



Caring Ambassadors Program Hepatitis C Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Dual therapy with the NS5A inhibitor BMS-790052 and the NS3 protease inhibitor BMS-650032 in HCV genotype 1b-infected null responders. Chayama K, Takahashi S, Toyota J, et al. *Hepatology*. 2011 Oct 10. doi: 10.1002/hep.24724. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21987462>

Patients with chronic hepatitis C virus (HCV) infection and prior null response to peginterferon and ribavirin have limited therapeutic options. HCV genotype 1 is the most common worldwide and the most difficult to treat; genotype 1b is the most common subtype of genotype 1 outside North America. The enhanced antiviral activity achieved by combining two direct-acting antiviral (DAA) agents may improve clinical outcomes. This open-label, phase 2a study included ten patients with chronic HCV genotype 1b infection and prior null response (<2 log₁₀ reduction in HCV RNA after 12 weeks) to peginterferon and ribavirin. Patients received dual DAA treatment for 24 weeks with the NS5A replication complex inhibitor BMS-790052 (60 mg once daily) and the NS3 protease inhibitor BMS-650032 (initially 600 mg twice daily, subsequently reduced to 200 mg twice daily). The primary efficacy endpoint was the proportion of patients with sustained virologic response at 12 weeks post-treatment (SVR(12)). Nine patients completed 24 weeks of treatment; one patient discontinued treatment after 2 weeks. In the nine patients who completed the full course of treatment, HCV RNA was undetectable at week 8 and remained undetectable through the end of treatment; all nine patients achieved SVR(12) and SVR(24). HCV RNA also remained undetectable post-treatment in the patient who discontinued after 2 weeks. There was no viral breakthrough. Diarrhea and headache, generally mild, were the most common adverse events; transaminase elevations were reported in three patients but did not result in discontinuation. **CONCLUSIONS:** Dual therapy with BMS-790052 and BMS-650032, without peginterferon and ribavirin, can achieve high SVR rates in difficult-to-treat patients with hepatitis C virus genotype 1b infection and prior null response to peginterferon and ribavirin.

Danazol improves thrombocytopenia in HCV patients treated with peginterferon and ribavirin. Alvarez GC, Gómez-Galicia D, Rodríguez-Fragoso L, et al. *Ann Hepatol.* 2011 Oct-Dec;10(4):458-68.

<http://www.ncbi.nlm.nih.gov/pubmed/21911886>

BACKGROUND: Thrombocytopenia is a common hematologic disorder observed in patients with chronic hepatitis C virus (HCV) infection. Combined peginterferon (PEG-INF) and ribavirin treatment may exacerbate thrombocytopenia in patients with HCV. **OBJECTIVE:** The aim of this pilot clinical trial was to assess the efficacy, tolerability and safety of Danazol in thrombocytopenia associated with PEG-INF and ribavirin treatment in patients with HCV. **MATERIAL AND METHODS:** We included patients whose platelets were $< 90,000/\text{mm}^3$ and who were undergoing antiviral treatment. Danazol (300-600 mg/day) was administered during and until the end of antiviral therapy [7.6 months (2 to 11 months)]. The monitoring was performed through platelet analysis and liver function tests. A viral load test was done at the beginning and end of treatment. Fortynine patients receiving a combined therapy of PEG-INF, ribavirin and Danazol increased their platelet levels to $121,081/\text{mm}^3$ ($46,000\text{-}216,000/\text{mm}^3$); 10.6% of patients gained $> 100,000$ platelets/ mm^3 , and 71% of patients maintained their initial platelet levels. Sustained viral response (SVR) was achieved in 63% of patients. SVR rates were high in patients with genotype non 1 (78.7%) and decreased in patients with genotype 1 (60.1%). The increase in platelet levels was associated to an increase in fibrinogen levels and a decrease in the activity of ALT. By contrast, patients without SVR presented a delayed response to increased platelet levels and showed no significant improvement in liver function when they received Danazol. **CONCLUSION:** Danazol can be used along with PEG-INF and ribavirin to treat thrombocytopenia in patients with HCV.

The protease inhibitor GS-9256 and non-nucleoside polymerase inhibitor tegobuvir alone, with RBV or peginterferon plus RBV in hepatitis C. Zeuzem S, Buggisch P, Agarwal K, et al. *Hepatology.* 2011 Oct 17. doi: 10.1002/hep.24744. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22006408>

Tegobuvir (GS-9190), a non-nucleoside NS5B polymerase inhibitor, and GS-9256, an NS3 serine protease inhibitor, individually have activity against hepatitis C virus (HCV) genotype 1. The antiviral activity of tegobuvir and GS-9256 as oral combination therapy, or together with ribavirin (RBV) or peginterferon alfa-2a (PEG-IFN) and RBV, was assessed in a phase 2, randomized, open-label trial. Treatment-naïve patients with genotype 1 HCV were assigned 28 days of tegobuvir 40 mg twice daily and GS-9256 75 mg twice daily (n=16), tegobuvir and GS-9256 plus RBV 1000-1200 mg daily (n=15), or tegobuvir and GS-9256 plus PEG-IFN alfa-2a (180 mcg qw)/RBV (n=15). The primary efficacy endpoint was rapid virologic response (RVR), HCV RNA < 25 IU/mL at Day 28. After 28 days, all patients received PEG-IFN/RBV. All patients with viral rebound or nonresponse, defined as $> 0.5\text{-log}(10)$ increase in HCV RNA from nadir or $< 2\text{-log}$ decrease at Day 5, initiated PEG-IFN/RBV immediately. Median maximal reductions in HCV RNA were $-4.1 \text{ log}(10)$ IU/mL for tegobuvir/GS-9256, $-5.1 \text{ log}(10)$ IU/mL for tegobuvir/GS-9256/RBV, and $-5.7 \text{ log}(10)$ IU/mL for tegobuvir/9256/PEG-IFN/RBV. RVR was observed in 7% (1/15) of patients receiving tegobuvir/GS-9256, 38% (5/13) receiving tegobuvir/GS-9256/RBV, and 100% (14/14) receiving tegobuvir/9256/PEG-IFN/RBV. The addition of PEG-IFN/RBV at Day 28 or earlier resulted in HCV RNA < 25 IU/mL at Week 24 in 67% (10/15), 100% (13/13) and 94% (13/14) of patients in the 3 treatment groups. Transient elevations in serum bilirubin occurred in all treatment groups. Conclusion: In genotype 1 HCV,

adding RBV or RBV with PEG-IFN provides additive antiviral activity to combination therapy with tegobuvir and GS-9256.

Efficacy and Safety of Combination Therapy of Natural Human Interferon Beta and Ribavirin in Chronic Hepatitis C patients. Arase Y, Suzuki Y, Suzuki F, et al. Intern Med. 2011;50(19):2083-8. Epub 2011 Oct 1.

<http://www.ncbi.nlm.nih.gov/pubmed/21963723>

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of combination therapy of natural human interferon-beta and ribavirin for patients for whom prior interferon therapy was discontinued due to depression induced by interferon-alpha. **METHODS:** Inclusion criteria were as follows; 1) HCV-genotype 1b, 2) serum HCV RNA level of ≥ 100 KIU/mL, 3) stopping the prior interferon-alpha monotherapy or combination therapy of interferon-alpha and ribavirin due to the appearance of depression. A total of 14 were enrolled in this prospective cohort study. The treatment period of combination therapy was 48 weeks. Depression states, reflected by Beck depression inventories and Hamilton depression rating scale, were assessed during combination therapy. Nonparametric procedures were employed for the analysis of background features of the patients with sustained virological response (SVR) and without SVR. A p value of <0.05 was considered to indicate a significant difference. **RESULTS:** Five of 14 patients (37.5%) had SVR by the intention to treat analysis. The SVR rate in patients who showed negative HCV RNA at 12 and 24 weeks after the initiation of combination therapy was 100% (4/4) and 83.3% (5/6), respectively. All of the patients continued the combination therapy owing to disappearance of severely adverse events contained the exacerbation of depression. Combination therapy did not yield a statistical difference in Beck depression inventories and Hamilton depression rating scale. **CONCLUSION:** The combination therapy of IFN-beta and ribavirin is a possible therapy selection for the patients for whom interferon therapy was discontinued due to depression induced by interferon-alpha.

Retrospective Chart Review to Assess the Relationship Between Depression and Sustained Virological Response From Interferon Treatment for Hepatitis C Virus. Wackernah RC, Lou M, Park SH. Clin Ther. 2011 Oct 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21982383>

BACKGROUND: Hepatitis C virus (HCV) is an infection that, if left untreated, may lead to liver complications and death. Current treatment requires peginterferon alfa (IFN) and ribavirin. Interferon can cause depression and irritability. The treatment goal is sustained virological response (SVR) and the impact of depression on SVR is currently inconclusive. **OBJECTIVE:** The objective of this study was to compare SVR in patients with and without comorbid depression between different viral genotypes to determine if depressive symptoms impact SVR. **METHODS:** In this retrospective chart review of HCV-treated patients, the Patient Health Questionnaire-9 (PHQ-9) scale for depression score was recorded to identify patients with depression versus patients without depression. Depression status was compared between SVR and non-SVR groups, as measured at 24 weeks posttreatment completion. Fisher exact or X(2) tests were used to evaluate differences between patients achieving SVR and those that did not. Known predictors of poor response were controlled with possible covariates in a multivariable analysis. **RESULTS:** A total of 101 patients were enrolled in the study; 74 completed treatment and were included in the analysis. Sixty-five percent (17/26) of patients with depression achieved SVR and 54% (26/48) of patients without depression had SVR. SVR was achieved in 58.1%

(43/74) of patients, and genotypes 1, 4 or 6 comprised 58.1% (43/74) of patients. We found 64.9% (48/74) had no depression, 20.3% (15/74) had baseline depression prior to IFN treatment, and 14.8% (11/74) had IFN-treatment-associated depression. The majority of patients were men (59.5%), more than 35 years old (91.9%), and Hispanic (55.4%). When these factors were controlled for, there was no statistical significant relationship between depression and SVR ($P = 0.2784$). **CONCLUSION:** In these preliminary results, depression status did not impact SVR in this small, selected population of HCV-infected patients. A larger sample size is needed to achieve sufficient power in this population.

Randomised clinical trial: escitalopram for the prevention of psychiatric adverse events during treatment with peginterferon-alfa-2a and ribavirin for chronic hepatitis C.

de Knecht RJ, Bezemer G, Van Gool AR, et al. *Aliment Pharmacol Ther.* 2011 Oct 17. doi: 10.1111/j.1365-2036.2011.04867.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21999489>

BACKGROUND: Treatment of hepatitis C with peginterferon and ribavirin is associated with psychiatric side-effects, frequently necessitating dose reduction or therapy cessation. Aim To assess the efficacy of prophylactic escitalopram to prevent psychiatric side-effects during peginterferon and ribavirin treatment in a randomised, double-blind, placebo-controlled trial.

METHODS: Seventy-nine hepatitis C patients were treated with peginterferon and ribavirin. Patients received escitalopram ($n = 40$, 10 mg) or placebo ($n = 39$), which was initiated together with peginterferon and ribavirin. Primary outcomes were an increase of two points or more on the items reported sadness, inner tension and impaired concentration of the Montgomery-Asberg Depression Rating Scale, and hostile feelings of the Brief Anxiety Scale. Secondary outcome was the development of depression diagnosed by the Mini-International Neuropsychiatric Interview. Measurements were performed at baseline, week 4, 12 and 24 during anti-viral treatment, and 24 weeks thereafter. **RESULTS:** The incidence of psychiatric side-effects was significantly lower in patients treated with escitalopram compared with placebo for all primary and secondary outcomes, except for impaired concentration: reported sadness 27.5 vs. 48.7% ($P = 0.052$), inner tension 17.5 vs. 38.5% ($P = 0.038$), impaired concentration 55.0 vs. 66.7% ($P = 0.288$) and hostile feelings 22.5 vs. 43.6% ($P = 0.046$) (escitalopram vs. placebo, Chi-squared test). The sum scores of all four endpoints showed an overall beneficial effect of escitalopram ($P = 0.009$, Mann-Whitney U-test). Depression occurred in 12.5% of the patients in the escitalopram-group vs. 35.9% in the placebo-group ($P = 0.015$, Chi-squared test).

CONCLUSIONS: Prophylactic treatment with escitalopram is effective in the prevention of psychiatric side-effects during interferon-based treatment of hepatitis C.

The study of relationship between neutropenia and infection during treatment with peginterferon α and ribavirin for chronic hepatitis C. Yu JW, Sun LJ, Zhao YH, Kang P, Yan BZ. *Eur J Gastroenterol Hepatol.* 2011 Oct 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21971375>

OBJECTIVE: Neutropenia is frequent during treatment of chronic hepatitis C (CHC) with peginterferon and ribavirin. It remains unclear whether neutropenia is associated with infection in CHC. The aim was to study the relationship between neutropenia and infection during treatment with peginterferon and ribavirin for CHC. **METHODS:** A retrospective cohort on 399 patients treated with peginterferon α and ribavirin derived from our hospital database was conducted. The occurrence of infections and their relationship to neutropenia were investigated.

Potential risk factors for infection were identified by multivariate analysis. **RESULTS:** During treatment, neutropenia [absolute neutrophil counts (ANC) $<1.5 \times 10^3/l$] occurred in 251 patients, mild neutropenia [ANC $(0.75-1.5) \times 10^3/l$] occurred in 132 patients, moderate neutropenia [ANC $(0.50-0.75) \times 10^3/l$] occurred in 103 patients, and severe neutropenia (ANC $<0.50 \times 10^3/l$) occurred in 16 patients. Eighty infections (20.1%) occurred, 14 infections (17.5%) were defined as severe. There was no significant difference in infection rate between patients with and without moderate and severe neutropenia (21.0%, 25/119 vs. 19.6%, 55/280; $\chi^2=0.097$, $P=0.755$). There was no significant difference in infection rate between patients with and without peginterferon dose modifications (21.5%, 31/144 vs. 19.2%, 49/255; $\chi^2=0.307$, $P=0.580$). In multivariate logistic regression analysis, the independent factors associated with infection were age ($P=0.021$), diabetes ($P=0.004$), and cirrhosis ($P=0.012$). **CONCLUSION:** Infections during treatment with peginterferon α and ribavirin for CHC are not associated with neutropenia. The independent factors associated with infection are age, diabetes, and cirrhosis.

Clinical and laboratory evaluation of patients with end-stage liver cell failure injected with bone marrow-derived hepatocyte-like cells. Amer ME, El-Sayed SZ, El-Kheir WA, et al. *Eur J Gastroenterol Hepatol.* 2011 Oct;23(10):936-41.

<http://www.ncbi.nlm.nih.gov/pubmed/21900788>

AIM: One of the defining features of the liver is the capacity to maintain a constant size despite injury. Extrahepatic stem cells especially bone marrow-derived stem cells are thought to undertake an important role in liver repopulation. This study was carried out to evaluate the outcome of autologous bone marrow-derived hepatocytes transplantation in patients with end-stage liver cell failure due to chronic hepatitis C. **METHODS:** Forty patients were included, divided into two groups. Group I: 20 patients receiving autologous bone marrow-derived mesenchymal stem cells stimulated to hepatic lineage. They were subdivided into two groups regarding the route of transplantation: intrasplenic (10) and intrahepatic (10). Group II: included 20 patients who received traditional supportive treatment. Patients were followed up using examination, laboratory investigations, abdominal ultrasonography, and evaluated by Child score, Model for End Stage Liver Disease score, fatigue scale, and performance status.

RESULTS: The results showed significant improvement in group I regarding ascites, lower limb edema, and serum albumin, over the control group. Group I also showed statistically significant improvement in Child score, Model for End Stage Liver Disease score, fatigue scale, and performance status over the controls. No difference was observed between intrahepatic and intrasplenic groups. **CONCLUSION:** This study demonstrated the safety and short-term efficacy of autologous bone marrow-derived mesenchymal stem cell injection in liver cell failure. Further study is necessary to standardize the cell dose, determine the life span of the injected cells, and detect the appearance of long-term complications.

Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. Grebely J, Pham ST, Matthews GV, et al. *Hepatology.* 2011 Oct 26. doi: 10.1002/hep.24754. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22031335>

BACKGROUND AND AIMS: To evaluate reinfection and superinfection during treatment for recent HCV. **METHODS:** ATACH was a prospective study of the natural history and treatment of recent HCV. Reinfection and superinfection were defined by detection of infection with an HCV strain distinct from the primary strain (using RT-PCR and subtype-specific nested RT-PCR

assays) in the setting of spontaneous or treatment-induced viral suppression (one HCV RNA <10 IU/ml) or persistence (HCV RNA >10 IU/mL from enrolment to week 12). **RESULTS:** Among 163, 111 were treated, 79% (88 of 111) had treatment-induced viral suppression and 60% (67 of 111) achieved SVR. Following treatment-induced viral suppression, recurrence was observed in 19% (17 of 88), including 12 with relapse and five with reinfection [4.7 cases per 100 person-years (py), 95% CI: 1.9, 11.2]. Among 52 untreated, 58% (30 of 52) had spontaneous viral suppression and recurrence was observed in 10% (3 of 30), including two with reinfection. Following reinfection, ALT levels >1.5x the upper limit of normal were observed in 71% (5 of 7). Among 37 with persistence, superinfection was observed in 16% (3 of 19) of those treated and 17% (3 of 18) of those untreated. In adjusted analysis, reinfection/superinfection occurred more often in participants with poorer social functioning at enrolment and more often in those with ongoing injecting drug use (IDU). **CONCLUSIONS:** Reinfection and superinfection can occur during treatment of recent HCV and are associated with poor social functioning and ongoing IDU. ALT levels may be a useful clinical marker of re-exposure.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin. Lee JE, van Heeswijk R, Alves K, Smith F, Garg V. *Antimicrob Agents Chemother.* 2011 Oct;55(10):4569-74. Epub 2011 Aug 8.

<http://www.ncbi.nlm.nih.gov/pubmed/21825288>

Telaprevir is a hepatitis C virus protease inhibitor that is both a substrate and an inhibitor of CYP3A. Amlodipine and atorvastatin are both substrates of CYP3A and are among the drugs most frequently used by patients with hepatitis C. This study was conducted to examine the effect of telaprevir on atorvastatin and amlodipine pharmacokinetics (PK). This was an open-label, single sequence, nonrandomized study involving 21 healthy male and female volunteers. A coformulation of 5 mg amlodipine and 20 mg atorvastatin was administered on day 1. Telaprevir was taken with food as a 750-mg dose every 8 h from day 11 until day 26, and a single dose of the amlodipine-atorvastatin combination was readministered on day 17. Plasma samples were collected for determination of the PK of telaprevir, amlodipine, atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin. When administration with telaprevir was compared with administration without telaprevir, the least-square mean ratios (90% confidence limits) for amlodipine were 1.27 (1.21, 1.33) for the maximum drug concentration in serum (C(max)) and 2.79 (2.58, 3.01) for the area under the concentration-time curve from 0 h to infinity (AUC(0-∞)); for atorvastatin, they were 10.6 (8.74, 12.9) for the C(max) and 7.88 (6.84, 9.07) for the AUC(0-∞). Telaprevir significantly increased exposure to amlodipine and atorvastatin, consistent with the inhibitory effect of telaprevir on the CYP3A-mediated metabolism of these agents.

An Objective Assessment of Conformational Variability in Complexes of Hepatitis C Virus Polymerase with Non-Nucleoside Inhibitors. Caillet-Saguy C, Simister PC, Bressanelli S. *J Mol Biol.* 2011 Oct 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22008450>

A major target for antiviral therapy against hepatitis C virus (HCV) is the HCV polymerase nonstructural protein 5B (NS5B). Huge efforts have been devoted to the development of nucleoside and non-nucleoside inhibitors (NNIs) of NS5B. An offshoot of these efforts has been

the structural characterization of the interaction of NS5B with NNIs by X-ray crystallography. These works have shown that the conformation of recombinant NS5B is very similar across strains, constructs and complexes, making evaluation of the long-range conformational effects of NNIs nontrivial. Using procedures appropriate to the evaluation of such minor but potentially important differences, we objectively assessed the conformational diversity in the 78 available genotype 1b NS5B structures in the Protein Data Bank. We find that there are 20 significantly different NS5B conformations available, but all are geometrically close to a closed, RNA synthesis initiation-competent one. Within this fairly restricted range, differences can be mapped to movements of NS5B domains and subregions. Most of this information is actually defined by small but significant changes in complexes with NNIs. We thus establish rigorously the moving parts of the NS5B molecular machine and the previously unrecognized hinge points that come into play upon NNI binding. We propose that NNIs binding at three of the four distinct sites specifically inhibit the initiation step by the same mechanism: they prevent NS5B's "thumb" from quite reaching the proper initiation-competent position. Furthermore, we suggest that a small number of critical hinges in the NS5B structure may emerge as sites of resistance mutations during future antiviral treatment.

Human leukocyte antigen B27 selects for rare escape mutations that significantly impair hepatitis C virus replication and require compensatory mutations. Neumann-Haefelin C, Oniangue-Ndza C, Kuntzen T, et al. *Hepatology*. 2011 Oct;54(4):1157-66. doi: 10.1002/hep.24541.

<http://www.ncbi.nlm.nih.gov/pubmed/22006856>

Human leukocyte antigen B27 is associated with spontaneous viral clearance in hepatitis C virus (HCV) infection. Viral escape within the immunodominant, HLA-B27-restricted, HCV-specific, cluster of differentiation (CD)8(+) T-cell epitope, nonstructural protein (NS)5B(2841-2849) (ARMILMTHF), has been shown to be limited by viral fitness costs as well as broad T-cell cross-recognition, suggesting a potential mechanism of protection by HLA-B27. Here, we studied the subdominant HLA-B27-restricted epitope, NS5B(2936-2944) (GRAAICGKY), to further define the mechanisms of protection by HLA-B27. We identified a unique pattern of escape mutations within this epitope in a large cohort of HCV genotype 1a-infected patients. The predominant escape mutations represented conservative substitutions at the main HLA-B27 anchor residue or a T-cell receptor contact site, neither of which impaired viral replication capacity, as assessed in a subgenomic HCV replicon system. In contrast, however, in a subset of HLA-B27(+) subjects, rare escape mutations arose at the HLA-B27 anchor residue, R(2937), which nearly abolished viral replication. Notably, these rare mutations only occurred in conjunction with the selection of two equally rare, and structurally proximal, upstream mutations. Coexpression of these upstream mutations with the rare escape mutations dramatically restored viral replication capacity from <5% to \geq 70% of wild-type levels.

CONCLUSION: The selection of rare CTL escape mutations in this HLA-B27-restricted epitope dramatically impairs viral replicative fitness, unless properly compensated. These data support a role for the targeting of highly constrained regions by HLA-B27 in its ability to assert immune control of HCV and other highly variable pathogens.

Activation of chemokine and inflammatory cytokine response in HCV-infected hepatocytes depends on TLR3 sensing of HCV dsRNA intermediates. Li K, Li NL, Wei D, Pfeffer SR, Fan M, Pfeffer LM. *Hepatology*. 2011 Oct 26. doi: 10.1002/hep.24763. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22030901>

Chemokines and inflammatory cytokines are key regulators of immunity and inflammation during viral infections. Hepatitis C virus (HCV) is a hepatotropic RNA virus frequently associated with chronic liver inflammation and hepatocellular carcinoma. Intrahepatic levels of chemokines and cytokines are elevated in chronic HCV infections, but the underlying mechanisms remain unclear. We find that Toll like receptor-3 (TLR3) senses HCV infection in cultured hepatoma cells, leading to NF- κ B activation and the production of numerous chemokines and inflammatory cytokines, such as RANTES, MIP-1 α , MIP-1 β , IP-10 and IL-6. The chemokine/cytokine induction occurred late in HCV infection and was abrogated when HCV was UV-inactivated prior to infection, indicating a dependence on cellular recognition of HCV replication products. Gel shift and chromatin immunoprecipitation assays revealed that NF- κ B plays a pivotal role in HCV-induced chemokine/cytokine transcription. Mutations specifically disrupting the dsRNA binding activity of TLR3 ablated the chemokine/cytokine response to HCV infection, indicating that HCV dsRNA was the pathogen associated molecular pattern triggering TLR3 signaling. In vitro synthesized HCV dsRNAs with a minimal length of ~80-100 bp activated TLR3-dependent chemokine expression, regardless of the genome position from which they derive. In contrast, HCV ssRNAs, including those derived from the structured 3'NTR highly potent for RIG-I activation, failed to do so. Moreover, robust production of chemokines and inflammatory cytokines was also observed in primary human hepatocytes following stimulation with extracellular poly-I:C, a TLR3 ligand. **CONCLUSION:** Our data suggest that TLR3-mediated chemokine and inflammatory cytokine responses may play an important role in host immune responses to HCV and the pathogenesis of HCV-associated liver diseases.

Redistribution of regulatory T-cells across the evolving stages of chronic hepatitis C. Ferri S, Lalanne C, Lanzoni G, et al. *Dig Liver Dis*. 2011 Oct;43(10):807-13. <http://www.ncbi.nlm.nih.gov/pubmed/21684822>

BACKGROUND: Hepatitis C virus infection frequently leads to chronic hepatitis, possibly evolving to end-stage liver disease and hepatocellular carcinoma. Regulatory T cells can affect antiviral immune response thus influencing the outcome of the disease. **AIM:** To determine numeric and functional distribution of regulatory T cells expressing CD4⁺CD25^{hi}Foxp3⁺ (T-regs) during the different stages of hepatitis C virus-related liver disease. **METHODS:** 90 hepatitis C viraemic patients and 50 healthy controls were included. Surface and intracellular (Foxp3) T-reg markers were evaluated by flow cytometry. Target cell proliferation and interferon-gamma production were evaluated in 37 HCV patients. In 16 cases intrahepatic distribution of Foxp3 by immuno-histochemistry was assessed. **RESULTS:** T-regs were increased in hepatitis C virus infected patients and correlated inversely with aminotransferases and directly with MELD score and disease duration. A preserved inhibitory ability of interferon-gamma production was distinctive of patients with normal aminotransferases. Circulating T-regs did not correlate with intrahepatic distribution of Foxp3. **CONCLUSIONS:** In chronic hepatitis C, selective expansion of peripheral T-regs in patients with normal aminotransferases and advanced disease suggests that, though a continual low level inflammation does not prevent liver

disease progression, once cirrhosis has developed it may represent an attempt to prevent immuno-mediated decompensation.

No association of promoter variations of HMOX1 and UGT1A1 genes with liver injury in chronic hepatitis C. Urbánek P, Leníček M, Muchová L, et al. *Ann Hepatol.* 2011 Oct-Dec;10(4):445-51.

<http://www.ncbi.nlm.nih.gov/pubmed/21911884>

BACKGROUND: Heme oxygenase-1 (HMOX1) and bilirubin UDP-glucuronosyltransferase (UGT1A1), both enzymes involved in bilirubin homeostasis, play an important role in oxidative stress defense. **OBJECTIVE:** To assess the effect of promoter variations of HMOX1 and UGT1A1 genes on the progression of fibrosis in patients chronically infected with the hepatitis C virus (HCV). **MATERIAL AND METHODS:** The study was performed on 146 chronic HCV infection patients, plus 146 age- and sex-matched healthy subjects. The (GT)_n and (TA)_n dinucleotide variations in HMOX1 and UGT1A1 gene promoters, respectively, were determined by fragment analysis in all subjects. **RESULTS:** No differences were found in the frequencies of each particular allele of both genes, between HCV patients and a control group ($p > 0.05$). Furthermore, no association was detected ($p > 0.05$) between either the HMOX1 or the UGT1A1 promoter variants and the individual histological stages of liver disease in the HCV positive patients. Finally, no differences in the HMOX1 and UGT1A1 genotype prevalence rates were found between pre-cirrhotic and cirrhotic patients ($p > 0.05$). **CONCLUSION:** Based on our data, microsatellite variations in the HMOX1 and UGT1A1 genes are not likely to protect from progression of liver disease in patients with chronic hepatitis C.

Monoclonal antibody 2-152a suppresses hepatitis C virus infection through betaine/GABA transporter-1. Satoh M, Saito M, Takano T, et al. *J Infect Dis.* 2011 Oct 15;204(8):1172-80.

<http://www.ncbi.nlm.nih.gov/pubmed/21917889>

BACKGROUND: We recently established a monoclonal antibody (2-152a MAb) that binds to 3 β -hydroxysterol- Δ 24-reductase (DHCR24) by immunizing mice with cells (RzM6-LC) persistently expressing hepatitis C virus (HCV). Here, we aimed to analyze the activity of 2-152a MAb against HCV replication and explore the molecular mechanism underlying the antiviral activity. **METHODS:** We characterized the effects of 2-152a MAb on HCV replication and performed a microarray analysis of antibody-treated HCV replicon cells. The molecules showing a significant change after the antibody treatment were screened to examine their relationship with HCV replication. **RESULTS:** The antibody had antiviral activity both in vitro and in vivo (chimeric mice). In the microarray analysis, 2-152a MAb significantly suppressed the expression of betaine/GABA transporter-1 (BGT-1) in 2 HCV replicon cell lines but not in HCV-cured cells. Silencing of BGT-1 expression by small interfering RNA (siRNA) revealed significant suppression of HCV replication and infection without cytotoxicity. Further, BGT-1 expression was significantly increased in the presence of HCV ($P < .05$). **CONCLUSIONS:** Our results suggest that 2-152a MAb suppresses HCV replication and infection through BGT-1. These findings highlight important roles of BGT-1 in HCV replication and reveal a possible target for anti-HCV therapy.

The hepatitis C virus core protein decreases lipid droplet turnover: A mechanism for core-induced steatosis. Harris C, Herker E, Farese RV, Ott M. J Biol Chem. 2011 Oct 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21984835>

Steatosis is a frequent complication of HCV infection. In mice, this condition is recapitulated by the expression of a single viral protein, the nucleocapsid core. Core localizes to the surface of lipid droplets (LDs) in infected liver cells through a process dependent on host diacylglycerol acyltransferase 1 (DGAT1), an enzyme that synthesizes triglycerides in the ER. Whether DGAT1 also plays a role in core-induced steatosis is uncertain. Here, we show that mouse embryonic fibroblasts isolated from DGAT1(-/-) mice are protected from core-induced steatosis, as are livers of DGAT1(-/-) mice expressing core, demonstrating that the steatosis is DGAT1-dependent. Surprisingly, core expression did not increase DGAT1 activity or triglyceride synthesis, thus excluding the possibility that core activates DGAT1 to cause steatosis. Instead, we find that DGAT1-dependent localization of core to LDs is prerequisite for core's steatogenic properties. Using biochemical and immunofluorescence microscopy techniques, we show that the turnover of lipids in core-coated droplets is decreased, providing a physiological mechanism for core-induced steatosis. **Our results** support a bipartite model in which core first requires DGAT1 to gain access to LDs, and then LD-localized core interferes with triglyceride turnover, thus stabilizing lipid droplets and leading to steatosis.

HIV/HCV COINFECTION

Evaluation of endothelial function and subclinical atherosclerosis in association with hepatitis C virus in HIV-infected patients: a cross-sectional study. Masia M, Padilla S, Robledano C, Ramos JM, Gutierrez F. BMC Infect Dis. 2011 Oct 3;11(1):265. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21967471>

BACKGROUND: Relationship of hepatitis C virus (HCV) infection with an increased risk of cardiovascular disease (CVD) in HIV-infected patients remains controversial. We evaluated endothelial function and subclinical atherosclerosis in HIV-infected patients with and without HCV. **METHODS:** Flow-mediated dilatation (FMD) of the brachial artery and circulating levels of cell adhesion molecules (CAM) were measured in HCV/HIV-coinfected and HIV-monoinfected patients. Subclinical atherosclerosis was assessed by carotid intima-media thickness (cIMT). **RESULTS:** 63 (31%) HCV/HIV-coinfected and 138 (69%) HIV-monoinfected patients were included. Median soluble vascular CAM-1 (sVCAM-1) and intercellular CAM-1 (sICAM-1) levels were significantly higher in HIV/HCV-coinfected patients ($P < 0.001$ for both cases). Median (interquartile range) FMD was 6.21% (2.86-9.62) in HCV/HIV-coinfected and 5.54% (2.13-9.13) in HIV-monoinfected patients ($P = 0.37$). Adjustment for variables associated with HCV and FMD disclosed similar results. FMD correlated inversely with cIMT and age. Carotid IMT did not differ between HCV/HIV-coinfected and HIV-monoinfected patients in unadjusted (0.61 [0.55-0.65] mm vs 0.60 [0.53-0.72] mm; $P = 0.39$) or adjusted analyses. **CONCLUSION:** HCV infection was associated with higher levels of sICAM-1 and sVCAM-1, but no evidence of increased subclinical atherosclerosis was found when endothelial function was evaluated through FMD, or when assessing the cIMT.

High FIB-4 index is associated with hepatocellular carcinoma risk in HIV-infected patients.

Park LS, Tate JP, Justice AC, et al. *Cancer Epidemiol Biomarkers Prev.* 2011 Oct 25. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22028407>

BACKGROUND: Chronic inflammation caused by hepatitis B virus infection, hepatitis C virus infection, and/or heavy alcohol use can lead to fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC). FIB-4 is an index score calculated from platelet count, alanine transaminase, aspartate transaminase, and age that predicts fibrosis and cirrhosis. We hypothesized that high FIB-4 would be associated with development of HCC in HIV-infected persons, who are at high risk due to high prevalence of viral hepatitis and alcohol consumption, and possibly due to HIV infection itself. **METHODS:** Using proportional hazards models, we tested this hypothesis among 22,980 HIV-infected men from the Veterans Aging Cohort Study. We identified incident HCC cases from the VA Central Cancer Registry. **RESULTS:** During follow-up, there were 112 incident HCC diagnoses. The age- and race/ethnic group-adjusted HR was 4.2 (95% CI: 2.4, 7.4) for intermediate FIB-4 and 13.0 (95% CI: 7.2, 23.4) for high FIB-4, compared to low FIB-4. After further adjustment for enrollment year, CD4 count, HIV-1 RNA level, antiretroviral therapy use, hepatitis B and C virus infection, alcohol abuse/dependency, and diabetes, FIB-4 remained a strong, significant, independent risk factor for HCC. The multivariate-adjusted HR was 3.6 (95% CI: 2.1, 6.4) for intermediate FIB-4 and 9.6 (95% CI: 5.2, 17.4) for high FIB-4. **CONCLUSIONS:** Calculated from routine, non-invasive laboratory tests, FIB-4 is a strong, independent HCC risk factor in HIV-infected patients. **IMPACT:** FIB-4 might prove valuable as an easily measured index to identify those at highest risk for HCC, even prior to development of clinical cirrhosis.

Early viral kinetics: a novel guide for optimal dosing frequency of pegylated interferon- α -2a in HIV/HCV-coinfected patients.

Milazzo L, Cesari M. *Expert Rev Anti Infect Ther.* 2011 Oct;9(10):859-62.

<http://www.ncbi.nlm.nih.gov/pubmed/21973297>

Twice-weekly pegylated interferon- α -2a and ribavirin results in superior viral kinetics in HIV/hepatitis C virus coinfecting patients compared with standard therapy. *AIDS* 25, 1179-1187 (2011). The success rate in HCV treatment of HIV/HCV-coinfected patients is still unsatisfactory and new strategies are required to improve the effectiveness of current regimens and eventually optimize the oncoming new antiviral drugs. This article assesses the findings of a recently published paper comparing pharmacokinetics, pharmacodynamics and HCV decay with twice-weekly dosing of pegylated IFN- α -2a versus the standard weekly dosing, and weight-based ribavirin. A more rapid HCV-RNA decline was observed in the twice-weekly pegylated interferon arm and associated with a higher induction of interferon-stimulated genes, despite a similar pharmacokinetic profile between the two dosing schedules. This promising novel therapeutic approach to improve sustained virologic response in difficult-to-treat populations is discussed in relation to the key findings of the article.

High uptake of hepatitis C virus treatment in HIV/hepatitis C virus co-infected patients attending an integrated HIV/hepatitis C virus clinic. Kieran J, Dillon A, Farrell G, et al. *Int J STD AIDS*. 2011 Oct;22(10):571-6.

<http://www.ncbi.nlm.nih.gov/pubmed/21998177>

Hepatitis C virus (HCV) is a major cause of liver disease in HIV-infected patients. The HCV treatment outcomes and barriers to HCV referral were examined in a centre with a HIV/HCV co-infection clinic. Patients who were antibody positive for both HIV and HCV between 1987 and January 2009 were identified. A retrospective chart review was undertaken. Multivariate analysis was performed to assess predictors of HCV clinic referral. Data were collected on 386 HIV/HCV patients; 202/386 had been referred to the co-infection clinic and 107/202 had HCV treatment. In addition, 29/202 were undergoing pretreatment work-up. Overall sustained virologic response (SVR) was 44%; SVR was equivalent in those who acquired HIV/HCV infection from intravenous drug use (IDU) and others. **On multivariate analysis**, patients who missed appointments, were younger, with active IDU and advanced HIV and who were not offered HCV treatment were less likely to be referred to the clinic. Patients attending the clinic were more likely to have been screened for hepatocellular carcinoma than those attending the general HIV service. Two-thirds of patients referred to the clinic had engaged with the HCV treatment programme. Dedicated co-infection clinics lower the threshold for treatment and improve management of liver disease in co-infected patients.

Satisfaction with care in HIV-infected patients treated with long-term follow-up antiretroviral therapy: the role of social vulnerability. Préau M, Protopopescu C, Raffi F, et al. *AIDS Care*. 2011 Oct 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21999644>

The aim of this study was to determine factors associated with complete satisfaction with the care provided (satisfaction with physicians and satisfaction with services and organization) among HIV-infected patients followed up in the French ANRS CO8 APROCO-COPILOTE cohort. Analyses focused on cross-sectional data collected during the ninth year of cohort follow-up. Satisfaction with care, sociodemographic characteristics, and behavioral data were collected using self-administered questionnaires, while clinical data were derived from medical records. Complete satisfaction with care was defined as being 100% satisfied. Two logistic regression models were used to identify predictors of (1) complete satisfaction with physicians (n=404) and (2) complete satisfaction with services and organization (n=396). Sixteen percent of patients were completely satisfied with physicians, while 15.9% were completely satisfied with services and organization. Being older and reporting fewer discomforting antiretroviral therapy (ART) side effects were factors independently associated with complete satisfaction with both physicians and services and organization. Strong support from friends and absence of hepatitis C (HCV) co-infection were independently associated with complete satisfaction with physicians, while strong support from one's family and comfortable housing conditions were independently associated with complete satisfaction with services and organization. Even after nine years of follow-up, social vulnerabilities still strongly influence HIV-infected patients' interactions with the health care system. Day-to-day experience with the disease, including perceived treatment side effects, appears to play a key role in the quality of these interactions. More attention should be given to patient satisfaction, especially for socially vulnerable patients, in order to avoid potentially detrimental consequences such as poor adherence to ART.

Prevalence and Temporal Trends of Hepatitis B, Hepatitis C, and HIV/AIDS Co-infection During Pregnancy Across the Decade, 1998-2007. Salihu HM, Connell L, Salemi JL, August EM, Weldeselashe HE, Alio AP. *J Womens Health (Larchmt)*. 2011 Oct 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22011209>

ABSTRACT BACKGROUND: Limited data are available on hepatitis rates during pregnancy by socio-demographic characteristics. This study examined temporal trends in hepatitis B virus (HBV) and hepatitis C virus (HCV) mono-infections and HIV/HBV and HIV/HCV co-infections in subpopulations among pregnant women in Florida between 1998 and 2007. **METHODS:** We analyzed all Florida live births from 1998 to 2007 using hospital discharge data linked to birth records. Results: The total sample size was 1,700,734 singleton live births. The prevalence of HBV in pregnancy rose from 65.4 per 100,000 births to 123.5 per 100,000 births ($p < 0.0001$ for trend), and the prevalence of HCV in pregnancy increased from 17.0 per 100,000 births to 125.1 per 100,000 births ($p < 0.0001$ for trend). Compared with white mothers, black mothers were more than twice as likely to have HBV in pregnancy (adjusted rate ratios [ARR]=2.24; 95% CI=1.97-2.53). Black mothers were 69% (ARR=0.31, 95% CI=0.25-0.39) and Hispanic mothers were 51% (ARR=0.49, 95% CI=0.41-0.60) less likely to have HCV compared with white mothers. **CONCLUSIONS:** Although the overall prevalence rate of HBV increased over the past decade, black women still had a noticeably higher rate of infection. Similarly, white women and those with HIV co-infection had noticeably higher rates of HCV infection over the study period. Our findings call for improved and increased HBV/HCV prevention, screening, and immunization programs among minority women of childbearing age.

Alcohol use among patients with HIV infection. Bonacini M. *Ann Hepatol*. 2011 Oct-Dec;10(4):502-7.

<http://www.ncbi.nlm.nih.gov/pubmed/21911892>

OBJECTIVE: To evaluate alcohol use in patients with HIV infection, assess ethnic and social associations, and describe outcomes. **MATERIAL AND METHODS:** design: cohort study. setting: Academic HIV-Liver Clinic. patients: 431 HIV-infected patients (371 men, 60 women); 249 patients with HIV/HCV coinfection, 115 HIV alone, and 67 with HIV/HBV. Intervention: alcohol use was estimated at first interview and reported as the estimated average lifetime consumption in grams/day. outcome measures: laboratory values, liver fibrosis, decompensation and mortality. **RESULTS:** Twenty-two percent of patients in the entire cohort had high risk lifetime average alcohol consumption, defined as ≥ 50 mg/day. Fifty-six percent of patients had quit all alcohol when first evaluated, but follow-up showed that 26% continued high risk consumption. By univariate analysis high alcohol consumption was associated with Latino ethnicity, injection drug use (IDU) and hepatitis C (HCV) coinfection. Multivariable analysis showed only IDU to be independently associated with high alcohol consumption (RR = 4.1, $p = 0.0005$). There were no significant differences in laboratory values, including CD4 cell counts, except for a trend towards higher transaminases and liver fibrosis scores, between high and low alcohol users. All-cause mortality was statistically higher in the high (37%) vs. low (25%, $p = 0.03$) alcohol use group, and was associated with both IDU (RR = 2.2, $p = 0.04$) and the amount of alcohol consumed (RR = 1.1, $p = 0.04$). Liver decompensation and mortality were both higher in the high use group but of borderline significance. Using an ordinal grouping, we found a strong correlation ($R = 0.88$) between alcohol consumption and the percentage of liver death over total deaths, with lowest mortality rates found in those use of 10 g/day or less.

CONCLUSIONS: Unsafe use of alcohol is prevalent in HIV-infected patients and stoppage is not universal. There is a significant impact on all-cause mortality and a trend towards higher liver morbidity and mortality. IDU is significantly and independently associated with high ethanol intake. Practitioners should strongly recommend that HIV patients minimize alcohol use.

Clinical contributors to cerebral white matter integrity in HIV-infected individuals.

Gongvatana A, Cohen RA, Correia S, et al. J Neurovirol. 2011 Oct 1. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21965122>

HIV-infected people frequently exhibit brain dysfunction characterized by preferential damage to the cerebral white matter. Despite suppressed viral load and reconstituted immune function afforded by combination antiretroviral therapy (CART), brain dysfunction continues to be observed even in medically stable individuals. To provide insight into the etiology of HIV-associated brain dysfunction in the CART era, we examined the effects of HIV disease markers, antiretroviral treatment, hepatitis C (HCV) coinfection, and age on DTI measures of white matter integrity in a cohort of 85 individuals aged 23 to 65 years with chronic HIV infection. Fractional anisotropy and mean diffusivity were derived from 29 cerebral white matter regions, which were segmented on each individual brain using a high-resolution T1-weighted image and registered to diffusion images. Significant effects of clinical variables were found on white matter abnormalities in nearly all brain regions examined. Most notably, HCV coinfection and older age were associated with decreased anisotropy or increased diffusivity in the majority of brain regions. Individuals with higher current CD4 levels exhibited higher anisotropy in parietal lobe regions, while those undergoing antiretroviral treatment exhibited higher anisotropy in temporal lobe regions. The observed diffuse pattern of white matter injury suggests that future neuroimaging studies should employ methodologies that are not limited to circumscribed regions of interest. **The current findings** underline the multifactorial nature of HIV-associated brain dysfunction in the CART era, and the importance of examining the effects of HIV disease in the context of other comorbidities, in particular HCV coinfection and aging.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Quantitative liver function tests improve the prediction of clinical outcomes in chronic hepatitis C: Results from the HALT-C trial. Everson GT, Shiffman ML, Hoefs JC, et al.

Hepatology. 2011 Oct 26. doi: 10.1002/hep.24752. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22030902>

Risk for future clinical outcomes is proportional to the severity of liver disease in patients with chronic hepatitis C. We measured disease severity by quantitative liver function tests (QLFTs) to determine cutoffs for QLFTs that identified patients who were at low and high risk for a clinical outcome. Two hundred twenty seven participants in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial underwent baseline QLFTs and were followed for a median of 5.5 years for clinical outcomes. QLFTs were repeated in 196 patients at month 24 and in 165 patients at month 48. Caffeine elimination rate (k), antipyrine (AP) clearance (Cl), MEGX concentration, methionine breath test (MBT), galactose elimination capacity (GEC), dual cholate (CA) clearances and shunt, and perfused hepatic mass (PHM) and liver and spleen volumes (SPECT) were measured. Baseline QLFTs were significantly worse ($p=0.0017$ to <0.0001) and spleen volumes larger ($p<0.0001$) in the 54 patients who subsequently experienced clinical outcomes. QLFT cutoffs that characterized patients as "low" and "high risk" for clinical

outcome yielded hazard ratios ranging from 2.21 (95%CI 1.29-3.78) for GEC to 6.52 (95%CI 3.63-11.71) for CA Cloral. QLFTs independently predicted outcome in models with Ishak fibrosis score, platelet count, and standard laboratory tests. In serial studies, patients with "high risk" results for CA Cloral or PHM had a nearly 15-fold increase in risk for clinical outcome. Less than 5% of patients with "low risk" QLFTs experienced a clinical outcome. **CONCLUSION:** QLFTs independently predict risk for future clinical outcomes. By improving risk assessment, QLFTs could enhance noninvasive monitoring, counseling, and management of patients with chronic hepatitis C.

A single IL28B genotype SNP rs12979860 determination predicts treatment response in patients with chronic hepatitis C Genotype 1 virus. Halfon P, Bourliere M, Ouzan D, et al.

Eur J Gastroenterol Hepatol. 2011 Oct;23(10):931-5.

<http://www.ncbi.nlm.nih.gov/pubmed/21900787>

BACKGROUND: Recent studies have suggested that host genetics may be useful for predicting drug response and have supported the recommendation that single polynucleotide polymorphisms (SNPs) of IL28B should be investigated when treating hepatitis C virus (HCV)-1 infected patients. The aim of this study was to determine whether a single IL-28B genotype SNP rs8099917 or rs12979860 determination is sufficient to predict treatment failure in patients with chronic HCV. **METHODS:** A total of 198 patients were included; mean (\pm standard deviation) age was 47 \pm 12 years and 140 (71%) were men. One hundred and fifty-six (79%) patients were infected with HCV genotype 1 and 42 (21%) with HCV genotypes 2 or 3. One hundred and eight (55%) patients had sustained virologic response (SVR). Two SNPs in the IL-28B were analyzed (rs8099917 and rs12979860). **RESULTS:** A total of 115 (58%) patients had rs8099917 TT genotype and 61 (31%) had rs12979860 CC genotype. Rs8099917 TT and rs12979860 CC genotypes were associated with SVR in HCV genotype 1 patients [odds ratio=2.60 (1.36-5.00), P=0.004 and odds ratio=3.30 (1.58-6.90), P=0.03 respectively]. No association was found between SNPs and SVR in HCV genotype 2 or 3 patients. **CONCLUSION:** This study confirms that SNPs rs8099917 and rs12979860 used alone may be useful for predicting the outcome of HCV treatment. In a rational and cost-effective approach, determination of only one of these two SNPs is sufficient for predicting SVR. Because of the highest predictive SVR associated with rs12979860 CC compared with the rs8099917 TT (respective positive predictive value: 72% vs. 63%, P=ns), rs12979860 determination alone is sufficient for predicting interferon response.

Genetic variation in Interleukin-28B predicts SVR in hepatitis C genotype 1 Argentine patients treated with PEG IFN and ribavirin. Ridruejo E, Solano A, Marciano S, et al. Ann Hepatol. 2011 Oct-Dec;10(4):452-7.

<http://www.ncbi.nlm.nih.gov/pubmed/21911885>

BACKGROUND AND AIMS: Genetic variations in the interleukin 28B (IL28B) gene have been associated with viral response to PEG-interferon- α /ribavirin (PR) therapy in hepatitis C virus (HCV) genotype 1 infected patients from North America, Europe and Asia. The importance of these IL28B variants for Argentine patients remains unknown. **MATERIAL AND METHODS:** IL28B host genotypes (rs8099917 and rs12979860) were determined in a population of Argentine patients with European ancestry. Results were analyzed looking for their association with sustained virologic response (SVR) to PR therapy and compared with other baseline hosts' biochemical, histological and virological predictors of response. **RESULTS:**

We studied 102 patients, 60% were men, and 40% of them were rs8099917 TT and 18% rs12979860 CC. Mean baseline serum HCV RNA was 1.673.092 IU/mL and mean F score was: 2.10 ± 1.18 (21% cirrhotic). SVR rate was higher in rs8099917 TT genotypes (55%) when compared to GT/GG (25%) ($p = 0.002$) and in rs12979860 CC (64%) than in CT/TT (30%) ($p = 0.004$). The univariate analysis showed that rs8099917 TT (OR 3.7; 95% CI 1.5-8.7; $p = 0.002$), rs12979860 CC (OR 4.6; 95% CI 1.5-13.7; $p = 0.006$), low viral load (OR 4.6; 95% CI 1.7-12.6; $p = 0.002$) and F0-2 (OR 8.5; 95% CI 2.3-30.6; $p = 0.001$) were significantly associated with SVR. In the multivariate analysis, rs12979860 CC, rs8099917 TT, viral load < 400.000 IU/mL and F0-2 were associated with SVR rates ($p = 0.029$, $p = 0.012$, $p = 0.013$ and $p = 0.004$, respectively). **CONCLUSION:** IL28B host genotypes should be added to baseline predictors of response to PR therapy in Latin American patients with European ancestry.

Naturally Occurring Genotype 2b/1a Hepatitis C Virus in the United States. Bhattacharya D, Accola MA, Ansari IH, Striker R, Rehrauer WM. *Virol J.* 2011 Oct 3;8(1):458. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21967740>

BACKGROUND: Hepatitis C Virus (HCV) infected patients are frequently repeatedly exposed to the virus, but very few recombinants between two genotypes have been reported. **FINDINGS:** We describe the discovery of an HCV recombinant using a method developed in a United States clinical lab for HCV genotyping that employs sequencing of both 5' and 3' portions of the HCV genome. Over twelve months, 133 consecutive isolates were analyzed, and a virus from one patient was found with discordant 5' and 3' sequences suggesting it was a genotype 2b/1a recombinant. We ruled out a mixed infection and mapped a recombination point near the NS2/3 cleavage site. **CONCLUSIONS:** This unique HCV recombinant virus described shares some features with other recombinant viruses although it is the only reported recombinant of a genotype 2 with a subtype 1a. This recombinant represents a conundrum for current clinical treatment guidelines, including treatment with protease inhibitors. This recombinant is also challenging to detect by the most commonly employed methods of genotyping that are directed primarily at the 5' structural portion of the HCV genome.

From proteomic multimarker profiling to interesting proteins: thymosin- β (4) and kininogen-1 as new potential biomarkers for inflammatory hepatic lesions. Henkel C, Schwamborn K, Zimmermann HW, et al. *J Cell Mol Med.* 2011 Oct;15(10):2176-2188. doi: 10.1111/j.1582-4934.2010.01204.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21496200>

Despite tremendous efforts in disclosing the pathophysiological and epidemiological factors associated with liver fibrogenesis, non-invasive diagnostic measures to estimate the clinical outcome and progression of liver fibrogenesis are presently limited. Therefore, there is a mandatory need for methodologies allowing the reasonable and reliable assessment of the severity and/or progression of hepatic fibrogenesis. We here performed proteomic serum profiling by matrix-assisted laser desorption ionization time-of-flight mass spectrometry in 179 samples of patients chronically infected with hepatitis C virus and 195 control sera. Multidimensional analysis of spectra allowed the definition of algorithms capable to distinguish class-specific protein expression profiles in serum samples. Overall about 100 peaks could be detected per single spectrum. Different algorithms including protein peaks in the range of 2000 and 10,000 Da were generated after pre-fractionation on a weak cation exchange surface. A

specificity of 93% with a sensitivity of 86% as mean of the test set results was found, respectively. The nature of three of these protein peaks that belonged to kininogen-1 and thymosin- β (4) was further analysed by tandem mass spectrometry (MS)/MS. We further found that kininogen-1 mRNA was significantly down-regulated in cirrhotic livers. We have identified kininogen-1 and thymosin- β (4) as potential new biomarkers for human chronic hepatitis C and conclude that serum profiling is a reliable technique to identify hepatitis-associated expression patterns. Based on the high throughput capability, the identified differential protein panel may serve as a diagnostic marker and warrants further validation in larger cohorts.

Comparison of Transient Elastography and Acoustic Radiation Force Impulse for Non-Invasive Staging of Liver Fibrosis in Patients With Chronic Hepatitis C. Rizzo L, Calvaruso V, Cacopardo B, et al. *Am J Gastroenterol.* 2011 Oct 4. doi: 10.1038/ajg.2011.341. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21971536>

OBJECTIVES: Transient elastography (TE) is adequate for a diagnosis of cirrhosis, but its accuracy for milder stages of fibrosis is much less satisfactory. The objective of this study was to compare the performance and the discordance rate of acoustic radiation force impulse (ARFI) and TE with liver biopsy in a cohort of chronic hepatitis C (CHC) patients. **METHODS:** One hundred thirty-nine consecutive patients with CHC were enrolled in two tertiary centers, and evaluated for histological (Metavir score) and biochemical features. All patients underwent TE and ARFI. **RESULTS:** TE was unreliable in nine patients (6.5%), while in no cases (0%) were ARFI invalid measurements recorded ($P=0.029$). By area under receiver operating characteristic curve (AUROC), the best cutoff values for TE and ARFI for significant fibrosis ($\geq F2$) were ≥ 6.5 kPa (AUROC: 0.78) and ≥ 1.3 m/s (AUROC: 0.86), respectively. For severe fibrosis (F3-F4), these cutoff values were 8.8 kPa (AUROC: 0.83) for TE and 1.7 m/s (AUROC: 0.94) for ARFI. For cirrhosis, TE had its best cutoff at ≥ 11 kPa (AUROC: 0.80) and ARFI at ≥ 2.0 m/s (AUROC: 0.89). By pairwise comparison of AUROC, ARFI was significantly more accurate than TE for a diagnosis of significant and severe fibrosis ($P=0.024$ and $P=0.002$, respectively), while this difference was only marginal for cirrhosis ($P=0.09$). By partial AUROC analysis, ARFI performance results significantly higher for all three stages of fibrosis. The average concordance rates of TE and ARFI vs. liver biopsy were 45.4 and 54.7%, respectively. By multivariate analysis, ARFI was not associated with alanine aminotransferase (ALT), body mass index, Metavir grade, and liver steatosis, while TE was significantly correlated with the ALT value ($P=0.027$). **CONCLUSIONS:** In a cohort of patients with CHC, ARFI imaging was more accurate than TE for the non-invasive staging of both significant and severe classes of liver fibrosis.

Upper limits of normal for alanine aminotransferase activity in the United States population. Ruhl E, Everhart JE. *Hepatology.* 2011 Oct 10. doi: 10.1002/hep.24725. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21987480>

BACKGROUND & RATIONALE: Alanine aminotransferase (ALT) is an important test for liver disease, yet there is no generally accepted upper limit of normal (ULN) in the United States. Furthermore, the ability of ALT to differentiate persons with and without liver disease is uncertain. We examined cut-offs for ALT for their ability to discriminate between persons with positive hepatitis C virus (HCV) RNA and those at low risk for liver injury in the U.S.

population. **METHODS:** Among adult participants in the 1999-2008 U.S. National Health and Nutrition Examination Survey, 259 were positive for serum HCV RNA and 3,747 were at low risk for liver injury (negative HCV RNA and hepatitis B surface antigen, low alcohol consumption, no evidence of diabetes, normal body mass index and waist circumference). Serum ALT activity was measured centrally. **RESULTS:** Maximum correct classification was achieved at ALT=29 IU/L for men (88% sensitivity, 83% specificity) and 22 (89% sensitivity, 82% specificity) for women. The cut-off for 95% sensitivity was an ALT=24 IU/L (70% specificity) for men and 18 (63% specificity) for women. The cut-off for 95% specificity was an ALT=44 IU/L (64% sensitivity) for men and 32 (59% sensitivity) for women. The area under the curve was 0.929 for men and 0.915 for women. If the cut-offs with the best correct classification were applied to the entire population, 36.4% of men and 28.3% of women would have had abnormal ALT. **CONCLUSION:** ALT discriminates persons infected with HCV from those at low risk of liver disease, but would be considered elevated in a large proportion of the U.S. population.

Body piercing and tattoos: a survey on young adults' knowledge of the risks and practices in body art. Quaranta A, Napoli C, Fasano F, et al. BMC Public Health. 2011 Oct 7;11:774.

<http://www.ncbi.nlm.nih.gov/pubmed/21981772>

BACKGROUND: The practice of tattooing and piercing has expanded in western society. In order to verify young adults' knowledge of the risk and practices related to body art, an investigation was conducted among freshmen of the University of Bari in the region of Apulia, Italy. **METHODS:** The study was carried out in the Academic Year 2009-2010 through an anonymous self-administered written questionnaire distributed to 1,656 freshmen enrolled in 17 Degree Courses. **RESULTS:** Of the 1,598 students included in the analysis, 78.3% believe it is risky to undergo piercing/tattoo practices. AIDS was indicated as a possible infection by 60.3% of freshmen, hepatitis C by 38.2%, tetanus by 34.3% and hepatitis B by 33.7% of the sample. 28.1% of freshmen were not aware that there are also non-infectious complications. 29% of the sample had at least one piercing or tattoo (this percentage does not include earlobe piercing in women). Of those with body art, the decision to undergo body art was made autonomously in 57.9% of the participants. 56.3% of freshmen undergoing body art had taken less than a month to decide. With regard to the reasons that led the sample to undergo body art, 28.4% were unable to explain it, 23.8% answered to improve their aesthetic aspect, 18.4% to distinguish themselves from others, 12.3% for fashion; 17.1% for other reasons. 25.4% of the sample declared that they had a piercing (79.8% female vs 20.2% male; ratio M/F 1:4.0). The average age for a first piercing was 15.3 years (range 10-27; SD \pm 2.9). 9.6% of the sample declared that they have a tattoo (69.9% female vs 30.1% male; ratio M/F 1:2.3). The average age for a first tattoo was 17.5 years (range 10-26, SD \pm 2.4). **CONCLUSIONS:** Most of the freshmen knew about AIDS-related risks but not other potential risks. Body art is fairly common among young adults (especially women). The decision is often not shared with the family and is undertaken mostly without a specific reason or for the improvement of aesthetic aspect. Information about freshmen's knowledge, attitudes and practices could help in effective planning of health promotion strategies.

Impact of Fibroscan on management of chronic viral hepatitis in clinical practice. van de Putte DF, Blom R, van Soest H, et al. *Ann Hepatol.* 2011 Oct-Dec;10(4):469-76.

<http://www.ncbi.nlm.nih.gov/pubmed/21911887>

BACKGROUND: Liver stiffness measurement (LSM) using Fibroscan is an increasingly popular non-invasive method for quantifying liver fibrosis in patients with chronic viral hepatitis. We aimed to explore potential impact of Fibroscan on clinical management. **MATERIAL AND METHODS:** 133 patients with chronic hepatitis B (HBV, n = 75) or C (HCV, n = 58) underwent Fibroscan measurement. LSM results were compared with liver biopsy results, ultrasound, and APRI-scores, and the impact of LSM on clinical management was evaluated. **RESULTS:** LSM results indicated fibrosis stage F0-F1 in 84 patients (63%), F2 in 28 (21%), F3 in 8 (6%), and F4 in 13 patients (10%). Nineteen patients had liver biopsies within one year of LSM. In ten patients, LSM and biopsy showed the same fibrosis stage, in 8 there was one stage difference, and in 1 three stages difference. Ultrasound only showed cirrhosis in three patients, who all exhibited advanced cirrhosis at LSM. There was a statistically significant, but weak correlation between LSM results and APRI scores ($r = 0.31$, p value < 0.001). LSM results changed clinical management in 39% of patients (55 cases): in 15 patients antiviral treatment was indicated, in 21 patients surveillance for hepatocellular carcinoma was indicated, and 19 successfully treated hepatitis C patients could be discharged from clinical follow-up in absence of severe fibrosis or cirrhosis. **CONCLUSION:** LSM appears to be a valuable non-invasive tool to manage patients with chronic viral hepatitis in clinical practice.

Mallory-denk bodies are associated with outcomes and histologic features in patients with chronic hepatitis C. Rakoski MO, Brown MB, Fontana RJ, et al. *Clin Gastroenterol Hepatol.* 2011 Oct;9(10):902-909.e1. Epub 2011 Jul 23.

<http://www.ncbi.nlm.nih.gov/pubmed/21782771>

BACKGROUND & AIMS: Mallory-Denk bodies (MDBs) are inclusions found in hepatocytes of patients with chronic liver diseases. Their clinical significance and prognostic value are not understood. **METHODS:** We performed cross-sectional and longitudinal analyses of patients with chronic hepatitis C (CHC) enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial to identify clinical features associated with MDBs and changes in MDBs over time. Biopsy specimens were obtained at baseline and 1.5 and 3.5 years after patients were assigned to groups for the HALT-C trial; and patients were followed up to assess clinical and histologic outcomes. **RESULTS:** Of biopsy samples collected from 1050 patients, MDBs were present in 15%. They were associated with insulin resistance and laboratory and histologic markers of advanced liver disease (higher levels of periportal fibrosis, pericellular fibrosis, steatosis, and inflammation). After adjusting for disease severity (the ratio of aspartate aminotransferase to alanine aminotransferase, albumin, platelets, fibrosis, steatosis), the presence of MDBs was associated with histologic progression (odds ratio, 1.97; $P = .04$). Of the 844 patients from whom serial biopsy samples were collected, 61 (7.2%) developed MDBs (MDB gain) and 101 (12.0%) lost MDBs (MDB loss). The presence or absence of diabetes mellitus was associated with MDB gain ($P = .006$) or loss ($P = .024$), respectively. Development of MDBs was associated with decompensation (adjusted hazard ratio, 2.81; $P < .001$) and histologic signs of progression (adjusted odds ratio, 4.02; $P = .004$). **CONCLUSIONS:** The presence of MDBs in liver biopsy samples from patients with CHC is associated independently with fibrosis progression. Gain of MDBs over time is associated with decompensation and progression to

cirrhosis; and occurs most frequently among diabetic patients. MDBs might be used as prognostic factors for patients with CHC.

Screening inventories to detect depression in chronic hepatitis C patients. Fábregas BC, Vitorino FD, Rocha DM, et al. *Gen Hosp Psychiatry*. 2011 Oct 14. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22001550>

OBJECTIVE: To settle the best cutoffs for inventories to diagnose depression in chronic hepatitis C (CHC) patients. **METHOD:** Seventy-five CHC patients were assessed using a standard psychiatric interview (Mini International Neuropsychiatric Interview) to establish Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) major depression diagnosis and the following inventories: the Beck Depression Inventory (BDI), its short form for Primary Care (BDI-PC) and the Hospital Anxiety and Depression Subscale for Depression (HAD-D). According to the receiver operative characteristic (ROC) curve, the best cutoff to screen for depression was settled, and sensitivity, specificity, and positive and negative predictive values were calculated. Agreement between each inventory and the diagnosis of depression was calculated through Cohen's Kappa. Internal consistency was measured through Cronbach's alpha. **RESULTS:** Twenty-one (28%) individuals met criteria for a depressive disorder. BDI, BDI-PC and HAD-D best scores were settled at 18, 5 and 8 points, respectively. They showed the following discriminative properties: sensitivity 81%, 76.2%, 85.7%; specificity 92.6%, 88.9%, 77.8%; positive predictive value 81%, 72.7%, 60%; negative predictive value 92.6%, 90.6%, 93.3%, respectively. ROC curve areas were similar between BDI and BDI-PC, but slightly lower for HAD-D. The agreement between inventories and DSM-IV depression diagnosis was substantial for BDI (0.91) and BDI-PC (0.91) and moderate for HAD-D (0.86). Internal consistency was 0.90, 0.86 and 0.75, respectively. **CONCLUSION:** BDI, BDI-PC and HAD-D showed good discriminative properties to screen for depression in CHC patients and should be considered in clinical practice.

Behavioural interventions for preventing hepatitis C infection in people who inject drugs: A global systematic review. Sacks-Davis R, Horyniak D, Grebely J, Hellard M. *Int J Drug Policy*. 2011 Oct 12. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22000602>

BACKGROUND: A systematic review was conducted to determine whether behavioural interventions are effective in preventing transmission of hepatitis C virus (HCV) amongst people who inject drugs. **METHODS:** Medline, EMBASE, the Cochrane Clinical Trial Database, PSYCHINFO and hand-searching of bibliographies were used to identify controlled trials of behavioural interventions for reducing HCV transmission amongst people who inject drugs. Behavioural interventions were defined as non-pharmacological interventions that aimed to change individual behaviours without explicitly attempting to change population norms. **RESULTS:** Six trials evaluating peer-education training and counselling interventions were included in the review. There was considerable variation between trials with respect to intervention duration, control and study population. Trials evaluated the impact of interventions on HCV incidence (three studies, 1041 participants) and frequency of injecting risk behaviours (six studies, 2472 participants). Amongst the three studies which measured the impact of the intervention on HCV incidence, none found a statistically significant difference between intervention and control groups. Measures of frequency of injecting risk behaviours varied greatly and could not be pooled. Only two studies (n=418, 854) showed significantly greater

reductions in injecting risk behaviours in the intervention group compared with the control group. **CONCLUSIONS:** There was considerable variation in study design, outcome measures and magnitude, direction and statistical significance of findings between studies. Nonetheless, it is unlikely that behavioural interventions can have a considerable effect on HCV transmission. It is likely that multi-component interventions are required.

Absenteeism and productivity among employees being treated for hepatitis C. Brook RA, Kleinman NL, Su J, Corey-Lisle PK, Iloeje UH. Am J Manag Care. 2011 Oct;17(10):657-64. <http://www.ncbi.nlm.nih.gov/pubmed/21999674>

OBJECTIVES: To compare productivity, absence days, and absence costs for treated (HCV-Tx) and untreated (HCV-NoTx) US employees with hepatitis C virus (HCV) infection. Study Design: Retrospective database study. **METHODS:** Employee records from multiple large employers in the United States with data about demographics, jobs, and healthcare use in the Human Capital Management Services database were assessed. HCV subjects were identified by International Classification of Diseases, 9th Revision codes. To test differences between cohorts, t tests and x2 tests were used. Regression modeling was used to compare absence days, costs, and objectively measured productivity, while controlling for confounding factors. For HCV-Tx employees, the index date was the date of the first treatment with interferon, peginterferon, and/or ribavirin. For HCV-NoTx employees, the index date was the average date by company among HCV-Tx employees. Absence and productivity were measured from each employee's index date to the last date the employee was enrolled in health benefits coverage. **RESULTS:** A total of 441 HCV-Tx and 1223 HCV-NoTx employees were evaluated. HCV-Tx workers had 0.52 more total monthly absence days and \$31.31 in additional monthly absence payments per employee than untreated employees. Treated employees' productivity was lower, with treated subjects processing 11.7% fewer units per hour and 17.4% fewer units per month than untreated employees. **CONCLUSIONS:** This study quantified the substantial indirect burden of illness associated with use of current HCV treatments. New treatments are needed with improved adverse effect profiles that result in reduced absence from work and improved productivity among HCV-infected persons.

LIVER CANCER

Molecular targets and oxidative stress biomarkers in hepatocellular carcinoma: an overview. Marra M, Sordelli IM, Lombardi A, et al. J Transl Med. 2011 Oct 10;9(1):171. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21985599>

Hepatocellular carcinoma (HCC) is a complex and heterogeneous tumor with multiple genetic aberrations. Several molecular pathways involved in the regulation of proliferation and cell death are implicated in the hepatocarcinogenesis. The major etiological factors for HCC are both hepatitis B virus (HBV) and hepatitis C virus infection (HCV). Continuous oxidative stress, which results from the generation of reactive oxygen species (ROS) by environmental factors or cellular mitochondrial dysfunction, has recently been associated with hepatocarcinogenesis. On the other hand, a distinctive pathological hallmark of HCC is a dramatic down-regulation of oxido-reductive enzymes that constitute the most important free radical scavenger systems represented by catalase, superoxide dismutase and glutathione peroxidase. The multikinase inhibitor sorafenib represents the most promising target agent that has undergone extensive

investigation up to phase III clinical trials in patients with advanced HCC. The combination with other target-based agents could potentiate the clinical benefits obtained by sorafenib alone. In fact, a phase II multicenter study has demonstrated that the combination between sorafenib and octreotide LAR (So.LAR protocol) was active and well tolerated in advanced HCC patients. The detection of molecular factors predictive of response to anti-cancer agents such as sorafenib and the identification of mechanisms of resistance to anti-cancer agents may probably represent the direction to improve the treatment of HCC.

Clinical presentation of hepatocellular carcinoma (HCC) in Asian-Americans versus non-Asian-Americans. Wong PY, Xia V, Imagawa DK, Hoefs J, Hu KQ. *J Immigr Minor Health*. 2011 Oct;13(5):842-8.

<http://www.ncbi.nlm.nih.gov/pubmed/20890660>

The incidence of HCC is rising worldwide. Studies on ethnicity-based clinical presentation of HCC remain limited. The aim is to compare the clinical presentation and stage of HCC between Asian-Americans and non-Asian-Americans. This retrospective study assessed ethnicity-based differences in HCC presentation, including demographics, laboratory results, diagnosis of underlying liver disease, and stage of HCC. Of 276 patients, 162 were Asian-Americans and 114 were non-Asian-Americans. Compared to non-Asian-Americans, Asian-Americans had a significantly higher incidence of history of hepatitis B virus (HBV) infection (55.0% vs. 4.9%, $P < 0.001$), family history of HBV infection (12.5% vs. 0.0%, $P < 0.001$) and HCC (15.2% vs. 2.9%, $P = 0.002$), but lower incidence of history of hepatitis C virus (HCV) infection (37.5% vs. 61.6%, $P < 0.001$). At diagnosis of HCC, Asian-American patients had a significantly lower frequency of hepatic encephalopathy (8.9% vs. 29.3%, $P = 0.001$), and ascites (26.7% vs. 57.3%, $P < 0.001$). Asian-Americans had lower Child-Pugh scores (class A: 62.0% vs. 31.4%, $P < 0.001$), and MELD scores (9.2 ± 4.4 vs. 12.0 ± 6.4 , $P = 0.02$), and presented with a lower stage of HCC by Okuda staging (I: 43.8% vs. 22.8%, $P = 0.001$). Asian-American patients with HCC presented with a higher incidence of history and family history of HBV infection, lower incidence of hepatic decompensation, lower Child and MELD scores, and an early stage HCC disease.

Effect of Previous Interferon Treatment on Outcome After Curative Treatment for Hepatitis C Virus-Related Hepatocellular Carcinoma. Miyatake H, Kobayashi Y, Iwasaki Y, et al. *Dig Dis Sci*. 2011 Oct 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21989822>

BACKGROUND AND AIMS: Treatment of chronic hepatitis C virus (HCV) infection with interferon (IFN) prevents the development of hepatocellular carcinoma (HCC). The purpose of this study was to clarify the effect of previous IFN treatment before the development of HCC on recurrence and survival in HCV-related HCC patients. **METHODS:** Three hundred ninety-five patients who underwent curative treatment for HCV-related HCC were enrolled. Of these, 124 had received IFN treatment before the development of HCC (17 achieved sustained virological response [SVR group] and 107 did not [non-SVR group]), whereas 271 patients had never received IFN treatment (IFN-untreated group). The first and second recurrence and survival rates in these patient groups were statistically analyzed. **RESULTS:** The first HCC recurrence rate was similar among patient groups. In contrast, the second HCC recurrence rate was significantly lower in the SVR group than in the non-SVR group ($p = 0.003$) and the IFN-untreated group ($p = 0.006$). In multivariate analysis, platelet count ($p = 0.033$) and number of tumors ($p = 0.001$)

were associated with the first HCC recurrence, while SVR ($p = 0.002$) was the only factor associated with the second HCC recurrence. The survival rate was higher in the SVR group than in non-SVR and IFN-untreated groups, and SVR to previous IFN treatment was an independent factor associated with better survival ($p < 0.001$). **CONCLUSIONS:** SVR to previous IFN treatment before the development of HCV-related HCC was associated with lower risk of the second recurrence of HCC and better survival.

Comparative Analysis of Outcome in Patients With Hepatocellular Carcinoma Exceeding the Milan Criteria Treated With Liver Transplantation Versus Partial Hepatectomy.

Canter RJ, Patel SA, Kennedy T, et al. *Am J Clin Oncol*. 2011 Oct;34(5):466-471.

<http://www.ncbi.nlm.nih.gov/pubmed/20938319>

INTRODUCTION: Proponents of orthotopic liver transplantation (TXP) for the treatment of hepatocellular carcinoma (HCC) advocate expanding the Milan criteria. We performed a matched analysis comparing patients treated with TXP to patients treated with partial hepatectomy (PHX) for HCC exceeding the Milan criteria. **METHODS:** From the United Network for Organ Sharing registry, we identified 92 US patients with HCC exceeding the Milan criteria who underwent TXP between 2002 and 2005. During the same period, 94 patients with similar tumor size criteria underwent PHX at a single center. Data were analyzed using χ^2 , parametric, nonparametric, and Kaplan-Meier methods. **RESULTS:** TXP patients were more commonly male (82% vs. 65%, $P=0.01$) and had a higher Model for End Stage Liver Disease score (median 11 vs. 7, $P<0.001$). Pathologic cirrhosis (79% TXP vs. 38% PHX, $P<0.001$), particularly secondary to hepatitis C virus (29% TXP vs. 5% PHX, $P<0.001$), was more common among TXP patients. Mean cumulative tumor size was 10.0 cm (63% exceeding University of California at San Francisco criteria) among PHX patients compared with 6.4 cm (20% exceeding University of California at San Francisco criteria) for TXP patients ($P<0.001$). With a median follow-up of 34 months (range, 1-86), 3-year survival was similar between the cohorts ($66\% \pm 10\%$ for TXP vs. $66\% \pm 10\%$ for PHX, $P=0.97$). Cancer deaths (26/37, 70%) were more prevalent among PHX patients, whereas noncancer deaths (25/37, 68%) were common in TXP patients ($P<0.001$). **CONCLUSIONS:** Among heterogeneous patients with HCC who exceed the Milan criteria, TXP and PHX achieve similar overall survival. Further study is needed to ensure appropriate patient selection for these disparate therapies.

Genetic risk of hepatocellular carcinoma in patients with hepatitis C virus: a case control study.

Tomoda T, Nouse K, Sakai A, et al. *J Gastroenterol Hepatol*. 2011 Oct 17. doi:

10.1111/j.1440-1746.2011.06948.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22004425>

BACKGROUND AND AIM: Chronic hepatitis C virus (HCV) infection is well known risk factor for hepatocellular carcinoma (HCC). The aim of this study is to elucidate the genetic risk of development and recurrence of HCC in patients with HCV. **METHODS:** A total of 468 patients with HCV, including 265 with HCC were enrolled. We genotyped 89 SNPs in 81 genes expected to influence hepatocarcinogenesis using the iPLEX assay. Risk of HCC was clarified by stratifying patients into risk groups based on the multiplied Odds Ratio (MOR) for SNPs associated with HCC, and the cumulative effects on the development and recurrence of HCC were analyzed. **RESULTS:** Six SNPs associated with risk of HCC were identified (OR range: 0.29~1.76). These included novel SNPs for hepatocarcinogenesis with HCV CCND2 rs1049606, RAD23B rs1805329, CEP164 rs573455, and GRP78rs430397 in addition to the known SNPs

MDM2 rs2279744 and ALDH2 rs671. MOR analysis revealed that the highest risk group exerted about a 19 fold higher relative OR compared to the lowest risk group ($p = 1.08 \times 10^{-5}$). Predicted 10 year HCC risk ranged from 1.7% to 96% depending on the risk group and the extent of fibrosis. Recurrence-free survival of RFA-treated HCC in the high risk group ($n = 53$) was lower than that of low risk group ($n = 58$, $p = 0.038$). **CONCLUSION:** SNPs of CCND2, RAD23B, GRP78, CEP164, MDM2, and ALDH2 genes were significantly associated with development and recurrence of HCC in Japanese patients with HCV.

Up-regulation of 42 kDa Tubulin Alpha-6 Chain Fragment in Well-differentiated Hepatocellular Carcinoma Tissues from Patients Infected with Hepatitis C Virus. Kuramitsu Y, Takashima M, Yokoyama Y, et al. *Anticancer Res.* 2011 Oct;31(10):3331-6.

<http://www.ncbi.nlm.nih.gov/pubmed/21965743>

We performed proteomic differential display analysis of hepatitis C virus-associated 21 human hepatocellular carcinoma (HCV-HCC) tissues by using two-dimensional gel electrophoresis (2-DE) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS). One of the numerous spots which was located next to three spots of glutamine synthetase showed stronger intensity in well-differentiated HCC tissues compared to non-cancerous tissues. Samples from 6 out of 21 patients showed up-regulation of this spot compared to non-cancerous tissues. After in-gel digestion, MALDI-TOF/MS identified the spot as tubulin alpha-6 chain. Two-dimensional immunoblot analysis confirmed that this spot was indeed tubulin alpha, and this spot was stronger in cancerous tissues than in noncancerous tissues. These results suggest that tubulin alpha-6 chain is one of the candidates for biomarkers for well-differentiated HCV-associated HCC.

Performance of premarket rapid hepatitis C virus antibody assays in 4 national human immunodeficiency virus behavioral surveillance system sites. Smith BD, Teshale E, Jewett A, et al. *Clin Infect Dis.* 2011 Oct;53(8):780-6.

<http://www.ncbi.nlm.nih.gov/pubmed/21921221>

SUMMARY: Performance characteristics of rapid assays for hepatitis C virus antibody were evaluated in 4 National HIV Behavioral Surveillance System injection drug use sites. The highest assay-specific sensitivities achieved for the Chembio, MedMira and OraSure tests were 94.0%, 78.9%, and 97.4%, respectively; the highest specificities were 97.7%, 83.3%, and 100%, respectively. **BACKGROUND:** The Centers for Disease Control and Prevention (CDC) estimates that 4.1 million Americans have been infected with hepatitis C virus (HCV) and 75%-80% of them are living with chronic HCV infection, many unaware of their infection. Persons who inject drugs (PWID) account for 57.5% of all persons with HCV antibody (anti-HCV) in the United States. Currently no point-of-care tests for HCV infection are approved for use in the United States. **METHODS:** Surveys and testing for human immunodeficiency virus (HIV) and anti-HCV were conducted among persons who reported injection drug use in the past 12 months as part of the National HIV Behavioral Surveillance System in 2009. The sensitivity and specificity of point-of-care tests (finger-stick and 2 oral fluid rapid assays) from 3 manufacturers (Chembio, MedMira, and OraSure) were evaluated in field settings in 4 US cities. **RESULTS:** Sensitivity (78.9%-97.4%) and specificity (80.0%-100.0%) were variable across assays and sites. The highest assay-specific sensitivities achieved for the Chembio, MedMira, and OraSure tests were 94.0%, 78.9% and 97.4%, respectively; the highest specificities were 97.7%, 83.3%, and 100%, respectively. In multivariate analysis, false-negative anti-HCV results were associated

with HIV positivity for the Chembio oral assay (adjusted odds ratio, 8.4-9.1; $P < .01$) in 1 site (New York City). **CONCLUSIONS:** Sensitive rapid anti-HCV assays are appropriate and feasible for high-prevalence, high-risk populations such as PWID, who can be reached through social service settings such as syringe exchange programs and methadone maintenance treatment programs.

Direct medical care costs among pegylated interferon plus ribavirin-treated and untreated chronic hepatitis C patients. Solomon M, Bonafede M, Pan K, et al. Dig Dis Sci. 2011 Oct;56(10):3024-31. Epub 2011 Jun 30.

<http://www.ncbi.nlm.nih.gov/pubmed/21717127>

BACKGROUND: Hepatitis C virus (HCV) is a common and expensive infectious disease. The current standard of care for HCV infection, pegylated interferon with ribavirin (PEG-RBV), is costly and has a significant adverse event profile. **AIM:** To quantify the direct economic burden of HCV infection and PEG-RBV treatment for HCV. **METHODS:** Using a large administrative claims database, we evaluated the medical and prescription drug costs of patients with HCV from 2002 to 2007. A cohort of patients with PEG-RBV was 1:1 propensity score-matched to a cohort of untreated HCV patients. Multivariate models adjusted for demographic and clinical characteristics in evaluating the effect of PEG-RBV treatment on direct medical expenditure. **RESULTS:** The matched analysis included 20,002 patients. PEG-RBV-treated patients had higher total direct medical costs (\$28,547 vs. \$21,752; $P < 0.001$), outpatient pharmacy costs (\$17,419 vs. \$2,900; $P < 0.001$), and outpatient physician visit costs (\$894 vs. \$787; $P < 0.001$), but lower inpatient costs (\$3,942 vs. \$9,543; $P < 0.001$) and emergency room costs (\$366 vs. \$505; $P < 0.001$). After multivariate adjustment, PEG-RBV use was associated with an additional \$9,423 in total direct medical costs and an additional \$12,244 in HCV-related total medical costs. **CONCLUSION:** Total HCV-related medical costs are higher for treated than untreated patients, driven mostly by higher outpatient pharmacy costs, which outweigh higher HCV-related inpatient costs incurred by untreated patients.

HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. Nkontchou G, Ziol M, Aout M, et al. J Viral Hepat. 2011 Oct;18(10):e516-22. doi: 10.1111/j.1365-2893.2011.01441.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21914071>

Liver steatosis is a main histopathological feature of Hepatitis C (HCV) infection because of genotype 3. Steatosis and/or mechanisms underlying steatogenesis can contribute to hepatocarcinogenesis. The aim of this retrospective study was to assess the impact of infection with HCV genotype 3 on hepatocellular carcinoma (HCC) occurrence in patients with ongoing HCV cirrhosis. Three hundred and fifty-three consecutive patients (193 men, mean age 58 ± 13 years), with histologically proven HCV cirrhosis and persistent viral replication prospectively followed and screened for HCC between 1994 and 2007. Log-rank test and Cox model were used to compare the actuarial incidence of HCC between genotype subgroups. The patients infected with a genotype 3 ($n = 25$) as compared with those infected with other genotypes ($n = 328$) had a lower prothrombin activity [78 (interquartile range 60-85) vs 84 (71-195) %, $P = 0.03$] and higher rate of alcohol abuse (48% vs 29%, $P = 0.046$). During a median follow-up of 5.54 years [2.9-8.6], 11/25 patients (44%) and 87/328 patients (26%) with a genotype 3 and non-3 genotype, respectively, develop a HCC. HCC incidences were significantly different among the genotype subgroups ($P = 0.001$). The 5-year occurrence rate of HCC was 34% (95% CI, 1.3-6.3)

and 17% (95% CI, 5.7-9.2) in genotype 3 and non-3 genotype groups, respectively (P = 0.002). In multivariate analysis, infection with a genotype 3 was independently associated with an increased risk of HCC occurrence [hazard ratio 3.54 (95% CI, 1.84-6.81), P = 0.0002], even after adjustment for prothrombin activity and alcohol abuse [3.58 (1.80-7.13); P = 0.003]. For patients with HCV cirrhosis and ongoing infection, infection with genotype 3 is independently associated with an increased risk of HCC development.