. **RESULTS:** Anti-HBc (as a marker of previous HBV infection) was present in the serum of 41.8% HCC cases and 45.6% controls (P=0.54); anti-HBc alone was present in 16.5% of HCC cases and 24.7% of controls. HBV DNA was detected in the serum of only one control subject and no patient with HCC. HBV DNA (as a marker of occult HBV infection) was detected in the liver of 10.7% HCC cases and 23.6% controls (P=0.18). **CONCLUSION:** Although almost half the patients in the HALT-C Trial had serological evidence of previous HBV infection there was no difference in prevalence of anti-HBc in serum or HBV DNA in liver between patients who did or did not develop HCC. In the United States, neither previous nor occult HBV infection is an important factor in HCC development among patients with advanced chronic hepatitis C.

Eradication of Hepatitis C Virus Reduces the Risk of Hepatocellular Carcinoma in Patients with Compensated Cirrhosis. Velosa J, Serejo F, Marinho R, Nunes J, Glória H. *Dig Dis Sci*. 2011 Mar 5. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21374066>

BACKGROUND: The effect of a sustained virological response (SVR) to interferon (IFN) on clinical outcomes of hepatitis C virus (HCV)-related cirrhosis is controversial. Aims: Evaluate the effect of SVR to IFN on the incidence of hepatocellular carcinoma (HCC) and mortality in patients with compensated HCV-induced cirrhosis. **METHODS:** A cohort of 130 consecutive patients (92 men, mean age 51.7 years) with histologically proven cirrhosis who received one or more courses of IFN monotherapy or combination therapy with ribavirin were analyzed. SVR was defined as undetectable serum HCV RNA by real-time polymerase chain reaction (PCR) 24 weeks after IFN discontinuation. HCC was assessed by alfa-fetoprotein and ultrasound every 6 months. Predictors of clinical outcomes, defined as HCC, orthotopic liver transplantation (OLT) and mortality, were assessed by Cox regression analysis. **RESULTS:** The mean follow-up was 6.4 ± 4.0 years (range 1-18). HCC developed in 21 patients: one with SVR versus 20 with non-SVR (P = 0.017). Logistic regression analysis showed that non-SVR (odds ratio [OR] = 27.0; confidence interval [CI], 1.6-452.1), male (OR = 11.6; CI, 1.8-75.4), and greater number of treatments (OR = 4.7; CI, 1.4-16.0) increased the probability of HCC development. Multivariate

analysis found that SVR was associated with lower risk of HCC (HR 0.09; CI, 0.01-0.77), OLT (HR 0.04; CI, 0.003-0.63) and any event (HR 0.11; CI, 0.02-0.46) as compared to non-SVR. **CONCLUSIONS:** In compensated HCV-related cirrhosis, SVR markedly reduces the risk of HCC and improves survival. Clearance of the virus should be intensively attempted in these patients.

Evaluation of metabolic factors on the prognosis of patients undergoing resection of hepatocellular carcinoma. Kaibori M, Ishizaki M, Matsui K, Kitade H, Matsui Y, Kwon AH. *J Gastroenterol Hepatol.* 2011 Mar;26(3):536-43. doi: 10.1111/j.1440-1746.2010.06439.x. <http://www.ncbi.nlm.nih.gov/pubmed/21332549>

BACKGROUND AND AIM: The metabolic factors including obesity, diabetes, and hypertension have been implicated as risk factors of hepatocellular carcinoma (HCC) in patients with chronic hepatitis. The effects of metabolic factors were investigated on the prognosis of patients undergoing resection of HCC. **METHODS:** A total of 469 HCC patients were classified into three groups; hepatitis B virus (HBV)-, hepatitis C virus (HCV)-, and non-HBV/HCV (NBC)-related HCC. Further, the patients with HCV-related HCC were sub-classified into three groups; the patients who did not have documented hypertension, hypertensive patients who received angiotensin II-blocking agents (ABA), and hypertensive patients who received no ABA. **RESULTS:** There were no significant difference of survival in the HBV-HCC and NBC-HCC patients with or without obesity, diabetes, and hypertension. In the patients with HCV-related HCC, however, hypertensive patients were significantly worse on both disease-free and overall survivals than non-hypertensive patients. Among the HCV-HCC patients with chronic hepatitis, hypertensive patients with ABA had significantly better preoperative liver function, and hypertensive patients without ABA were significantly worse on both disease-free and overall survivals than those of hypertensive patients with ABA and non-hypertensive patients. **CONCLUSIONS:** Results suggest that hypertension is a risk factor for a poor prognosis after resection of HCV-related HCC. Angiotensin II blockade may improve the prognosis of hypertensive patients with early hepatic fibrosis after resection in HCV-related HCC.

Clinical features and prognosis in patients with hepatocellular carcinoma that developed after hepatitis C virus eradication with interferon therapy. Nagaoki Y, Aikata H, Miyaki D, et al. *J Gastroenterol.* 2011 Mar 4. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21373851>

BACKGROUND: We evaluated the clinical features and the prognostic factors of hepatocellular carcinoma (HCC) developed after hepatitis C virus (HCV) eradication with interferon (IFN) therapy. **METHODS:** Forty-one consecutive patients who developed HCC after HCV eradication with IFN therapy were enrolled. Clinical features were reviewed, and overall survival and associated factors were analyzed. The recurrence rate in 26 patients receiving radical therapy was also analyzed. **RESULTS:** Twenty patients developed HCC within 5 years after the end of IFN therapy, 9 patients developed the disease from 5 to 10 years after the end of the therapy, 9 patients developed the disease from 10 to 15 years after the end of the therapy, and 3 patients developed the disease from 15 years after the end of the therapy. Multivariate analysis of independent variables for the development of HCC within 5 years identified age >55 years at HCV eradication (P = 0.007) and heavy alcohol intake (P = 0.009). The 5-year survival rate was 64%. On multivariate analysis of overall survival for the 41 patients, the only risk factor with prognostic influence was radical therapy (P = 0.010), which was associated with a cumulative 5-

year survival rate of 91%. The only independent factor for the receipt of radical therapy was regular surveillance for HCC ($P = 0.004$). Among patients receiving radical therapy, the 3- and 5-year recurrence rates were 18 and 18%, respectively. **CONCLUSION:** We found that, despite HCV eradication, patients with the risk factors of high age at HCV eradication and heavy alcohol intake might be at heightened risk for the development of HCC within 5 years after HCV eradication. In contrast, risk factors for the development of HCC more than 10 years after HCV eradication were uncertain. These findings indicate the need for long-term surveillance for HCC after HCV eradication.

Resection of a Transplantable Single-Nodule Hepatocellular Carcinoma in Child-Pugh Class A Cirrhosis: Factors Affecting Survival and Recurrence. Muscari F, Foppa B, Carrere N, Kamar N, Peron JM, Suc B. *World J Surg.* 2011 Mar 1. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/21360309>

BACKGROUND: The aim of this study was to estimate the survival rates and define risk factors for tumor recurrence after resection surgery for single hepatocellular carcinomas (HCCs) ≤ 5 cm (on preoperative imaging) that developed on compensated cirrhosis. **METHODS:** A retrospective review studied patients treated by surgical resection. Overall survival (OS), disease-free survival (DFS), recurrence rates, and risk factors were studied for all patients. **RESULTS:** A total of 49 patients were treated by resection. The 5-year OS and DFS rates were 52 and 41%, respectively, after 2000. Three independent risk factors were found for OS and DFS: macroscopic vascular invasion, satellite nodules, R1 resection. In the absence of these three factors, the 5-year OS was 59%. Recurrence rates were 63%. Delayed recurrence was significantly related to the 5-year OS. One factor was correlated with early recurrence: the presence of satellite nodules; and one factor was correlated with late recurrence: hepatitis C virus infection. **CONCLUSIONS:** R0 resection for HCC on compensated cirrhosis may offer good long-term survival in the absence of satellites nodules and macrovascular invasion. Thus, a "first approach" resection is proposed with the possibility of "salvage transplantation." In other cases, resection may be a bridge to transplantation ("transplantation de principe").

Does interferon therapy prevent hepatocellular carcinoma in patients with chronic viral hepatitis? Vezali E, Aghemo A, Lampertico P, Colombo M. *Clin Res Hepatol Gastroenterol.* 2011 Mar 22. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/21435968>

Chronic hepatitis C and B are well-recognized and potentially preventable risk factors for hepatocellular carcinoma (HCC) development. Clinical and epidemiological studies suggest that therapy with interferon- α may reduce the overall risk of HCC development in patients with chronic hepatitis C, who achieve sustained virological response, but even in those who fail to eradicate the infection. In chronic hepatitis B, interferon therapy reduces the risk of HCC development in HBeAg-positive and cirrhotic patients who achieve persistent suppression of viral replication, while in HBeAg-negative patients the beneficial effect of interferon- α is not definitively confirmed. The preventive role of interferon- α after potentially curative treatment for HCC in both chronic hepatitis B and C is uncertain due to methodological flaws of the existing studies and prospective randomized controlled trials with pegylated interferon- α are needed to clarify this issue.

Tumor-related factors do not influence the prognosis of solitary hepatocellular carcinoma after partial hepatectomy. Kobayashi T, Itamoto T, Tashiro H, et al. J Hepatobiliary Pancreat Sci. 2011 Mar 29. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21445633>

BACKGROUND/PURPOSE: Although many factors related to the tumor or the hepatic functional reserve may affect the outcome of partial hepatectomy for hepatocellular carcinoma (HCC), these factors have not yet been intensively investigated in patients with solitary HCC. The purpose of this study is to determine the clinicopathological factors influencing the long-term outcomes of partial hepatectomy for solitary HCC. **METHODS:** Data on 266 consecutive patients with a solitary HCC who underwent curative hepatectomy between 1997 and 2006 were analyzed with regard to prognosis. **RESULTS:** Overall survival rates at 3, 5, and 10 years were 89.5, 79.6, and 56.1%, respectively. The significant independent predictors for overall survival included hepatitis C virus infection, liver cirrhosis, and prolonged prothrombin activity. Disease-free survival rates at 3, 5, and 10 years were 51.7, 41.1, and 20.4%, respectively. The significant independent predictors for disease-free survival included elevated levels of aspartate amino transferase, decreased platelet counts, presence of liver cirrhosis, and prolonged prothrombin activity. Tumor-related factors such as tumor size and microscopic vascular invasion were not significant predictors of overall or disease-free survival. **CONCLUSIONS:** The long-term outcomes of patients with a solitary HCC who underwent partial hepatectomy mainly depended on the background liver status but not on tumor-related factors; this suggests that partial hepatectomy is a remarkably effective antitumor therapy. If the hepatic functional reserve is within the permissible range, partial hepatectomy should be considered as the treatment of choice for patients with a solitary HCC.