Caring Ambassadors Hepatitis C Program Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Estimating the likelihood of sustained virological response in chronic hepatitis C therapy. Mauss S, Hueppe D, John C, et al. J Viral Hepat. 2010 Sep 16. doi: 10.1111/j.1365-2893.2010.01372.x. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20849436
The likelihood of a sustained virological response (SVR) is the most important factor for physicians and patients in the decision to initiate and continue therapy for chronic hepatitis C (CHC) infection. This study identified predictive factors for SVR with peginterferon plus ribavirin (RBV) in patients with CHC treated under 'real-life' conditions. The study cohort consisted of patients from a large, retrospective German multicentre, observational study who had been treated with peginterferon alfa-2a plus RBV or peginterferon alfa-2b plus RBV between the years 2000 and 2007. To ensure comparability regarding peginterferon therapies, patients were analysed in pairs matched by several baseline variables. Univariate and multivariate logistic regression analyses were used to determine the effect of nonmatched baseline variables and treatment modality on SVR. Among 2378 patients (1189 matched pairs), SVR rates were 57.9% overall, 46.5% in HCV genotype 1/4-infected patients and 77.3% in genotype 2/3-infected patients. In multivariate logistic regression analysis, positive predictors of SVR were HCV genotype 2 infection, HCV genotype 3 infection, low baseline viral load and treatment with peginterferon alfa-2a. Negative predictors of SVR were higher age (≥40 years), elevated baseline gamma-glutamyl transpeptidase (GGT) and low baseline platelet count (<150 000/μL). Among patients treated with peginterferon plus RBV in routine clinical practice, genotype, baseline viral load, age, GGT level and platelet levels all predict the likelihood of treatment success. In patients matched by baseline characteristics, treatment with peginterferon alfa-2a may be a positive predictor of SVR when compared to peginterferon alfa-2b.

Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. Manolakopoulos S, Deutsch MJ, Anagnostou O, et al. Liver Int. 2010 Sep 16. doi: 10.1111/j.1478-3231.2010.02341.x. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20846344
INTRODUCTION AND AIMS: International guidelines and routine clinical practice express concerns about antiviral treatment in intravenous drug users (IDUs). We analysed the effect of IDU and/or substitution therapy on chronic hepatitis C (CHC) treatment adherence and response.

PATIENTS AND METHODS: Intravenous drug users with CHC were divided into three groups: (A) patients on a substitution programme; (B) active users; and (C) past IDUs. Patients were treated according to the standard of care and followed by a specialist team. **RESULTS:** A total of 175 patients (mean age 39.4±8.8) were included. One hundred and forty-four (65%) were adherent to therapy (completing treatment and 6 months of follow-up). Twenty-two patients (36%) discontinued because of side effects, 28 (46%) discontinued on their own and 11 (18%) completed treatment but did not present at follow-up. Of 142 patients with available treatment outcome, 99 (69.7%) achieved a sustained virological response (SVR), with no differences among the study groups. Patients with genotypes 2-3 and those who completed the treatment schedule had 2.78-fold (95% CI: 1.3-5.8) and 6.4-fold (95% CI: 2.6-15.6) higher probability of achieving SVR. **CONCLUSION:** Active use of illicit drugs and/or drug substitution do not affect the treatment outcome in patients with CHC as long as they are closely followed and remain adherent to the treatment.

Effectiveness of chronic hepatitis C treatment in drug users in routine clinical practice: results of a prospective cohort study. Melin P, Chousterman M, Fontanges T, et al. Eur J Gastroenterol Hepatol. 2010 Sep;22(9):1050-7.
http://www.ncbi.nlm.nih.gov/pubmed/20351554
OBJECTIVE: Injection drug users are often excluded from hepatitis C virus (HCV) treatment. This study compares sustained virological response, adherence, and quality of life in patients with or without a history of illicit drug use in routine clinical practice.
METHODS: This is a post-hoc analysis of a prospective, observational study conducted in 1860 patients who received peginterferon alpha-2b/ribavirin combination therapy. Nondrug users (NDUs) were defined as patients without a history of drug addiction; former drug users (FDUs) as patients who had stopped using illicit drugs or opioid maintenance therapy and active drug users (ADUs) as patients using illicit drugs or on opioid maintenance therapy. Virological response, adherence, and the health-related quality of life were assessed by the measure of HCV RNA in the serum, self-report and 36-item short-form health survey Questionnaire, respectively.
RESULTS: The analyzed population included 1038 (56%) NDUs, 578 (31%) FDUs, and 244 (13%) ADUs. About 85% of ADUs were on opioid maintenance therapy and 25% used illicit drugs. Although ADUs had a more chaotic lifestyle and more psychiatric disorders, sustained virological response of ADUs (58%) did not differ from that of NDUs (49%) and FDUs (51%) (P=0.133). Adherence rates were 39% in NDUs and FDUs, and 37% in ADUs (P=0.883). Health-related quality of life was improved in the three groups after the end of treatment.
CONCLUSION: Our study suggests that HCV therapy in ADUs on opioid maintenance therapy is as effective as in other HCV patients. The effectiveness of HCV therapy in illicit drug users needs to be evaluated in further studies.

Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. Muir AJ, Shiffman ML, Zaman A, et al. Hepatology. 2010 Sep;52(3):822-32.
http://www.ncbi.nlm.nih.gov/pubmed/20564352
Interferon lambda 1 (IFN-lambda1) is a type III IFN that produces intracellular responses similar to those of IFN-alpha but in fewer cell types because of differences in the receptor distribution pattern, and this could potentially result in an improved safety profile. This was an open-label three-part study of patients with chronic hepatitis C virus (HCV) genotype 1 infection. Part 1

evaluated single-agent pegylated interferon lambda (PEG-IFN-lambda) at 1.5 or 3.0 microg/kg administered every 2 weeks or weekly for 4 weeks in patients who had relapsed after previous IFN-alpha-based treatment. Part 2 evaluated weekly doses of PEG-IFN-lambda ranging from 0.5 to 2.25 microg/kg in combination with ribavirin (RBV) for 4 weeks in treatment-relapse patients. Part 3 evaluated weekly PEG-IFN-lambda at 1.5 microg/kg in combination with RBV for 4 weeks in treatment-naive patients. Fifty-six patients were enrolled: 24 patients in part 1, 25 patients in part 2, and 7 patients in part 3. Antiviral activity was observed at all PEG-IFN-lambda dose levels (from 0.5 to 3.0 microg/kg). Two of seven treatment-naive patients (29%) achieved rapid virological response. Treatment was well tolerated with minimal flu-like symptoms and no significant hematologic changes other than RBV-associated decreases in hemoglobin. The most common adverse events were fatigue (29%), nausea (12%), and myalgia (11%). Six patients experienced increases in aminotransferases that met protocol-defined criteria for dose-limiting toxicity (DLT) or temporarily holding therapy with PEG-IFN-lambda. Most DLT occurred in patients with high PEG-IFN-lambda exposure. **CONCLUSION:** Weekly PEG-IFN-lambda with or without daily RBV for 4 weeks is well tolerated with minimal adverse events and hematologic effects and is associated with clear antiviral activity across a broad range of doses in patients with chronic HCV.

Impact of depressive symptoms and their treatment on completing antiviral treatment in patients with chronic hepatitis C. Liu SS, Schneekloth TD, Talwalkar JA, et al. J Clin Gastroenterol. 2010 Sep;44(8):e178-85.
http://www.ncbi.nlm.nih.gov/pubmed/20495464
BACKGROUND/GOALS: Interferon-induced depression affects 20% to 40% of patients treated for chronic hepatitis C virus (HCV). The aim of our study was to examine the influence of antidepressant treatment and whether this improves the likelihood of completing therapy. **METHODS:** One hundred randomly selected patients with chronic HCV undergoing antiviral therapy at a single center were identified. Patients were categorized as Group 1 (no depressive symptoms during treatment), Group 2 (depressive symptoms without antidepressant therapy), Group 3 (preexisting or prophylactic antidepressants before therapy), and Group 4 (on-demand antidepressant therapy for depressive symptoms). **RESULTS:** Mean age was 49 years with 72% men. Genotype 1 infection was noted in 65% of patients, and the mean pretreatment HCV RNA level was 1,419,919 IU. Patients without earlier depression receiving on-demand therapy (Group 4) had a significantly higher rate of antiviral treatment completion compared with Group 3 (92% vs. 52%; P=0.01). Patients in groups 1 and 4 with no baseline history of depression had similar treatment completion rates. No significant relationship between the use of antidepressant therapy, SVR or premature cessation of therapy was observed. **CONCLUSIONS:** Preexisting depression was associated with lower antiviral treatment completion rates despite the use of prophylactic antidepressant therapy. In patients without preexisting depression, however, on-demand antidepressant therapy for depressive symptoms was strongly associated with the highest treatment completion rates in the cohort. Antidepressant therapy for new or worsening depressive symptoms independent of baseline depression status did not affect the probability of achieving SVR or stopping treatment prematurely.

Danoprevir, an HCV NS3/4A protease inhibitor, improves insulin sensitivity in patients with genotype 1 chronic hepatitis C. Moucari R, Forestier N, Larrey D, et al. Gut. 2010 Sep 21. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20861007
BACKGROUND/AIM: Insulin resistance (IR) is a major predictor of treatment failure in patients with hepatitis C virus (HCV) infection treated with peginterferon/ribavirin. The aim of this study was to evaluate the short-term effect of an HCV protease inhibitor monotherapy on IR in parallel with an antiviral effect. **PATIENTS/METHODS:** In a phase 1b placebo-controlled study, four cohorts of treatment-naïve patients with genotype 1 HCV received danoprevir (ITMN-191/RG7227), a protease inhibitor, or placebo (8/2 patients in each cohort respectively) in a gelatin capsule every 12 h (100, 200 mg) or 8 h (100, 200 mg) for 14 days. A fifth cohort including prior non-responders to peginterferon/ribavirin was similarly randomised to receive placebo or 300 mg danoprevir every 12 h. IR was assessed with the homeostasis model (HOMA-IR) at baseline and days 7, 14 and 15. **RESULTS:** Serum HCV-RNA and HOMA-IR correlated significantly (Spearman rho=0.379, p<0.0001). At baseline, mean±SD serum HCV-RNA level and mean±SD HOMA-IR score were 6.2±0.5 log(10)IU/ml and 3.8±1.9, respectively. At the end of 14 days of monotherapy the mean±SD decrease in viral load was 2.2±1.3 log(10)IU/ml (p<0.0001) in patients who received the active drug (n=40). In parallel, the mean±SD HOMA-IR score also decreased in these patients by 1.6±1.1 (p<0.0001), with a close correlation between the extent of HOMA-IR improvement and the decrease in viral load. By contrast, serum HCV-RNA and HOMA-IR remained unchanged in patients who received placebo (n=10; 6.3±0.5 log(10)IU/ml and 3.8±2.5, respectively). **CONCLUSION:** HCV protease inhibitor may restore insulin sensitivity in patients with genotype 1 HCV. The place of insulin sensitisers remains to be determined in the era of triple therapy.

Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Morgan TR, Ghany MG, Kim HY, et al. Hepatology. 2010 Sep;52(3):833-44.
http://www.ncbi.nlm.nih.gov/pubmed/20564351
Retrospective studies suggest that subjects with chronic hepatitis C and advanced fibrosis who achieve a sustained virological response (SVR) have a lower risk of hepatic decompensation and hepatocellular carcinoma (HCC). In this prospective analysis, we compared the rate of death from any cause or liver transplantation, and of liver-related morbidity and mortality, after antiviral therapy among patients who achieved SVR, virologic nonresponders (NR), and those with initial viral clearance but subsequent breakthrough or relapse (BT/R) in the HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) Trial. Laboratory and/or clinical outcome data were available for 140 of the 180 patients who achieved SVR. Patients with nonresponse (NR; n = 309) or who experienced breakthrough or relapse (BT/R; n = 77) were evaluated every 3 months for 3.5 years and then every 6 months thereafter. Outcomes included death, liver-related death, liver transplantation, decompensated liver disease, and HCC. Median follow-up for the SVR, BT/R, and NR groups of patients was 86, 85, and 79 months, respectively. At 7.5 years, the adjusted cumulative rate of death/liver transplantation and of liver-related morbidity/mortality in the SVR group (2.2% and 2.7%, respectively) was significantly lower than that of the NR group (21.3% and 27.2%, P < 0.001 for both) but not the BT/R group (4.4% and 8.7%). The adjusted hazard ratio (HR) for time to death/liver transplantation (HR = 0.17, 95% confidence interval [CI] = 0.06-0.46) or development of liver-related morbidity/mortality (HR = 0.15, 95% CI = 0.06-0.38) or HCC (HR = 0.19, 95% CI = 0.04-0.80)

was significant for SVR compared to NR. Laboratory tests related to liver disease severity improved following SVR. **CONCLUSION:** Patients with advanced chronic hepatitis C who achieved SVR had a marked reduction in death/liver transplantation, and in liver-related morbidity/mortality, although they remain at risk for HCC.

Pretreatment prediction of response to peginterferon plus ribavirin therapy in genotype 1 chronic hepatitis C using data mining analysis. Kurosaki M, Sakamoto N, Iwasaki M, et al. J Gastroenterol. 2010 Sep 10. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20830599
BACKGROUND: This study aimed to develop a model for the pre-treatment prediction of sustained virological response (SVR) to peg-interferon plus ribavirin therapy in chronic hepatitis C. **METHODS:** Data from 800 genotype 1b chronic hepatitis C patients with high viral load (>100,000 IU/ml) treated by peg-interferon plus ribavirin at 6 hospitals in Japan were randomly assigned to a model building (n = 506) or an internal validation (n = 294). Data from 524 patients treated at 29 hospitals in Japan were used for an external validation. Factors predictive of SVR were explored using data mining analysis. **RESULTS:** Age (<50 years), alpha-fetoprotein (AFP) (<8 ng/mL), platelet count (≥120 × 10(9)/l), gamma-glutamyltransferase (GGT) (<40 IU/l), and male gender were used to build the decision tree model, which divided patients into 7 subgroups with variable rates of SVR ranging from 22 to 77%. The reproducibility of the model was confirmed by the internal and external validation (r (2) = 0.92 and 0.93, respectively). When reconstructed into 3 groups, the rate of SVR was 75% for the high probability group, 44% for the intermediate probability group and 23% for the low probability group. Poor adherence to drugs lowered the rate of SVR in the low probability group, but not in the high probability group. **CONCLUSIONS:** A decision tree model that includes age, gender, AFP, platelet counts, and GGT is useful for predicting the probability of response to therapy with peg-interferon plus ribavirin and has the potential to support clinical decisions regarding the selection of patients for therapy.

Statin therapy improves sustained virologic response among diabetic patients with chronic hepatitis C. Rao GA, Pandya PK. Gastroenterology. 2010 Sep 9. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20833169
BACKGROUND & AIMS: Patients with chronic hepatitis C infection are 2-3-fold more likely to develop type-2 diabetes, which reduces their chances of achieving a sustained virologic response (SVR). To identify differences in predictors of SVR in patients with and without diabetes who received combination antiviral therapy, we conducted a retrospective analysis of national Veterans Affairs (VA) administrative database. **METHODS:** We analyzed data from VA Medical SAS Datasets and Decision Support System for entire cohort and separately for diabetics (n=1704) and non-diabetics (n=6589). Significant predictors of SVR were identified by logistic regression analysis. **RESULTS:** Diabetics had a lower SVR compared to non-diabetics (21% vs. 27%, p < 0.001). Diabetics had higher clustering of previously established negative predictors of SVR. On multivariate analysis of diabetics for SVR, the positive predictors were higher low density lipoprotein (OR=1.45, p=0.0129), use of statin (OR = 1.52, p = 0.0124) and lower baseline viral load (OR = 2.31, p < 0.001), while insulin therapy (0.7, p = 0.0278) was a negative predictor. Diabetics on statins had a higher pre-treatment viral loads (log 6.2vs.6.4, p= 0.006) but better early virologic response. There was a graded inverse relationship between HbA1c and SVR rate (p=0.0482). This relationship was highest among insulin users (p=0.0154)

and lost among metformin users (p=0.5853). **CONCLUSIONS:** Statin use was associated with an improved SVR among both diabetics and non-diabetics receiving combination antiviral therapy. Diabetics who received insulin achieved lower SVR compared to those not receiving insulin. Poor diabetes control was associated with lower SVR rates.

An open-safety study of dual antiviral therapy in real-world patients with chronic hepatitis C. Tinè F, Graviano D, Giannuoli G, et al. Pharmacoepidemiol Drug Saf. 2010 Sep 16. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20848397
PURPOSE: Treatment of patients with chronic hepatitis C with alpha-interferon and ribavirin usually produces adverse events within the first 3 months. We aimed to assess safety and predictors of discontinuation or dose modification of these drugs. **METHODS:** Observational study of 312 patients with predominantly genotype 1 chronic hepatitis C treated openly along 5 years in a clinical practice setting. RESULTS: Eighty-four percent of patients experienced at least one adverse event (853 events in total, 3.3 per patient on average). Incidence rate was higher during the first 90 days and decreased thereafter (<5%). Discontinuation rates at 30 and 90 days and at end of treatment were 2, 4 and 8%, respectively. Seventy percent of discontinuation cases were due to adverse events rather than to laboratory abnormalities. Serious adverse events were rare (<1%). Dose modifications were made in 158 patients (51%) on 237 occasions. After adjusting for covariates, older age was a predictor of early discontinuation, whereas HCV genotypes 1-4 and daily ribavirin dose of 1000 mg or more were predictors of dose modification. **CONCLUSIONS:** The majority of real-world patients with chronic hepatitis C tolerate acceptably dual therapy and very few discontinue it. Subjective decisions on dose reduction of either compound appears to have a major impact on adherence of patients. There is a need to better define, collect and analyse clinical features which may predict adverse events and safety-related decisions during therapy of chronic hepatitis C.

Predictive factors for response to peginterferon-alpha and ribavirin treatment of chronic HCV infection in patients aged 65 years and more. Giannini EG, Basso M, Savarino V, Picciotto A. Dig Dis Sci. 2010 Sep 18. [Epub ahead of print] Dig Dis Sci. 2010 Sep 18. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20848200
BACKGROUND: Elderly patients with chronic hepatitis C virus (HCV) infection represent an understudied population, and little is known regarding the predictive factors for sustained virological response (SVR) to antiviral therapy in these patients. **AIMS:** To evaluate the efficacy of pegylated interferon (PEG-IFN) and ribavirin therapy in chronic HCV patients aged 65 years, and identify pre- and on-treatment predictors of SVR.
METHODS: We studied 57 patients aged ≥65 years who underwent PEG-IFN and ribavirin treatment, evaluating the SVR rate and its association with pre-treatment demographic, clinical, biochemical, and virological parameters. Furthermore, we assessed whether 12-week serum HCV-RNA assessment might predict SVR. **RESULTS:** A SVR was obtained in 25 patients (45%). The only pre-treatment predictor of SVR was HCV genotype 2 and 3 (P = 0.02). A positive serum HCV-RNA or a decline in viral load ≤2log(10) at week 12 had 100% negative predictive value for SVR. No major liver-related events or deaths occurred during therapy. Treatment was discontinued due to side effects-mainly cardiovascular-in 10 patients (17%).

CONCLUSION: Pre- and on-treatment virological parameters can be used to identify elderly patients who are more likely to obtain a SVR to standard-of-care antiviral therapy for chronic HCV infection.

Prophylactic antidepressant treatment in patients with hepatitis C on antiviral therapy: a double-blind, placebo-controlled trial. Morasco BJ, Loftis JM, Indest DW, et al. Psychosomatics. 2010 Sep-Oct;51(5):401-8.
http://www.ncbi.nlm.nih.gov/pubmed/20833939
BACKGROUND: Approximately one-third of patients undergoing interferon-α (IFN-α) therapy for treatment of the hepatitis C virus (HCV) develop major depression, which decreases functioning and may lead to the reduction or discontinuation of treatment. **OBJECTIVE:** The authors examined the efficacy of citalopram in preventing IFN-α-induced depression in HCV patients. **METHOD:** This was a randomized, controlled trial comparing citalopram with placebo in 39 HCV patients. **RESULTS:** The rate of IFN-α-induced depression in the sample was 15.4% (6/39). Randomization to citalopram did not decrease the statistical likelihood of developing IFN-α-induced depression (10.5% for citalopram vs. 20.0% for placebo). **CONCLUSION:** Citalopram does not prevent depression onset; however, an empirically-supported treatment recommendation for IFN-α-induced depression includes monitoring depressive symptoms throughout antiviral therapy and initiating psychiatric treatment at the initial signs of depression.

Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. Harrison SA, Rossaro L, Hu KQ, et al. Hepatology. 2010 Sep;52(3):864-74.
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http://www.ncbi.nlm.nih.gov/pubmed/20568303
Elevated low-density lipoprotein (LDL) levels and statin use have been associated with higher sustained virological response (SVR) rates in patients receiving chronic hepatitis C therapy. However, these relationships have not been well characterized in randomized controlled trials. Furthermore, little is known about the relationship between high-density lipoprotein (HDL) and virological response. To determine whether baseline LDL or HDL levels and statin use affect SVR rates, we retrospectively evaluated the IDEAL (Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy) trial, in which 3070 treatment-naive, hepatitis C virus (HCV) genotype 1-infected patients were treated for up to 48 weeks in one of the following arms: (1) peginterferon (PEG-IFN) alfa-2b at 1.5 microg/kg/week with ribavirin (RBV) at 800 to 1400 mg/day, (2) PEG-IFN alfa-2b at 1.0 microg/kg/week with RBV at 800 to 1400 mg/day, or (3) PEG-IFN alfa-2a at 180 microg/week with RBV at 1000 to 1200 mg/day. Virological responses were assessed by pretreatment statin use and baseline elevated LDL levels (> or =130 mg/dL) or low HDL levels (<40 mg/dL for men and <50 mg/dL for women). In 1464 patients with baseline elevated LDL levels or low HDL levels, the SVR rate was significantly higher than that in patients with normal levels (44.9% versus 34.0%, P < 0.001). In 66 patients receiving a statin pretreatment, the SVR rate was higher than the rate of those not receiving it (53.0% versus 39.3%, P = 0.02). In a multivariate logistic regression analysis using the stepwise selection method with baseline characteristics, a high LDL level [odds ratio (OR) = 1.6, 95% confidence interval (CI) = 1.4-1.8, P < 0.001], a low HDL level (OR = 0.5, 95% CI = 0.3-0.8, P = 0.004), and statin use (OR = 2.0, 95% CI = 1.1-3.7, P = 0.02) were independently associated with SVR. **CONCLUSION:** Baseline elevated LDL levels or low HDL levels and preemptive

statin usage were associated with higher SVR rates. Prospective studies may be considered to explore the biological impact of these factors on HCV RNA replication and treatment response.

Associations between serum lipids and hepatitis C antiviral treatment efficacy. Ramcharran D, Wahed AS, Conjeevaram HS, et al. Hepatology. 2010 Sep;52(3):854-63.
http://www.ncbi.nlm.nih.gov/pubmed/20690192
Approximately one half of patients who undergo antiviral therapy for chronic hepatitis C virus (HCV) genotype 1 infection do not respond to treatment. African Americans (AAs) are less responsive to treatment than Caucasian Americans (CAs), but the reasons for this disparity are largely unknown. Recent studies suggest that serum lipids may be associated with treatment response. **The aims of this study** were to evaluate baseline and changes in serum lipids during therapy, determine whether serum lipids are associated with virological response, and assess whether these measures explain the racial difference in efficacy. The study participants were from Virahep-C, a prospective study of treatment-naïve patients with genotype 1 HCV infection who received peginterferon (PEG-IN) alfa-2a plus ribavirin therapy for up to 48 weeks. Fasting serum lipids were analyzed at baseline and during and after therapy in 160 AAs and 170 CAs. A relative risk (RR) model was employed to evaluate characteristics associated with sustained virological response (SVR). Antiviral therapy was associated with changes in serum lipids during and after antiviral therapy, with the changes differing by race and the amount of PEG-IFN taken. Baseline lipid measures independently associated with higher rates of SVR were lower triglyceride and higher low-density lipoprotein cholesterol, with an interaction between high-density lipoprotein cholesterol (HDLc) and gender. Lipid measures did not contribute significantly to an explanation of the racial difference in SVR. **CONCLUSION:** Serum lipids are associated with SVR, although these paramaters did not explain the racial difference in treatment response. The results of this study are compatible with proposed biological mechanisms of HCV entry, replication, and secretion, and may underscore new potential therapeutic targets for HCV eradication.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Hepatitis C virus induces the cannabinoid receptor 1. van der Poorten D, Shahidi M, Tay E, et al. PLoS One. 2010 Sep 17;5(9). pii: e12841.
http://www.ncbi.nlm.nih.gov/pubmed/20862263
BACKGROUND: Activation of hepatic CB(1) receptors (CB(1)) is associated with steatosis and fibrosis in experimental forms of liver disease. However, CB(1) expression has not been assessed in patients with chronic hepatitis C (CHC), a disease associated with insulin resistance, steatosis and metabolic disturbance. We aimed to determine the importance and explore the associations of CB(1) expression in CHC. **METHODS:** CB(1) receptor mRNA was measured by real time quantitative PCR on extracted liver tissue from 88 patients with CHC (genotypes 1 and 3), 12 controls and 10 patients with chronic hepatitis B (CHB). The Huh7/JFH1 Hepatitis C virus (HCV) cell culture model was used to validate results. **PRINCIPAL FINDINGS:** CB(1) was expressed in all patients with CHC and levels were 6-fold higher than in controls ($P<0.001$). CB(1) expression increased with fibrosis stage, with cirrhotics having up to a 2 fold up-regulation compared to those with low fibrosis stage ($p<0.05$). Even in mild CHC with no steatosis (F0-1), CB(1) levels remained substantially greater than in controls ($p<0.001$) and in those with mild CHB (F0-1; $p<0.001$). Huh7 cells infected with JFH-1 HCV showed an 8-fold

upregulation of CB(1), and CB(1) expression directly correlated with the percentage of cells infected over time, suggesting that CB(1) is an HCV inducible gene. While HCV structural proteins appear essential for CB(1) induction, there was no core genotype specific difference in CB(1) expression. CB(1) significantly increased with steatosis grade, primarily driven by patients with genotype 3 CHC. In genotype 3 patients, CB(1) correlated with SREBP-1c and its downstream target FASN (SREBP-1c; R=0.37, FASN; R=0.39, $p<0.05$ for both). **CONCLUSIONS/SIGNIFICANCE:** CB(1) is up-regulated in CHC and is associated with increased steatosis in genotype 3. It is induced by the hepatitis C virus.

Peripheral blood B cell subset skewing is associated with altered cell cycling and intrinsic resistance to apoptosis and reflects a state of immune activation in chronic hepatitis C virus infection. Sugalski JM, Rodriguez B, Moir S, Anthony DD. J Immunol. 2010 Sep 1;185(5): 3019-27. Epub 2010 Jul 23.
http://www.ncbi.nlm.nih.gov/pubmed/20656924
Chronic hepatitis C virus (HCV) infection is associated with B cell activation, although underlying mechanisms are unclear. To investigate B cell regulation during HCV infection, we measured bulk B cell CpG and Staphylococcus aureus Cowan-induced IgG Ab-secreting cell (ASC) frequency, HCV and tetanus-specific ASC frequency, BCR- and CD40L-dependent CD80/CD86 expression, and activation of memory CD4 cells. Immature transitional, naive, resting memory, mature activated, tissue-like memory, and plasma B cell subset frequencies, cell cycling, and intrinsic apoptosis were quantified. We observed intact or enhanced tetanus-specific and total IgG ASC frequency, serum IgG, BCR- and CD40L-dependent CD80/CD86 expression, and CD40L-dependent bulk B cell activation of memory CD4 cells in HCV infection. HCV-specific ASCs were observed in HCV-infected but not control subjects, although frequencies were lower compared with tetanus-specific cells. Immature transitional and mature activated B cell subset frequencies were increased in HCV-infected subjects, with immature transitional frequency associated with liver inflammation and serum B cell-activating factor. Mature activated B cells less commonly expressed Ki67, more commonly expressed Bcl2, and were more intrinsically resistant to apoptosis, whereas immature transitional B cells more commonly expressed Ki67, the latter associated with plasma HCV level. **Taken together, these results indicate** that in the setting of chronic HCV infection, a state of activation results in B cell subset skewing that is likely the result of alterations in homeostasis, cell cycling, and intrinsic resistance to apoptosis and that results in an overall intact or enhanced B cell response to BCR and CD40L.

Quantitative analysis of interferon alpha receptor subunit 1 and suppressor of cytokine signaling 1 gene transcription in blood cells of patients with chronic hepatitis C. Sedeno-Monge V, Santos-Lopez G, Rocha-Gracia RC, et al. Virol J. 2010 Sep 18;7(1):243. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20849643
BACKGROUND: Interferon (IFN)-alfa receptor 1 (ifnar1) and suppressor of cytokine signaling 1 (socs1) transcription levels were quantified in peripheral blood mononuclear cells (PBMC) of 59 patients infected with hepatitis C virus (HCV) and 17 non-infected individuals. Samples were obtained from patients infected with HCV that were either untreated or treated with IFN-alfa2 plus ribavirin for 1 year and divided into responders and non-responders based on viral load reduction 6 months after treatment. Ifnar1 and socs1 transcription was quantified by real-time RT-PCR, and the fold difference (2 exponent[-delta delta CT])with respect to hprt housekeeping

gene was calculated. **RESULTS:** Ifnar1 transcription increased significantly in HCV-infected patients either untreated (3.26 +/- 0.31), responders (3.1 +/- 0.23) and non-responders (2.18 +/- 0.23) with respect to non-infected individuals (1 +/- 0.34; P = 0.005). Ifnar1 transcription increased significantly (P = 0.003) in patients infected with HCV genotypes 1a (4.74 +/- 0.25) and 1b (2.81 +/- 0.25) but not in 1a1b (1.58 +/- 0.21). No association was found of Ifnar1 transcription with disease progress, initial viral load or other clinical factors. With respect to socs1 transcription, values were similar for non-infected individuals (1 +/- 0.28) and untreated patients (0.99 +/- 0.41) but increased in responders (2.81 +/- 0.17) and non-responder patients (1.67 +/- 0.41). Difference between responder and non-responder patients was not statistically significant. Socs1 transcription increased in patients infected with HCV genotypes 1a and 1b (2.87 +/- 0.45 and 2.22 +/- 0.17, respectively) but not in 1a1b (1.28 +/- 0.40). Socs1 transcript was absent in three patients infected with HCV genotype 1b. A weak correlation between IFNAR1 and SOCS1 transcription was found, when Spearman's correlation coefficient was calculated. **CONCLUSION:** Our results suggest that HCV infection may up-regulate ifnar1 transcription. HCV genotypes differ in their capacity to affect ifnar1 and socs1 transcription, as well as in the ability to evade the antiviral response.

A novel small molecule inhibitor of hepatitis C virus entry. Baldick CJ, Wichroski MJ, Pendri A, et al. LoS Pathog. 2010 Sep 2;6(9). pii: e1001086.
http://www.ncbi.nlm.nih.gov/pubmed/20838466
Small molecule inhibitors of hepatitis C virus (HCV) are being developed to complement or replace treatments with pegylated interferons and ribavirin, which have poor response rates and significant side effects. Resistance to these inhibitors emerges rapidly in the clinic, suggesting that successful therapy will involve combination therapy with multiple inhibitors of different targets. The entry process of HCV into hepatocytes represents another series of potential targets for therapeutic intervention, involving viral structural proteins that have not been extensively explored due to experimental limitations. To discover HCV entry inhibitors, we utilized HCV pseudoparticles (HCVpp) incorporating E1-E2 envelope proteins from a genotype 1b clinical isolate. Screening of a small molecule library identified a potent HCV-specific triazine inhibitor, EI-1. A series of HCVpp with E1-E2 sequences from various HCV isolates was used to show activity against all genotype 1a and 1b HCVpp tested, with median EC50 values of 0.134 and 0.027 μM, respectively. Time-of-addition experiments demonstrated a block in HCVpp entry, downstream of initial attachment to the cell surface, and prior to or concomitant with bafilomycin inhibition of endosomal acidification. EI-1 was equally active against cell-culture adapted HCV (HCVcc), blocking both cell-free entry and cell-to-cell transmission of virus. HCVcc with high-level resistance to EI-1 was selected by sequential passage in the presence of inhibitor, and resistance was shown to be conferred by changes to residue 719 in the carboxy-terminal transmembrane anchor region of E2, implicating this envelope protein in EI-1 susceptibility. Combinations of EI-1 with interferon, or inhibitors of NS3 or NS5A, resulted in additive to synergistic activity. **These results suggest** that inhibitors of HCV entry could be added to replication inhibitors and interferons already in development.

Association of serum adipocytokines with hepatic steatosis and fibrosis in patients with chronic hepatitis C. Baranova A, Jarrar MH, Stepanova M, et al. Digestion. 2010 Sep 15;83(1-2):32-40. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20847561
BACKGROUND: The pathogenic mechanisms of hepatic steatosis in hepatitis C (HCV) remain unclear. Aim: To assess the potential role of cytokines and adipokines in HCV-related steatosis and fibrosis. **METHODS:** We profiled several adipokines, cytokines, and related soluble molecules in 99 HCV patients and analyzed their potential associations with hepatic steatosis and fibrosis. **RESULTS:** Serum leptin and IL-1RA were significantly higher in HCV genotype 1 as compared to genotype 3. On the other hand, serum resistin, IL-8, IL-1B and sIL-6R, were significantly higher in HCV genotype 3. No differences were observed for adiponectin, visfatin, IL-6 and TNF-α. Regardless of HCV genotype, steatosis could be predicted by a combination of IL-8, IL-6, and sIL-6R/IL-6. When analysis was repeated for each of the genotypes, the reliability of models improved. Regardless of HCV genotype, moderate to severe fibrosis (Metavir score >F2), was predicted by IL-8 and resistin levels. **CONCLUSIONS:** Analysis of adipocytokines associated with steatosis supports the hypothesis that steatogenic pathways differ in HCV genotype 3 from those infected with non-genotype 3 infections.

HIV/HCV/HBV COINFECTION

Assessing the impact of hepatitis C virus coinfection on lopinavir/ritonavir through concentrations in HIV-infected patients. Calza L, Mosca L, Pocaterra D, et al. Eur J Clin Pharmacol. 2010 Sep 28. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20878151
PURPOSE: Chronic hepatitis C is an emerging issue in the management of human immunodeficiency virus (HIV) disease because both diseases have the same route of transmission, leading to a very high prevalence of hepatitis C virus (HCV)-coinfection in the HIV-positive patient population. Lopinavir is extensively metabolized by the hepatic cytochrome P450 3A4, and the pharmacokinetics of this protease inhibitor (PI) could be influenced by liver impairment. However, data currently available on the impact of HCV-coinfection on lopinavir plasma concentrations are both limited and conflicting. **METHODS:** This was an observational, open-label study in which adult HIV-infected outpatients on stable antiretroviral treatment that included two nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir for at least 4 weeks were asked to participate. The trough plasma concentration (C (trough)) of lopinavir and ritonavir was assessed at steady state by a validated high-performance liquid chromatography-tandem mass spectrometry method. **RESULTS:** A total of 65 HIV-positive patients were enrolled in the study. These patients were stratified into two groups based on the absence/presence of HCV-coinfection: 45 were monoinfected (HIV+/HCV-) and 20 were coinfected (HIV+/HCV+). The lopinavir C (trough) in plasma was comparable between HIV+/HCV+ and HIV+/HCV- patients, without any statistically significant difference (geometric mean ratio 0.89, 95% confidence interval 0.61-1.42; p = 0.581). The mean ritonavir C (trough) was also comparable in the two groups. Almost all samples were found to be within the therapeutic plasma level range (97% in HIV+/HCV- group and 100% in HIV+/HCV+ group). No correlation was found between lopinavir plasma levels and adverse events (such as diarrhoea and hypertriglyceridaemia) or immune-virological parameters of HIV disease.
CONCLUSIONS: Among the HIV-positive patients participating in this study, the

pharmacokinetics of lopinavir/ritonavir did not significantly change in those HIV-positive patients coinfected with HCV and in the absence of liver cirrhosis.

Proteome-wide anti-hepatitis C virus (HCV) and anti-HIV antibody profiling for predicting and monitoring the response to HCV therapy in HIV-coinfected patients. Burbelo PD, Kovacs JA, Ching KH, et al. J Infect Dis. 2010 Sep 15;202(6):894-8.
http://www.ncbi.nlm.nih.gov/pubmed/20684729
We quantified antibody responses to the hepatitis C virus (HCV) proteome that are associated with sustained virologic response (SVR) in human immunodeficiency virus (HIV)/HCV-coinfected patients treated with pegylated interferon and ribavirin. Analysis of pre- and posttreatment samples revealed significant decreases in the combined anti-core, anti-E1, and anti-NS4 HCV antibody titers in those with SVRs but not in those who experienced relapse or who did not respond. Furthermore, anti-HIV p24 antibody titers inversely correlated with treatment response. These results suggest that profiling anti-HCV antibody is useful for monitoring HCV therapy, especially in discriminating between those who experience relapse and those who have SVRs at 48 weeks.

Serological and molecular expression of hepatitis b infection in patients with chronic hepatitis C from Tunisia, North Africa. Ben Halima S, Bahri O, Maamouri N, et al. Virol J. 2010 Sep 15;7(1):229. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20843308
BACKGROUND: This study reports the prevalence and viral aspects of HBV infection in HCV-positive patients from Tunisia, a country with intermediate and low endemicity for hepatitis B and C, respectively. **RESULTS:** HBV infection was assessed in serum samples of 361 HCV positive patients and compared to group of HCV negative individuals. Serological markers and HBV DNA were determined by ELISA and real-time PCR (Roche) respectively. HBV serological markers were found in 43% and 44% of patients and controls respectively. However, the serological and molecular expression of HBV infection differed in the two groups: The group of patients included more individuals with ongoing HBV infection, as defined by the presence of detectable HBsAg and or HBV DNA (17% vs 12%, respectively). Furthermore, while most of controls with ongoing infection expressed HBsAg, the majority of HCV positive patients were HBsAg (-) and HBV DNA(+). Genotyping of HCV isolates showed large predominance of subtype 1b as already reported in Tunisia. Comparison of the replicative status of the two viruses found low viral load for HBV in all co-infected patients in comparison with single HBV infected patients. However, high HCV viremia levels were observed in most of cases with no difference between the group of co-infected patients and the group with single HCV infection. **CONCLUSIONS:** This study adds to the knowledge on the prevalence and the virological presentation of HCV/HBV dual infection, providing data from the North African region. It shows that, given the local epidemiology of the two viruses, co-infected patients are likely to have low replication levels of HBV suggesting a suppressive effect of HCV on HBV, high replication levels of HCV in most cases indicating that the presence of circulating HBV-DNA does not necessarily influence HCV replication.

Impact of interferon-ribavirin treatment on hepatitis C virus (HCV) protease quasispecies diversity in HIV- and HCV-coinfected patients. Chary A, Winters MA, Kottilil S, et al. J Infect Dis. 2010 Sep 15;202(6):889-93.
http://www.ncbi.nlm.nih.gov/pubmed/20677940
Patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection for whom prior treatment of HCV with interferon-ribavirin has failed may require subsequent treatment with new HCV protease inhibitors (PIs). We evaluated the diversity of HCV nonstructural protein 3 (NS3) in 26 HCV- and HIV-coinfected patients receiving stable antiretroviral therapy (ART) who were treated with interferon-ribavirin. Plasma HCV RNA clonal analysis was performed. There was greater baseline NS3 diversity in patients with nonresponse or relapse than in those with sustained virologic response. Interferon-ribavirin treatment did not result in significant changes in HCV protease gene diversity or significant HCV PI resistance mutations. The effect of prior interferon-ribavirin treatment on HCV NS3 will likely not impact HCV PI efficacy in HIV-coinfected patients receiving ART.

Long-term immunovirogical effect and tolerability of a maraviroc-containing regimen in routine clinical practice. Genebat M, Ruiz-Mateos E, Pulido I, et al. Curr HIV Res. 2010 Sep 1;8(6):482-6.
http://www.ncbi.nlm.nih.gov/pubmed/20642436
OBJECTIVES: to analyze the long-term immunovirological effect and tolerability of a maraviroc-containing antiretroviral therapy in viraemic and pretreated HIV-infected patients with a high prevalence of hepatitis C virus (HCV) coinfection. **METHODS:** forty-six R5 HIV-infected patients (48% HCV-coinfected) started a maraviroc-containing antiretroviral regimen, including patients with multidrug resistant virus and patients after first virologic failure. A retrospective study was performed, analysing percentage of patients with undetectable viral load, mean CD4+ gain, liver enzymes, clinical events and treatment modification up to week 48. **RESULTS:** Raltegravir plus a boosted protease inhibitor was combined with maraviroc in 65.2% of the patients (mainly patients with multidrug resistant virus), while the coformulation lamivudine/abacavir was combined with maraviroc in 26.1% (all of them patients after first virologic failure). After 48 weeks on maraviroc-containing regimen, 96.3% of the patients had achieved undetectability and a mean CD4+ count increase of 151 cells/mm3 was observed. Liver enzymes did not increase along the follow up. One patient died after 24 weeks follow up due to heroin overdose. One patient developed a non-Hodgkin lymphoma after 36 weeks follow up, despite undetectable viral load and significant CD4+ increase was achieved (the only AIDS-defining event observed). Treatment modification was performed in 19.6% of the patients: 77.7% of them experienced a treatment simplification and only 1/46 suspended maraviroc. **CONCLUSIONS:** maraviroc-containing regimen is long-term effective and well tolerated in HIV-infected patients in routine clinical practice and in different clinical scenarios.

Hepatitis C virus core protein induces neuroimmune activation and potentiates human immunodeficiency virus-1 neurotoxicity. Vivithanaporn P, Maingat F, Lin LT, et al. PLoS One. 2010 Sep 21;5(9). pii: e12856.
http://www.ncbi.nlm.nih.gov/pubmed/20877724
BACKGROUND: Hepatitis C virus (HCV) genomes and proteins are present in human brain tissues although the impact of HIV/HCV co-infection on neuropathogenesis remains unclear. Herein, we investigate HCV infectivity and effects on neuronal survival and neuroinflammation

in conjunction with HIV infection. **METHODOLOGY:** Human microglia, astrocyte and neuron cultures were infected with cell culture-derived HCV or exposed to HCV core protein with or without HIV-1 infection or HIV-1 Viral Protein R (Vpr) exposure. Host immune gene expression and cell viability were measured. Patch-clamp studies of human neurons were performed in the presence or absence of HCV core protein. Neurobehavioral performance and neuropathology were examined in HIV-1 Vpr-transgenic mice in which stereotaxic intrastriatal implants of HCV core protein were performed. **PRINCIPAL FINDINGS:** HCV-encoded RNA as well as HCV core and non-structural 3 (NS3) proteins were detectable in human microglia and astrocytes infected with HCV. HCV core protein exposure induced expression of pro-inflammatory cytokines including interleukin-1β, interleukin-6 and tumor necrosis factor-α in microglia ($p<0.05$) but not in astrocytes while increased chemokine (e.g. CXCL10 and interleukin-8) expression was observed in both microglia and astrocytes ($p<0.05$). HCV core protein modulated neuronal membrane currents and reduced both β-III-tubulin and lipidated LC3-II expression ($p<0.05$). Neurons exposed to supernatants from HCV core-activated microglia exhibited reduced β-III-tubulin expression ($p<0.05$). HCV core protein neurotoxicity and interleukin-6 induction were potentiated by HIV-1 Vpr protein ($p<0.05$). HIV-1 Vpr transgenic mice implanted with HCV core protein showed gliosis, reduced neuronal counts together with diminished LC3 immunoreactivity. HCV core-implanted animals displayed neurobehavioral deficits at days 7 and 14 post-implantation ($p<0.05$). **CONCLUSIONS:** HCV core protein exposure caused neuronal injury through suppression of neuronal autophagy in addition to neuroimmune activation. The additive neurotoxic effects of HCV- and HIV-encoded proteins highlight extrahepatic mechanisms by which HCV infection worsens the disease course of HIV infection.

Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. Barth RE, Huijgen Q, Taljaard J, Hoepelman AI. Int J Infect Dis. 2010 Sep 24. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20870439
OBJECTIVES: Hepatitis B virus (HBV), hepatitis C virus (HCV), and the human immunodeficiency virus (HIV) are endemic in Africa. However, hepatitis co-infection rates among HIV-infected individuals remain controversial. The aim of this review was to determine the prevalence of HBV and HCV in HIV-infected patients in sub-Saharan Africa and to analyze whether HIV is associated with a higher HBV/HCV prevalence in that region.
DESIGN AND METHODS: We performed a systematic review and meta-analysis. Studies reporting HBV and HCV prevalence data amongst HIV-infected patients in sub-Saharan Africa were included. Weighted means and medians across studies were calculated. Studies including an HIV-negative control group were used for meta-analysis. Risk ratios (RRs) were calculated using a random effects model. **RESULTS:** Sixty studies were included. Among HIV-infected individuals, mean HBsAg and anti-HCV prevalence rates were 15% and 7%, respectively. RRs for a positive HBsAg and a positive anti-HCV were 1.40 (95% confidence interval (CI) 1.16-1.69) and 1.60 (95% CI 1.05-2.45) for HIV-infected, as compared to HIV-uninfected, patients.
CONCLUSIONS: Many HIV-positive individuals in sub-Saharan Africa are HBV or HCV co-infected. HIV is associated with a higher prevalence of both HBV and HCV in this region. However, this association is less evident than that observed in Western countries and varies between studies.

Prevalence and characteristics of hepatitis B and C virus infections in treatment-naïve HIV-infected patients. Reuter S, Oette M, Wilhelm FC, et al. Med Microbiol Immunol. 2010 Sep 19. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20853118
In HIV-infected treatment-naïve patients, we analyzed risk factors for either chronic hepatitis B (HBV) infection, occult HBV infection (OHBV) or a positive hepatitis C (HCV) serostatus. A total of 918 patients of the RESINA-cohort in Germany were included in this study. Before initiating antiretroviral therapy, clinical parameters were collected and blood samples were analyzed for antibodies against HIV, HBV and HCV, HBs antigen and viral nucleic acids for HIV and HBV. Present or past HBV infection (i.e. HBsAg and/or anti-HBc) was found in 43.4% of patients. HBsAg was detected in 4.5% (41/918) and HBV DNA in 6.1% (34/554), resulting in OHBV infection in 2.9% (16/554) of patients. OHBV infection could not be ruled out by the presence of anti-HBs (50.1%) or the absence of all HBV seromarkers (25%). A HCV-positive serostatus was associated with the IVDU transmission route, non-African ethnicity, elevated liver parameters (ASL or GGT) and low HIV viral load. Replicative HBV infection and HCV-positive serostatus both correlated with HIV resistance mutations (P = 0.001 and P = 0.028). HBV and HCV infection are frequent co-infections in HIV treatment-naive patients. These co-infections influence viral evolution, clinical parameters and serological markers. **Consequently,** HIV patients should routinely be tested for HBV and HCV infection before initiating HIV treatment. OHBV infection constituted almost half of all HBV infections with detectable HBV DNA. Due to a lack of risk factors indicating OHBV infection, HBV diagnosis should not only include serological markers but also the detection of HBV DNA.

Elevated TGF-β1 levels might protect HCV/HIV-coinfected patients from liver fibrosis. Rallón NI, Barreiro P, Soriano V, et al. Eur J Clin Invest. 2010 Sep 27. doi: 10.1111/j.1365-2362.2010.02381.x. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20868448
BACKGROUND: HIV accelerates hepatitis C virus (HCV)-induced liver fibrosis by mechanisms not well understood. As HIV dysregulates transforming growth factor-β1 (TGF-β1) and T regulatory (Treg) cells, both of which are involved in hepatic fibrogenesis, herein we describe their influence on liver fibrosis staging in patients with chronic hepatitis C with and without HIV coinfection. **METHODS:** Eighty-eight subjects (42 HIV/HCV co-infected patients, 20 HCV-monoinfected patients, and 26 healthy controls) were examined. Treg cells (CD4+Foxp3+) were measured in peripheral blood using flow cytometry. An enzyme immunoassay was used to measure TGF-β1 in plasma. Liver fibrosis staging was estimated using elastometry and advanced liver fibrosis was considered for ≥9•5 kPa (F3-F4 Metavir estimates). **RESULTS:** Treg cells were increased in HIV/HCV-coinfected patients compared with HCV-monoinfected patients (P=0•004), whereas TGF-β1 levels were similar in both groups of patients. While Treg cells levels were similar in both null-mild and advanced liver fibrosis patients, a high level of TGF-β1 was found in patients with low levels of liver fibrosis compared with those with advanced liver fibrosis [14•9ng mL(-1) (5•6-37•9) vs. 5•5ng mL(-1) (1•9-7•9) respectively P=0•007]. In a multivariate logistic regression model, elevated TGF-β1 levels were significantly associated with not having advanced liver fibrosis [OR: 0•13 (95% CI: 0•02-0•71), P = 0•019]. **CONCLUSIONS:** While Treg cells do not influence liver fibrosis staging, elevated TGF-β1, probably through its anti-inflammatory effects, might protect HCV/HIV-coinfected patients from liver fibrosis.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

S-adenosyl methionine improves early viral responses and interferon-stimulated gene induction in hepatitis C nonresponders. Feld JJ, Modi AA, El-Diwany R, et al. Gastroenterology. 2010 Sep 17. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20854821
BACKGROUND & AIMS: Fewer than half of patients infected with Hepatitis C virus (HCV) achieve sustained viral clearance after peginterferon and ribavirin therapy. S-adenosyl methionine (SAMe) increases interferon signaling in cell culture. We assessed the effect of SAMe on the kinetics of the early anti-viral response and interferon signaling in patients that did not respond to previous therapy (nonresponders) and investigated its mechanisms. **METHODS:** Nonresponders with HCV genotype-1 were given 2 weeks of peginterferon alfa-2a and ribavirin (Course A, baseline/control). After a 1-month period, patients received SAMe (1600 mg daily) for 2 weeks and then peginterferon and ribavirin for 48 weeks (Course B; completed by 21 of 24 patients). Viral kinetics and interferon-stimulated gene (ISG) expression in peripheral blood mononuclear cells (PBMCs) were compared between courses. **RESULTS:** The decrease in HCV RNA from 0 to 48 hours (phase 1) was similar before and after administration of SAMe. However, the slope increased for the second-phase decrease in HCV between courses A and B (Course A=0.11±0.04 log(10)IU/mL/week, Course B=0.27±0.06; P=0.009); 11 patients (53%) achieved an early virological response and 10 (48%) had undetectable HCV RNA by week 24. Induction of ISGs in PBMCs was significantly greater after Course B. In cultured cells, SAMe increased induction of ISGs, compared with only peginterferon and ribavirin, and the antiviral effects of interferon by increasing STAT1 methylation, which might promote binding of STAT1 to DNA. **CONCLUSIONS:** The addition of SAMe to peginterferon and ribavirin improves the kinetics of the early anti-viral response and induces ISGs in patients with HCV genotype 1 that do not respond to interferon therapy. SAMe might be used with peginterferon-based therapies in patients with chronic HCV infections.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Validation of Biochemical Markers for the Prediction of Liver Fibrosis and Necro-inflammatory Activity in Hemodialysis Patients with Chronic Hepatitis C.
Canbakan M, Senturk H, Canbakan B, et al. Nephron Clin Pract. 2010 Sep 18;117(3):c289-c295. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20847572
BACKGROUND: Liver biopsy is an imperfect gold standard for assessing the disease severity in hemodialysis patients with chronic hepatitis C. Our purpose was to compare the accuracy of the FibroTest (FT) and ActiTest (AT) with liver biopsy and the AST-to-platelet ratio index (APRI) in determining hepatic fibrosis and necroinflammatory activity in hemodialysis patients with hepatitis C virus (HCV). **METHODS:** The FT-AT index combining 6 biochemical markers was assessed in 33 hemodialysis patients with HCV. Liver fibrosis and necroinflammatory activity was staged and graded according to the METAVIR scoring system. **RESULTS:** The accuracy of FT-AT versus biopsy was 0.46 for significant fibrosis and 0.36 for severe necroinflammatory activity. The FT index had a positive predictive value of 20% for scores greater than 0.6 and a negative predictive value of 45% for scores less than 0.2. Eleven of the 33 patients had scores ≤0.2, 6 had significant fibrosis on biopsy. Four out of 5 patients with FT

scores >0.6 had mild fibrosis. APRI correlated well with the biopsy. **CONCLUSION:** The FT-AT test does not seem to be a reliable noninvasive marker for the prediction of necroinflammatory activity and fibrosis in hemodialysis patients with HCV and cannot be used as an alternative to either liver biopsy or APRI.

Comparison of transient elastography, serum markers and clinical signs for the diagnosis of compensated cirrhosis. Malik R, Lai M, Sadiq A, et al. J Gastroenterol Hepatol. 2010 Sep;25(9):1562-8.
http://www.ncbi.nlm.nih.gov/pubmed/20796156
BACKGROUND AND AIMS: Non-invasive diagnosis of compensated cirrhosis is important. We therefore compared liver stiffness by transient elastography, APRI score, AST/ALT ratio, hyaluronic acid and clinical signs to determine which modality performed best at identifying compensated cirrhosis. **METHODS:** Patients undergoing evaluation at a single center were recruited and had clinical, serological, endoscopy, radiological imaging, liver stiffness measurement and liver biopsy. Patients were stratified into cirrhotic and non-cirrhotic. **RESULTS:** In 404 patients (124 cirrhosis), transient elastography was diagnostically superior to the other modalities yielding an AUC 0.9 +/- 0.04 compared with hyaluronic acid (AUC 0.81 +/- 0.04: $P < 0.05$), clinical signs (AUC 0.74 +/- 0.04: $P < 0.05$), APRI score (AUC 0.71 +/- 0.03: $P < 0.05$) and AST/ALT ratio (AUC 0.66 +/- 0.03: $P < 0.05$). The optimum cut-off for transient elastography was 12 kPa giving a sensitivity of 89% and specificity of 87% for cirrhosis. In 238 hepatitis C patients (87 cirrhosis), transient elastography yielded an AUC 0.899 +/- 0.02 for cirrhosis and in 166 non-HCV patients (37 cirrhosis) the results were similar with an AUC 0.928 +/- 0.03; with transient elastography being superior to HA, APRI, AST/ALT and clinical signs for all etiologies of cirrhosis ($P < 0.05$ for all). Importantly, transient elastography was statistically superior at identifying cirrhosis in 38 biopsy proven Childs Pugh A cirrhotics with no clinical, biochemical or radiological features of cirrhosis or portal hypertension (AUC 0.87 +/- 0.04). **CONCLUSION:** Transient elastography accurately identified compensated cirrhosis; a liver stiffness of >12 kPa represents an important clinical measurement for the diagnosis of cirrhosis.

Selective atrophy of the middle hepatic venous drainage area in hepatitis c-related cirrhotic liver: Morphometric Study by Using Multidetector CT. Ozaki K, Matsui O, Kobayashi S, et al. Radiology. 2010 Sep 15. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20843994
PURPOSE: To retrospectively analyze the morphologic changes of hepatitis C-related cirrhosis, which commonly show macronodular cirrhosis, in relation to the portal venous supply and hepatic venous drainage, by using multidetector computed tomographic volumetry. Materials and **METHODS:** Institutional ethics committee approval and informed consent were obtained. The volume of the entire liver, each portal segment, and hepatic venous drainage area with the respective proportion relative to the entire liver and the volume of hepatic area with the respective proportion relative to the anterior segment of the right lobe were measured in 74 patients without cirrhosis and with normal liver function and in 64 patients with cirrhosis classified as Child-Pugh class A and in 68 with that classified as Child-Pugh class B. The diameter and length of each hepatic vein were measured in normal liver. All measurements were statistically analyzed by using the Kruskal-Wallis test, and multiple comparisons were made by using a Bonferroni correction ($P < .05$). **RESULTS:** The entire liver volume was significantly

smaller in patients with Child-Pugh class B cirrhosis (P = .002), whereas there was no significant difference in volume between the normal liver and the liver with Child-Pugh class A cirrhosis (P > .99). Middle hepatic venous (MHV) drainage area revealed significant atrophy in cirrhosis (P < .0001), more markedly in Child-Pugh class B. The right hepatic venous (RHV) and left hepatic venous drainage areas showed significant hypertrophy in cirrhosis (P < .0001). The anterior and medial segments showed significant atrophy (P < .0001), and the lateral and posterior segments and caudate lobe showed significant hypertrophy in cirrhosis (P < .05). In the anterior segment, the MHV drainage area showed significant atrophy (P < .0001), and the RHV drainage area demonstrated relative hypertrophy in cirrhosis, more definitely in Child-Pugh class B. The diameter of MHV was significantly the smallest (P < .0001), and the length of MHV was relatively longer in normal livers. **CONCLUSION:** The morphologic changes in hepatitis C-related cirrhosis (mainly macronodular cirrhosis) were attributed to a selective volume reduction of the MHV drainage area and relative enlargement of the other areas.

End-stage liver disease: challenges and practice implications. Hansen L, Sasaki A, Zucker B. Nurs Clin North Am. 2010 Sep;45(3):411-26.
http://www.ncbi.nlm.nih.gov/pubmed/20804886
As the seventh leading cause of death among people aged 25 to 64 years, end-stage liver disease (ESLD) affects many Americans in the most productive years of their lives. Despite the increasing number of individuals who are dying of ESLD, little is documented about their end of life challenges as the disease progresses. The purpose of this article is to highlight specific challenges for people with ESLD, their families, and their implications for health care providers: ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, malnutrition, altered drug metabolism, renal insufficiency and hyponatremia, hepatocellular carcinoma, and pain. The authors also present a case study to illustrate disease progression and difficulties facing patients, family members, and providers.

Diagnosis of occult hepatitis C without the need for a liver biopsy. Castillo I, Bartolomé J, Quiroga JA, Barril G, Carreño V. J Med Virol. 2010 Sep;82(9):1554-9.
http://www.ncbi.nlm.nih.gov/pubmed/20648609
The diagnosis of occult hepatitis C virus (HCV) infection is based on the presence of HCV-RNA in the liver. This study aimed to evaluate the use of combining non-invasive assays to diagnose occult HCV. A total of 122 patients with occult HCV (HCV-RNA in the liver without detectable anti-HCV and serum HCV-RNA) and 45 patients with cryptogenic chronic hepatitis (without HCV-RNA in the liver and negative for anti-HCV and serum HCV-RNA) were included. HCV-RNA was tested in peripheral blood mononuclear cells (PBMCs) and in 2 ml of ultracentrifuged serum. Anti-core HCV was examined by a non-commercial enzyme-linked immunosorbent assay. All controls were negative for the three HCV markers studied. Among patients with occult HCV, 36% were anti-core HCV positive, 57% had serum HCV-RNA after ultracentrifugation, and 61% had HCV-RNA in PBMCs. Combining the results of the assays, 91% of the patients were positive for at least one marker. Intrahepatic HCV-RNA load was significantly higher in patients who were positive simultaneously for the three HCV markers than in patients who were negative for all markers (P = 0.006) and than in those with one or two HCV markers (P = 0.039). Replication of HCV in liver was detected more frequently in patients with three (93%, P = 0.002), two (82%, P = 0.001), and one HCV marker (73%, P = 0.011) than in those without markers (27%). **In conclusion**, testing for all these markers allows diagnosis of occult HCV

without the need for a liver biopsy and these assays may help to elucidate the clinical significance of occult HCV infection.

Hepatitis C virus genotyping using an oligonucleotide microarray based on the NS5B sequence. Gryadunov D, Nicot F, Dubois M, et al. J Clin Microbiol. 2010 Sep 15. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20844214
The genotype of the hepatitis C virus (HCV) is essential for determining treatment duration in clinical practice and for epidemiological and clinical studies. Currently, few genotyping assays that determine the HCV subtype are available. This report describes a microarray-based molecular technique for identifying the HCV genotype and subtype. It uses low density hydrogel-based biochips containing genotype and subtype-specific oligonucleotides based on the sequences of the NS5B region of the HCV genome. The biochip contains 120 oligonucleotides that identify genotypes 1-6 and 36 (1a, 1b, 1c, 1d, 1e, 2a, 2b, 2c, 2d, 2i, 2j, 2k, 2l, 2m, 3a, 3b, 3k, 4a, 4c, 4d, 4f, 4h, 4i, 4k, 4n, 4o, 4p, 4r, 4t, 5a, 6a, 6b, 6d, 6g, 6h, 6k) subtypes. The procedure included amplification of a 380-nt fragment of NS5B and its hybridization on the biochip. Tests on 345 HCV-positive samples showed that the assay agreed with NS5B sequencing 100% for the genotype and 99.7% for the subtype. The hybridization on the microarray and the NS5B sequence were in 100% agreement for identifying the most common subtypes 1a, 1b, 4a, 4d, and 3a. This approach is a promising tool for HCV genotyping, especially for implementing the new anti-HCV drugs that require accurate identification of clinically relevant subtypes.

Use of gloves and reduction of risk of injury caused by needles or sharp medical devices in healthcare workers: results from a case-crossover study. Kinlin LM, Mittleman MA, Harris AD, Rubin MA, Fisman DN. Infect Control Hosp Epidemiol. 2010 Sep;31(9):908-17.
http://www.ncbi.nlm.nih.gov/pubmed/20658920
OBJECTIVE: Standard precautions are advocated for reducing the number of injuries caused by needles and sharp medical devices ("sharps injuries"), but the effectiveness of gloves in preventing such injuries has not been established. We evaluated factors associated with gloving practices and identified associations between gloving practices and sharps-injury risk. **DESIGN:** Usual-frequency case-crossover study. **SETTING:** Thirteen medical centers in the United States and Canada. **PARTICIPANTS:** Six hundred thirty-six healthcare workers who presented to employee health clinics after sharps injury. **METHODS:** Structured telephone questionnaires were administered to assess usual behaviors and circumstances at the time of injury. **RESULTS:** Of 636 injured healthcare workers, 195 were scrubbed in an operating room or procedure suite when injured, and 441 were injured elsewhere. Nonscrubbed individuals were more commonly gloved when treating patients who were perceived to have a high risk of human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection than when treating other patients (adjusted odds ratio [aOR], 2.53 [95% confidence interval {CI}, 1.30-4.91]). Nurses (aOR, 0.11 [95% CI, 0.04-0.32]) and other employees (aOR, 0.24 [95% CI, 0.07-0.77]) were less commonly gloved at injury than were physicians and physician trainees. Gloves reduced injury risk in case-crossover analyses (incidence rate ratio [IRR], 0.33 [95% CI, 0.22-0.50]). In scrubbed individuals, involvement in an orthopedic procedure was associated with double gloving at injury (aOR, 13.7 [95% CI, 4.55-41.3]); this gloving practice was associated with decreased injury risk (IRR, 0.20 [95% CI, 0.10-0.42]). **CONCLUSIONS:** Although the use of gloves reduces the risk of sharps injuries in health care, use among healthcare workers is

inconsistent and may be influenced by risk perception and healthcare culture. Glove use should be emphasized as a key element of multimodal sharps-injury reduction programs.

Diagnosis and management of interstitial pneumonitis associated with interferon therapy for chronic hepatitis C. Ji FP, Li ZX, Deng H, Xue HA, Liu Y, Li M. World J Gastroenterol. 2010 Sep 21;16(35):4394-9.
http://www.ncbi.nlm.nih.gov/pubmed/20845505
Interstitial pneumonitis (IP) is an uncommon pulmonary complication associated with interferon (IFN) therapy for chronic hepatitis C virus (HCV) infection. Pneumonitis can occur at any stage of HCV treatment, ranging from 2 to 48 wk, usually in the first 12 wk. Its most common symptoms are dyspnoea, dry cough, fever, fatigue, arthralgia or myalgia, and anorexia, which are reversible in most cases after cessation of IFN therapy with a mean subsequent recovery time of 7.5 wk. Bronchoalveolar lavage in combination with chest high resolution computed tomography has a high diagnostic value. Prompt discontinuation of medication is the cornerstone, and corticosteroid therapy may not be essential for patients with mild-moderate pulmonary functional impairment. The severity of pulmonary injury is associated with the rapid development of IP. We suggest that methylprednisolone pulse therapy followed by low dose prednisolone for a short term is necessary to minimize the risk of fatal pulmonary damage if signs of significant pulmonary toxicity occur in earlier stage. Clinicians should be aware of the potential pulmonary complication related to the drug, so that an early and opportune diagnosis can be made.

Expanding access to hepatitis C virus treatment--Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. Arora S, Kalishman S, Thornton K, et al. Hepatology. 2010 Sep;52(3):1124-33.
http://www.ncbi.nlm.nih.gov/pubmed/20607688
The Extension for Community Healthcare Outcomes (ECHO) Model was developed by the University of New Mexico Health Sciences Center as a platform to deliver complex specialty medical care to underserved populations through an innovative educational model of team-based interdisciplinary development. Using state-of-the-art telehealth technology, best practice protocols, and case-based learning, ECHO trains and supports primary care providers to develop knowledge and self-efficacy on a variety of diseases. As a result, they can deliver best practice care for complex health conditions in communities where specialty care is unavailable. ECHO was first developed for the management of hepatitis C virus (HCV), optimal management of which requires consultation with multidisciplinary experts in medical specialties, mental health, and substance abuse. Few practitioners, particularly in rural and underserved areas, have the knowledge to manage its emerging treatment options, side effects, drug toxicities, and treatment-induced depression. In addition, data were obtained from observation of ECHO weekly clinics and database of ECHO clinic participation and patient presentations by clinical provider. Evaluation of the ECHO program incorporates an annual survey integrated into the ECHO annual meeting and routine surveys of community providers about workplace learning, personal and professional experiences, systems and environmental factors associated with professional practice, self-efficacy, facilitators, and barriers to ECHO. The initial survey data show a significant improvement in provider knowledge, self-efficacy, and professional satisfaction through participation in ECHO HCV clinics. Clinicians reported a moderate to major benefit from participation. We conclude that ECHO expands access to best practice care for underserved populations, builds communities of practice to enhance professional development and

satisfaction of primary care clinicians, and expands sustainable capacity for care by building local centers of excellence.

Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. Kral AH, Malekinejad M, Vaudrey J, et al. J Urban Health. 2010 Sep;87(5):839-50.
http://www.ncbi.nlm.nih.gov/pubmed/20582573
The objective of this article is to compare demographic characteristics, risk behaviors, and service utilization among injection drug users (IDUs) recruited from two separate studies in San Francisco in 2005, one which used targeted sampling (TS) and the other which used respondent-driven sampling (RDS). IDUs were recruited using TS (n = 651) and RDS (n = 534) and participated in quantitative interviews that included demographic characteristics, risk behaviors, and service utilization. Prevalence estimates and 95% confidence intervals (CIs) were calculated to assess whether there were differences in these variables by sampling method. There was overlap in 95% CIs for all demographic variables except African American race (TS: 45%, 53%; RDS: 29%, 44%). Maps showed that the proportion of IDUs distributed across zip codes were similar for the TS and RDS sample, with the exception of a single zip code that was more represented in the TS sample. This zip code includes an isolated, predominantly African American neighborhood where only the TS study had a field site. Risk behavior estimates were similar for both TS and RDS samples, although self-reported hepatitis C infection was lower in the RDS sample. In terms of service utilization, more IDUs in the RDS sample reported no recent use of drug treatment and syringe exchange program services. **Our study suggests** that perhaps a hybrid sampling plan is best suited for recruiting IDUs in San Francisco, whereby the more intensive ethnographic and secondary analysis components of TS would aid in the planning of seed placement and field locations for RDS.

LIVER CANCER

Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. Thomas MB, Jaffe D, Choti MM, et al. J Clin Oncol. 2010 Sep 1;28(25):3994-4005. Epub 2010 Aug 2.
http://www.ncbi.nlm.nih.gov/pubmed/20679622
Hepatocelluar carcinoma (HCC) is the most common primary malignancy of the liver in adults and the third most common cause of cancer death worldwide. The incidence of HCC in the United States is rising steadily because of the prevalence of hepatitis C viral infection and other causes of hepatic cirrhosis. The majority of patients have underlying hepatic dysfunction, which complicates patient management and the search for safe and effective therapies. The Clinical Trials Planning Meeting (CTPM) in HCC was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee to identify the key knowledge gaps in HCC and define clinical research priorities. The CTPM structured its review according

Administration of interferon for two or more years decreases early stage hepatocellular carcinoma recurrence rate after radical ablation: A retrospective study of hepatitis C virus-related liver cancer. Ikeda K, Kobayashi M, Seko Y, et al. Hepatol Res. 2010 Sep 16. doi: 10.1111/j.1872-034X.2010.00720.x. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20849431

BACKGROUND: Since hepatocellular carcinoma often recurs after surgical resection or radiofrequency ablation, we analyzed a retrospective large cohort of patients with small hepatocellular carcinoma caused by hepatitis C virus (HCV). **METHODS:** Among 379 patients with HCV RNA-positive small hepatocellular carcinoma (multiple up to three nodules, 3 cm or less each), 77 received interferon-alpha injection and 302 received no anti-viral therapy. **RESULTS:** Four patients (5.2%) attained sustained virological response (SVR). Cumulative recurrence rates in the treated and untreated groups were 41.1% and 57.5% at the end of the third year, and 63.0% and 74.5% at the fifth year, respectively (P=0.013). Fifth year-recurrence rates in treated group were 25.0% in SVR, 85.7% in biochemical response, 71.1% in no response, and 46.7% in patients with continuous administration. When four patients with SVR were excluded, recurrence rates in short-term interferon therapy (<2 years) and long-term therapy (≥2 years) were 46.2% and 39.3% at the third year, and 66.2% and 57.4% at the fifth year, respectively (P=0.012). Multivariate analysis showed that long-term interferon therapy significantly decreased recurrence rate (hazard ratio for interferon <2 years 0.80, interferon ≥2 years 0.60, P =0.044), after adjustment with background covariates including indocyanine green retention rate (P=0.018), alpha-fetoprotein (P=0.051), and tumor treatment (P=0.066). **CONCLUSION:** A long-term administration of low-dose interferon significantly decreased recurrence of hepatocellular carcinoma after surgical resection or radiofrequency ablation.

Effects of branched-chain amino acid-enriched nutrient for patients with hepatocellular carcinoma following radiofrequency ablation: a one-year prospective trial. Kuroda H, Ushio A, Miyamoto Y, et al. J Gastroenterol Hepatol. 2010 Sep;25(9):1550-5.
http://www.ncbi.nlm.nih.gov/pubmed/20796154
BACKGROUND AND AIM: This prospective control study examined whether supplementation with branched-chain amino acid (BCAA)-enriched nutrients can help maintain and improve residual liver function and nutritional status in cirrhotic patients with hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA). **METHODS:** Subjects were 49 patients with hepatitis C-related HCC who underwent RFA. Two groups were formed: BCAA group (BCAA-enriched nutrient, aminoleban EN) and controls (standard diet only). Event-free survival rate, liver function tests, and Short Form (SF)-8 scores were evaluated in both groups before and one year after RFA. Energy metabolism using indirect calorimetry was measured before and after 3 months. **RESULTS:** Complete data were obtained from 35 patients (BCAA group, n = 20; controls, n = 15). Six events (death, recurrence of HCC, rupture of esophageal varices and liver failure) occurred during the observation period, but frequencies of these events did not differ between groups. Event-free survival rate tended to be higher in the BCA group than in controls. Among the parameters of liver function, serum albumin level was only significantly increased over 6 months, and remained at similar values for one year ($P < 0.05$). SF-8 scores for general health, physical functioning, and social functioning were significantly elevated in the BCAA group ($P < 0.05$). Non-protein respiratory quotient was significantly improved in the BCAA group ($P < 0.01$). **CONCLUSION:** Supplementation with BCAA-enriched nutrients for one year in cirrhotic patients with HCC after RFA therapy can perform safety and improve both nutritional state and quality of life.

Survival rates are comparable following radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. Hung HH, Chiou YY, Hsia CY, et al. Clin Gastroenterol Hepatol. 2010 Sep 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/20831902
BACKGROUND & AIMS: Differences in efficacy of radiofrequency ablation (RFA) and surgical resection (SR) are not clear for patients with hepatocellular carcinoma (HCC).
METHODS: From 2002 to 2007, 419 patients with HCCs ≤5 cm were enrolled consecutively in the study. Among these patients, 190 and 229 patients received RFA and SR, respectively, as their first treatment. Factors were analyzed in terms of overall survival and recurrence by multivariate analysis and propensity score matching analysis.
RESULTS: The SR group had younger age, a higher male-to-female ratio, higher prevalence of hepatitis B virus, lower prevalence of hepatitis C virus, better liver function reserve, and larger tumor size than the RFA group. The cumulative 5-year overall survival rates were 79.3% in the SR and 67.4% in the RFA groups. During the follow-up period, tumors recurred in 244 patients, in a median time of 14.5±15.7 months. Before propensity-score matching, the RFA group had shorter overall survival time (P=0.009) and a higher tumor recurrence rate (P<0.001) than the SR group. After matching, RFA was comparable to SR in overall survival time (P=0.519), but the RFA group still had a greater incidence of tumor recurrence (P<0.001). In patients with Barcelona-Clinic Liver Cancer (BCLC) stage 0 HCC, RFA was as effective as SR for overall survival time and total recurrence by both multivariate and propensity-score-matching analyses.
CONCLUSIONS: Patients with small HCCs (≤5 cm) have a higher rate of tumor recurrence following RFA than surgery, but overall survival rates are comparable between therapies. RFA is as effective as surgery in patients BCLC stage 0 HCC.

Population-based risk factors and resource utilization for HCC: US perspective. Sanyal A, Poklepovic A, Moyneur E, Barghout V. Curr Med Res Opin. 2010 Sep;26(9):2183-91.
http://www.ncbi.nlm.nih.gov/pubmed/20666689
OBJECTIVE: Hepatocellular carcinoma (HCC) is a deadly cancer with limited treatment options. HCC cases in the United States (US) were identified from a claims database to analyze the risk factors, the health care provider referral patterns, and treatment options in actual (real-world) clinical settings.
METHODS: MarketScan, a health care claims database from Thomas Reuters covering 18 million lives yearly and all US census regions from 2002 to 2008, was used to identify HCC patients and obtain data on patient characteristics, health care providers, and treatment utilization (i.e., medications, interventions).
RESULTS: HCC cases (n = 4406) were identified with an annual incidence of 0.4 per 1000 covered lives (i.e., those currently enrolled in a health care plan) from 2002 to 2008. Nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) was the most common underlying etiologic risk factor (59%), followed by diabetes (36%) and hepatitis C virus infection (22%). Primary care/internal medicine providers managed the majority of cases (55%); a minority were seen by an oncologist (24%). Only 22% of cases known to have cirrhosis were undergoing HCC screening prior to diagnosis. Type of provider did not change significantly after the diagnosis was made. Systemic chemotherapy was the most commonly used treatment (32.8%); however, only 6% received sorafenib, the only approved drug for HCC. Limitations include lack of patient records and potential for physician coding variances.
CONCLUSION: The incidence of HCC in the database was 0.4 per 1000 persons. NAFLD/NASH and type 2 diabetes mellitus, along with hepatitis C virus infection, were the major etiologic risk factors associated with HCC. This claims database analysis suggests a gap

exists between screening and treatment guidelines and practice patterns, implying a need for greater health care provider awareness and education.

Effects of preceding interferon therapy on outcome after surgery for hepatitis C virus-related hepatocellular carcinoma.
Tomimaru Y, Nagano H, Eguchi H, et al. J Surg Oncol. 2010 Sep 15;102(4):308-14.
http://www.ncbi.nlm.nih.gov/pubmed/20589711
BACKGROUND AND OBJECTIVES: Interferon (IFN) can eradicate hepatitis C virus (HCV)-RNA from serum and hepatic tissue, and suppress the development of hepatocellular carcinoma (HCC). Despite such effectiveness, HCC develops even in HCV patients successfully treated with IFN therapy. **METHODS:** HCV-related HCC patients who underwent curative hepatectomy for HCC were divided into three groups according to preceding IFN for HCV infection therapy and the therapeutic effect: responders group (n = 23), non-responders group (n = 46), and no-IFN group (n = 215). Postoperative outcome was retrospectively examined in the three groups. **RESULTS:** AST and ALT were significantly lower in responders group than non-responders group (P < 0.001, P = 0.001) and no-IFN group (P = 0.001, P = 0.002). Platelet count was significantly higher in responders group than other groups (P = 0.008, P = 0.001). The percentage of cirrhotic patients in responders group was significantly lower than other groups (P = 0.017, P = 0.014). Multivariate analysis identified preceding IFN therapy to be associated with disease-free survival at marginal significance (P = 0.086), and as a significant independent factor for overall survival (P = 0.042). **CONCLUSIONS:** Preceding IFN therapy for HCV infection improves postoperative outcome in HCV-related HCC patients treated successfully with IFN.

Cirrhosis is Present in Most Patients with Hepatitis B and Hepatocellular Carcinoma.
Yang JD, Kim WR, Coelho R, et al. Clin Gastroenterol Hepatol. 2010 Sep 7. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20831903
BACKGROUND & AIMS: There is not much data available about the prevalence or effects of cirrhosis in patients with hepatocellular carcinoma (HCC) from viral hepatitis. We compared patients with HCC and hepatitis B virus (HBV) or hepatitis C virus (HCV) infections to determine the proportions of cirrhosis in each group, virologic and tumor characteristics, and overall survival. **METHODS:** This analysis includes patients with HBV (n=64) or HCV (n=118) infection who were diagnosed with HCC at the Mayo Clinic in Rochester MN from 1994 to 2008; groups were matched for age and sex. The diagnosis of cirrhosis was based on histology and, if histologic information was insufficient or unavailable, clinical indicators that included ascites or varices, thrombocytopenia or splenomegaly, and radiographic configuration of cirrhosis. Virologic characteristics, tumor stage, and patient survival were also assessed. **RESULTS:** The prevalence of histologic cirrhosis was 88% among patients with HBV infection and 93% among those with HCV infection (P=0.46). When the most inclusive criteria for cirrhosis were applied, cirrhosis was present in 94% of patients with HBV and 97% with HCV (P=0.24). Among HCV patients, 5.2% were negative for HCV RNA following antiviral treatment; 63.4% of HBV patients had HBV DNA < 2000 u/ml with or without treatment. Patients with HBV tended to have less surveillance and more advanced stages of HCC, without differences in survival from those with HCV infection (P=0.75). **CONCLUSION:** Most patients with HCC and chronic viral hepatitis had evidence of cirrhosis, including those with HBV infection and those without active viral replication.