

# Caring Ambassadors Hepatitis C Program Newsletter

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## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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**Establishment of a successful assessment and treatment service for Australian prison inmates with chronic hepatitis C.** Boonwaat L, Haber PS, Levy MH, Lloyd AR. Med J Aust. 2010 May 3;192(9):496-500.

<http://www.ncbi.nlm.nih.gov/pubmed/20438418>

**OBJECTIVE:** To evaluate the assessment and treatment outcomes of a prison hepatitis service.

**DESIGN AND SETTING:** A retrospective, observational cohort study of prison inmates who attended hepatitis clinics from 1996 to 2005 at correctional centres in New South Wales.

**PATIENTS:** Inmates who attended the clinics, including a nested case-control series of patients who received antiviral treatment and age- and sex-matched patients who did not receive treatment.

**MAIN OUTCOME MEASURES:** Demographic and clinical characteristics of patients who attended the service; correlates of selection for antiviral treatment; and clinical and virological outcomes of treatment. **RESULTS:** Of the 1043 inmates who attended the clinics, 851 were men (82%) and 994 (95%) were referred for HCV infection; the mean age for this group was 33 years (range, 18-74 years). In the case-control series (185 treated and 186 untreated patients), selection for treatment was not biased by culturally and linguistically diverse background, current methadone treatment or psychiatric status. In the treated group, 76 of 138 genotyped patients had a genotype that is predictive of favourable treatment response, and a small minority of those with available liver biopsy results had established cirrhosis (7/119 patients). Of treated patients for whom complete follow-up data were available, 55% achieved sustained virological response and 100% adhered to therapy. In addition, treatment episodes were not especially complicated. **CONCLUSION:** Although the prison population has high rates of injecting drug use and poor mental health, imprisonment offers an opportunity for assessment and treatment of chronic HCV infection.

**Digital quantification is more precise than traditional semiquantitation of hepatic steatosis: correlation with fibrosis in 220 treatment-naïve patients with chronic hepatitis C.** Rawlins SR, El-Zammar O, Zinkievich JM, Newman N, Levine RA. Dig Dis Sci. 2010 May 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20458626>

**BACKGROUND:** Steatosis, as associated with chronic hepatitis C (CHC) and non-alcoholic fatty liver disease (NAFLD), has been considered a risk factor for development of fibrosis.

**AIMS:** Our aims were to determine if correlations existed between the degree of steatosis and fibrosis in treatment-naïve CHC patients, and to compare the accuracy of digital image analysis

with semiquantification (manual assessment) to quantify hepatic steatosis. **METHODS:** We studied 220 treatment-naïve, liver biopsy-proven CHC patients, including a serial biopsy sub-cohort of 37 patients with a mean interval of 3.82 years. Steatosis and fibrosis % were evaluated using digital quantification of steatosis (DQS) and fibrosis contrasted with manual assessment. **RESULTS:** Most patients had <6% steatosis measured manually and digitally. Overall, manual assessment of steatosis was 3.78 times greater than DQS. Increasing steatosis % was associated with advancing fibrosis stage, both manually and digitally. Intraobserver reliability for DQS showed higher intraclass correlation reproducibility ( $r = 0.98$ ,  $P < 0.001$ ) than the manual method ( $r = 0.81$ ,  $P < 0.01$ ). Interobserver concordance for DQS had an average measure intraclass correlation of  $r = 0.99$ . Cirrhotics were more likely than non-cirrhotics to have grade 2 steatosis. **CONCLUSIONS:** Increased steatosis was associated with increased fibrosis. DQS was consistently more precise and reproducible than manual assessment of steatosis in grades 1 (1 to <6%) and 2 (6 to <34%), and may prove to be especially preferable in clinical trials of pharmacotherapeutic agents.

**Non-invasive assessment of liver fibrosis progression in hepatitis C patients retreated for 96 weeks with antiviral therapy: a randomized study.** Zarski JP, Sturm N, Desmorat H, et al. Liver Int. 2010 May 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20492512>

**BACKGROUND:** The efficacy of a maintenance therapy in non-responder patients with chronic hepatitis C has been essentially evaluated by histological semiquantitative scores. Aim: The aim was to evaluate the efficiency of 2 years of treatment with peginterferon alpha-2a vs alpha-tocopherol in these patients by histology, morphometry and blood markers of fibrosis.

**METHOD:** Hundred and five HCV patients with a Metavir fibrosis score  $\geq 2$  were randomized to receive peginterferon alpha-2a 180 mug/week (PEG) ( $n=55$ ) or alpha-tocopherol (TOCO) 1000 mg/day ( $n=50$ ) for 96 weeks. The primary endpoint was improvement or stabilization of the Metavir fibrosis score by biopsy performed at week 96. Secondary endpoints included a quantitative assessment of fibrosis by morphometry and changes in blood markers of fibrosis.

**RESULTS:** There was no difference at baseline between PEG and TOCO according to the metavir (83.3 vs 86.8%,  $P=0.751$ ) stage. The median fibrosis rate, measured with morphometry was 2.72 and 2.86% at day 0, and 3.66 and 2.82% at week 96, in the PEG and TOCO groups ( $P=0.90$ ) respectively. However, the percentage of patients with metavir activity grade improvement was significantly higher in the PEG group vs the TOCO group (52.8 vs 23.7%,  $P=0.016$ ). Non-invasive markers analysis did not show any significant change in both groups.

**CONCLUSION:** Long-term therapy with peginterferon alpha-2a did not reduce liver fibrosis degree assessed by morphometry and blood tests as compared with alpha-tocopherol. Blood tests could be useful to assess liver fibrosis changes in clinical trials.

**Enhanced adherence to HCV therapy with higher dose ribavirin formulation: final analyses from the ADHERE registry.** Alam I, Stainbrook T, Cecil B, Kistler KD. Aliment Pharmacol Ther. 2010 May 25. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20500732>

**BACKGROUND:** Poor adherence to Hepatitis C virus (HCV) treatment is an important cause of treatment failure. Traditional ribavirin 200mg (RBV) treatment is associated with a significant daily pill burden. RibaPak(R) (RBP), available as 400mg and 600mg ribavirin tablets, offers simplified dosing at two pills daily. Aim: To examine whether improved adherence was

associated with RBP vs. RBV. **METHODS:** Accurate Dosing in Hepatitis C: Examining the RibaPak(R) Experience (ADHERE) was a U.S., multi-center, prospective registry capturing data on adherence with RBP vs. RBV in adults with HCV. Adherence was measured by the proportion of subjects remaining on treatment at weeks 4, 12, and 24; by pill counts; and by the proportion of subjects who took  $\geq 80\%$  of their prescribed dose. **RESULTS:** 503 patients (RBP=346, RBV=157) from 38 sites were included. A greater proportion of RBV vs. RBP subjects prematurely discontinued treatment. At 12 and 24 weeks a greater proportion of RBP vs. RBV subjects took  $\geq 80\%$  of their prescribed doses ( $p < 0.05$ ). For patients who remained on treatment, the mean milligrams missed per day was significantly greater for RBV vs. RBP at 24 weeks. **CONCLUSIONS:** First line treatment with RBP may offer the best prospect for less discontinuation and improved treatment adherence.

**Identifying HCV genotype 1 patients at risk of relapse.** Deschênes M, Bain VG, Lee SS, et al. Eur J Gastroenterol Hepatol. 2010 May;22(5):546-51.

<http://www.ncbi.nlm.nih.gov/pubmed/20216320>

**OBJECTIVE:** The objective of this analysis was to identify predictors of relapse in genotype 1 patients after 48 weeks of treatment with peginterferon plus ribavirin. **METHODS:** Retrospective analysis of data from treatment-naïve genotype 1 patients with an end-of-treatment response after 48 weeks of treatment with peginterferon alpha-2a plus ribavirin 1000/1200 mg/day in the Canadian Pegasys Expanded Access Program. **RESULTS:** Among treatment-naïve genotype 1 patients with an end-of-treatment response ( $n = 432$ ), the sustained virological response status was known for 405 individuals (sustained virological response  $n = 328$ , 81%; relapse  $n = 77$ , 19%). Early virological response rates at week 12 were similar in relapsers (98.7%) and sustained responders (98.5%). More relapsers (12 of 77, 15.6%) than sustained responders (15 of 328, 4.6%) had quantifiable hepatitis C virus (HCV) RNA ( $\geq 600$  IU/ml) at week 12 and, among these patients, mean and maximum HCV RNA levels were higher in relapsers, although the median values were similar. Factors significantly associated with relapse in the multiple logistic regression analysis include older age (odds ratio: 1.48 per decade, 95% confidence interval: 1.06-2.07;  $P = 0.023$ ), Caucasian ethnicity (odds ratio: 3.23, confidence interval: 1.25-8.33;  $P = 0.016$ ), higher baseline serum HCV RNA level ( $P = 0.005$ ), the drop in HCV RNA between baseline and week 12 ( $P = 0.026$ ), and the interaction between baseline HCV RNA level and the decrease in HCV RNA between baseline and week 12 ( $P = 0.032$ ). **CONCLUSION:** Older age, Caucasian ethnicity, and high baseline HCV RNA level, and a smaller decrease in HCV RNA between baseline and week 12 predict a relapse in genotype 1 patients.

**Do steatosis and steatohepatitis impact on sustained virological response (SVR) rates in patients receiving pegylated interferon and ribavirin for chronic hepatitis C infection?**

Cross TJ, Quaglia A, Nolan J, Hughes S, Harrison PM. J Med Virol. 2010 May;82(6):958-64.

<http://www.ncbi.nlm.nih.gov/pubmed/20419809>

The impact of steatosis on treatment response in chronic hepatitis C infection is controversial. **The aim of this study** was to determine whether steatosis +/- steatohepatitis on pre-treatment liver biopsy influenced sustained virological response (HCV RNA negative 6 months after completing therapy) in patients with chronic hepatitis C infection treated with pegylated interferon-alpha and ribavirin. One hundred and seventy-nine patients, median age 46 years (interquartile range 40-52), treated between 2001 and 2005. Histological evidence of steatosis was present in 93 patients (52%) and steatohepatitis in 33 patients (18%), 31 patients (17.3%)

were cirrhotic. There were 106 (59%) responders, who were similar to non-responders in respect to gender, age, and pre-treatment ALT. On univariate analysis, infection with genotype 2 or 3 was associated with sustained virological response (odds ratio 6.5 (95% CI, 3.3-12.5);  $P < 0.0001$ ), whereas cirrhosis and patient weight were associated with a reduced response (odds ratios 0.23 (95% CI, 0.11-0.48);  $P < 0.0001$ , and 0.97 (95% CI, 0.95-0.99);  $P < 0.01$ , respectively); steatohepatitis but not steatosis impacted on the likelihood of achieving sustained virological response (odds ratio 0.37 (95% CI, 0.17-0.77);  $P = 0.009$ , and  $P = 0.18$ , respectively). Multivariate analysis revealed that infection with genotype 1 or 4 (odds ratio 0.09 (95% CI, 0.03-0.32);  $P < 0.001$ ) and pre-treatment weight (odds ratio 0.94 (95% CI, 0.90-0.98);  $P = 0.002$ ) were the only variables associated independently with sustained virological response. In chronic hepatitis C infection, although steatosis was associated with steatohepatitis, neither was shown to affect sustained virological response, which was influenced by genotype, patient weight and the presence of cirrhosis.

**Hepatitis C virus infection, age, and hispanic ethnicity increase mortality from liver cancer in the United States.** Younossi ZM, Stepanova M. Clin Gastroenterol Hepatol. 2010 May 17. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20435163>

**BACKGROUND & AIMS:** We performed a population-based study to assess factors that are associated independently with hepatocellular carcinoma (HCC)-related mortality. **METHODS:** We evaluated clinicodemographic, laboratory, and mortality data collected from 15,866 individuals in the Third National Health and Nutrition Examination Survey from 1988 to 1994. The etiology of chronic liver disease was determined using serologic tests to measure hepatitis C virus (HCV) RNA, hepatitis B surface antigen, and iron; excessive alcohol consumption and nonalcoholic fatty liver disease (NAFLD) were determined. Cohorts were compared with controls using a stratum-specific chi-squared test. The Cox proportional hazard model was used to identify independent predictors of HCC-related mortality. **RESULTS:** After a follow-up period of 160 months, 14.55% of the individuals died; 83 deaths were liver-related (25 HCC and 58 non-HCC liver related). Factors that independently predicted HCC-related mortality were age (hazard ratio [HR], 1.10; 1.04-1.16;  $P = .0021$ ), Hispanic ethnicity (HR, 5.14; 1.75-15.06;  $P = .0036$ ), and HCV infection (HR, 18.12; 3.57-91.98;  $P = .0008$ ). Factors that independently predicted non-HCC liver-related mortality included age (HR, 1.07; 1.04-1.10;  $P < .0001$ ), male sex (HR, 3.29; 1.15-9.42;  $P = .0277$ ), alcoholic liver disease (HR, 10.81; 1.32-88.26;  $P = .0271$ ), HCV (HR, 27.00; 4.70-155.1;  $P = .0004$ ), iron overload (HR, 6.18; 1.82-20.97;  $P = .0043$ ), or NAFLD (HR, 11.56; 3.21-41.67;  $P = .0004$ ). **CONCLUSIONS:** This population-based study showed that HCV infection and Hispanic ethnicity independently increase the risk for HCC-related mortality. All liver diseases, including NAFLD, increase the risk for non-HCC liver-related mortality.

**Intermediate hepatobiliary cells predict an increased risk of hepatocarcinogenesis in patients with hepatitis c virus-related cirrhosis.** Ziol M, Nault JC, Aout M, et al.

Gastroenterology. 2010 May 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20399781>

**BACKGROUND & AIMS:** The expression of biliary lineage markers such as cytokeratin (K) 7 by hepatocytes is thought to reflect an altered regeneration pathway recruiting a stem cell compartment, more prone to carcinogenesis. We aimed to investigate the presence of these so-

called intermediate hepatobiliary cells (IHC) in liver biopsies of patients with hepatitis C-related cirrhosis and its potential influence on the subsequent occurrence of hepatocellular carcinoma (HCC). **METHODS:** From a cohort of patients with hepatitis C-related cirrhosis, prospectively screened for HCC, we retrospectively selected those with a liver biopsy performed for the initial diagnosis of cirrhosis. Presence of IHC was recorded when foci of K7-positive, intermediate-sized hepatocytes were detected. **RESULTS:** A total of 150 patients were included (87 men; mean age, 57 y; range, 19-84 y; body mass index, 25 kg/m<sup>2</sup>). After a median follow-up period of 4.85 years, HCC was diagnosed in 36 patients (24%). Baseline liver biopsy showed intermediate hepatobiliary cell foci in 61 patients (41%). Intermediate cells co-expressed both hepatocytes markers and the progenitor cell markers Ep-CAM and K19. The presence of intermediate hepatobiliary cells was associated independently with HCC occurrence (Fine and Gray model; hazard ratio, 2.48; 95% confidence interval, 1.24-4.96; P = .01). Other predictors of HCC were diabetes and low platelet count. The HCC annual incidence rate was significantly higher in patients with IHC compared with patients without (8.14 vs 3.12%, Gray's test, P = .003). **CONCLUSIONS:** The aberrant expression of biliary K by hepatocytes in patients with HCV-related cirrhosis is related independently to HCC occurrence.

**Prognostic factors associated with hepatitis C disease: a case-control study utilizing U.S. multiple-cause-of-death data.** Wise M, Finelli L, Sorvillo F. Public Health Rep. 2010 May-Jun;125(3):414-22.

<http://www.ncbi.nlm.nih.gov/pubmed/20433036>

**OBJECTIVE:** Hepatitis C, an important cause of premature mortality, is the most common chronic bloodborne infection in the United States. The severity of disease is strongly affected by a number of other medical conditions and health behaviors. We sought to estimate the association of several exposures with hepatitis C on death certificates. **METHODS:** We enrolled 63,189 hepatitis C deaths as cases in a case-control study using multiple-cause-of-death data for the U.S. from 1999 to 2004. Three control groups were assembled from all remaining deaths with no mention of hepatitis C, including a random sample of all deaths, digestive disease deaths, and circulatory disease deaths. **RESULTS:** Hepatitis B, human immunodeficiency virus (HIV), hemochromatosis, and alcohol use were all strongly associated with hepatitis C, even after controlling for confounding variables. The simultaneous presence of many of these exposures had a synergistic association with hepatitis C being listed as a cause of death. Hepatitis B, HIV, and alcohol use were recorded among 6.4%, 10.5%, and 18.2% of case deaths, respectively. **CONCLUSIONS:** The strong association of alcohol use, HIV, and hepatitis B with hepatitis C, as well as the frequent occurrence of these conditions, indicates that targeted interventions for mitigating the potential effect of these exposures may present an efficient means of limiting progression of hepatitis C-related liver disease and reducing the population burden of hepatitis C mortality.

**Efficacy and safety of pegylated IFN alfa 2b alone or in combination with ribavirin in thalassemia major with chronic hepatitis C.** Sood A, Sobti P, Midha V, et al. Indian J Gastroenterol. 2010 Mar;29(2):62-5. Epub 2010 May 5.

<http://www.ncbi.nlm.nih.gov/pubmed/20443101>

**BACKGROUND:** Treatment of HCV infection in patients with thalassemia major (TM) is limited by the lack of large clinical trials and concerns about ribavirin-induced hemolysis. **METHODS:** We conducted a prospective, randomized, open-label study to determine efficacy

and tolerability of pegylated-interferon alfa 2b (1.5 microg/kg/week) alone (group A) or with ribavirin (12-15 mg/kg/day; group B) in patients with TM and chronic HCV infection. Patients with genotype 1 or 4 HCV were treated for 48 weeks and those with genotype 3 or 2 HCV for 24 weeks. Early viral response (EVR; after 12 weeks of treatment), end-of-treatment virological response (ETR) and sustained virological response (SVR; 6 months after stopping therapy) were assessed. **RESULTS:** Of 40 patients, 20 each were allocated to the two treatment groups. EVR rates in group A and B were 15 (75%) and 18 (90%), respectively. ETR occurred in 17/20 (85%) patients in each group. SVR occurred in 8 (40%) patients in group A and 14 (70%) in group B. Blood transfusion requirements increased in one patient in group A and four patients in group B. One patient in group A had severe sepsis and one in group B had nephrotic syndrome. Two patients in each group required reduction in drug dose. **CONCLUSIONS:** In patients with TM and chronic HCV infection, pegylated interferon alfa 2b and ribavirin combination therapy achieves a higher SVR rate than pegylated interferon alone, and is well tolerated except for an increase in blood transfusion requirement.

**Rituximab plus Peg-Interferon {alpha} /ribavirin compared to Peg- Interferon {alpha} /ribavirin in Hepatitis C related mixed cryoglobulinemia.** Saadoun D, Resche Rigon M, Sene D, et al. Blood. 2010 May 3. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20439619>

Treatment of hepatitis C (HCV)-mixed cryoglobulinemia (MC) may target either the viral trigger (HCV) or the downstream B cell clonal expansion. Prospective cohort study of thirty eight HCV-MC patients who received a combination of Rituximab (375mg/m<sup>2</sup>) once a week for one month followed by Peg-interferon (IFN)-alpha (2a, 180microg or 2b, 1.5microg/kg) weekly plus ribavirin (600-1,200 mg) daily for 48 weeks were compared to fifty five HCV-MC patients treated by Peg-IFN alpha/ribavirin with the same modalities. In the whole population of HCV-MC patients (n=93), a complete clinical response was achieved in 73.1% (68/93), cryoglobulin clearance in 52.7% (49/93) and a sustained virological response in 59.1% (55/93). Compared with Peg-IFN alpha/ribavirin, Rituximab plus Peg-IFN alpha/ribavirin treated patients had a shorter time to clinical remission (5.4 +/- 4 versus 8.4 +/- 4.7 months, p=0.004), better renal response rates (80.9% versus 40% of complete response, p=0.040), and higher rates of cryoglobulin clearance (68.4% versus 43.6%, p=0.001) and clonal VH1-69(+) B cells suppression (p<0.01). Treatment was well tolerated with 11% of discontinuation due to antiviral therapy and no worsening of HCV RNA under rituximab. Our findings indicate that Rituximab combined with Peg-IFN alpha/ribavirin is well tolerated and more effective than Peg-IFN alpha/ribavirin in HCV-MC.

**Thyroid function outcomes following pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C.** Tran HA, Reeves GE, Ianna EA, Leembruggen N. Endocr Pract. 2010 May 3:1-16. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20439240>

**OBJECTIVE:** Interferon-alpha in combination with ribavirin has been well documented to cause thyroid diseases, particularly thyroiditis whilst undergoing therapy. It remains unknown if the effects on thyroid tissues extend beyond the completion of therapy. The aim of this study was to assess the frequency of new thyroid disease in patient, who did not develop thyroid disease during treatment for hepatitis C, in the 6 months after the end of therapy. **METHODS:** A prospective study was performed in 190 patients who underwent combination of interferon-alpha

and ribavirin therapy for hepatitis C infection over a 36-month period between 2006 and 2008. Thyroid function tests were performed at the completion of treatment, 4, 12 and 24 weeks of follow-ups. **RESULTS:** One hundred and ninety patients had satisfactory thyroid outcomes at 6 months after the completion of therapy. There were 2 cases of thyroid disease: one was the typical bi-phasic thyroiditis and the other primary hypothyroidism. The prevalence of thyroid disease in this setting is 2/190 (1.0%). **CONCLUSIONS:** The majority (99%) of patients had normal thyroid outcome at 6 month follow-up. Only 1 patient had symptoms. This finding is reassuring and removes the need for ongoing thyroid surveillance during this time and probably longer. In the absence of symptoms, only a single TSH value at 6 month review is recommended.

**Prevalence and impact of manic traits in depressed patients initiating interferon therapy for chronic hepatitis c infection.** Lim C, Olson J, Zaman A, Phelps J, Ingram KD. J Clin Gastroenterol. 2010 May 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20495465>

**GOALS:** To evaluate the impact of manic traits on adverse events in depressed hepatitis C patients initiating interferon therapy. **BACKGROUND:** Interferon alpha therapy for hepatitis C can exacerbate preexisting depression. Bipolar disorder frequently presents as depressive symptoms that are indistinguishable from or misdiagnosed as major depressive disorder. The impact of bipolar disorder on adverse psychiatric events during therapy is unknown. **STUDY:** A retrospective study was performed on consecutive patients initiating interferon therapy in the Hepatology clinic at a tertiary-care center between December 2004 and October 2007. All patients completed the Physicians Health Questionnaire (PHQ-9), a validated survey for major depressive disorder. Patients with a positive PHQ screen completed the Mood Disorders Questionnaire (MDQ), a validated screening tool for manic traits. Patients with a negative PHQ served as controls. All adverse psychiatric events were documented through retrospective record review for 6 months after interferon initiation. **RESULTS:** A total of 165 patients were treated with interferon alpha. One hundred thirty-two (80%) had a negative PHQ (controls) and 33 had a positive PHQ. Forty-one (30%) of the control patients had adverse psychiatric events. Psychiatric events occurred in 8 of 22 (36%) patients with positive PHQ but negative MDQ; 8 of 11 (73%) with positive PHQ and positive MDQ had psychiatric adverse events. This finding was statistically significant compared with the control group ( $P=0.007$ ). The overall sustained viral response rate was 58% and was not statistically significant among groups. **CONCLUSIONS:** Baseline manic traits, as detected by the MDQ, were associated with high rates of adverse psychiatric events among individuals receiving antiviral therapy.

**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 May 20. [Epub ahead of print]

<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.

**Prevalence and impact of occult hepatitis B infection in chronic hepatitis C patients treated with pegylated interferon and ribavirin.** Levast M, Larrat S, Thelu MA, et al. *J Med Virol.* 2010 May;82(5):747-54.

<http://www.ncbi.nlm.nih.gov/pubmed/20336715>

The prevalence of occult hepatitis B, defined by absence of HBsAg and HBV DNA, ranges widely in patients with hepatitis C. This may influence the treatment of hepatitis C and the severity of liver disease. Sensitive and specific real-time PCR techniques are available commercially and can detect more reliably low HBV DNA levels. The aim of this study was to determine the prevalence of occult hepatitis B virus infection using the COBAS Taqman assay (Roche Diagnostics, Meylan, France) in the serum and liver of HBsAg negative patients with chronic hepatitis C and to evaluate its clinical consequences on liver pathology and its impact on the response to treatment with peg-IFNalpha and Ribavirin. HBV DNA detection was assessed retrospectively on 140 sera and 113 liver biopsies of HCV positive/HBsAg negative patients before treatment. A 4.4% (5/113) prevalence of occult hepatitis B was recorded in liver samples and in none of the sera. Anti-HBc was not detected in one, three of whom were sustained virological responders to treatment, one was relapsed responder and one was non-responder. Furthermore, in this cohort composed of 12% anti-HBs negative/anti-HBc positive and 20% anti-HBs positive/anti-HBc positive patients, anti-HBc was not associated with pre-therapeutic viral load, ALT serum levels, and histological activity or fibrosis. Using a commercial real-time PCR assay, we observed a low prevalence of occult B hepatitis. This, just as anti-HBc status, had no clinical impact in a large cohort of hepatitis C patients. It therefore does not appear useful to screen for occult hepatitis B in these patients with this test before beginning HCV treatment.

**HBsAg profiles in patients receiving peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses.** Yu ML, Lee CM, Chuang WL, et al. *J Infect Dis.* 2010 May 18. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20482252>

**BACKGROUND:** With use of peginterferon alfa-2a and ribavirin combination therapy in patients with dual chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, 11.2% of patients achieved clearance of hepatitis B surface antigen (HBsAg) at 6 months after treatment; however, reactivation of HBV DNA was observed in 36.3%. We investigated the predictive potential of HBsAg quantification. **METHODS:** HBsAg quantification was

performed in 120 e antigen-negative patients dually infected with HBV and hepatitis C virus and treated with peginterferon alfa-2a/ribavirin for 48 weeks (HCV genotype 1; [Formula: see text]) or 24 weeks (HCV genotype 2/3; [Formula: see text]). HBsAg was quantified at baseline, week 4, week 12, end of treatment, and 24 weeks after treatment. **RESULTS:** The baseline median serum HBsAg level was 120 IU/mL and decreased gradually during treatment. Low baseline HBsAg was significantly associated with HBsAg clearance (40% for HBsAg level 20 IU/mL vs 2.2% for HBsAg level >20 IU/mL; [Formula: see text]). A decrease in HBsAg level from baseline to week 12 of 50% was associated with a reduced likelihood of HBV DNA reactivation in patients with baseline undetectable serum HBV DNA (positive predictive value, 89.5%). **CONCLUSIONS:** HBsAg quantification appears to be a useful indicator of posttreatment outcome in patients dually infected with HBV and hepatitis C virus.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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### **Large-scale candidate gene analysis of spontaneous clearance of hepatitis C virus.**

Mosbruger TL, Duggal P, Goedert JJ, et al. *J Infect Dis.* 2010 May 1;201(9):1371-80.

<http://www.ncbi.nlm.nih.gov/pubmed/20331378>

Human genetic variation is a determinant of recovery from acute hepatitis C virus (HCV) infection; however, to date, single-nucleotide polymorphisms (SNPs) in only a limited number of genes have been studied with respect to HCV clearance. We determined whether SNPs in 112 selected immune response genes are important for HCV clearance, by genotyping 1536 SNPs in a cohort of 343 persons with natural HCV clearance and 547 persons with HCV persistence. PLINK (version 1.05) and Haploview (version 4.1) software packages were used to perform association, permutation, and haplotype analyses stratified by African American and European American race. Of the 1536 SNPs tested, 1426 (92.8%) were successfully genotyped. In African Americans, we identified 18 SNPs located in 11 gene regions that were associated with HCV infection outcome (empirical P value, < .01). In European Americans, there were 20 SNPs located in 8 gene regions associated with HCV infection outcome. Four of the gene regions studied (TNFSF18, TANK, HAVCR1, and IL18BP) contained SNPs for which the empirical P value was < .01 in both of the race groups. In this large-scale analysis of 1426 genotyped SNPs in 112 candidate genes, we identified 4 gene regions that are likely candidates for a role in HCV clearance or persistence in both African Americans and European Americans.

### **La protein required for internal ribosome entry site-directed translation is a potential therapeutic target for hepatitis C virus replication.**

Shirasaki T, Honda M, Mizuno H, et al. *J Infect Dis.* 2010 May 24. [Epub ahead of print]

**BACKGROUND:** Translation of the hepatitis C virus (HCV) is mediated by an internal ribosome entry site (IRES). Here, we analyzed the functional relevance of La protein for replication of HCV using an infectious HCV clone, JFH-1. **METHODS:** A single-nucleotide mutation from A to U was introduced at the 338th nucleotide in the stem-loop domain IV structure of HCV IRES, which stabilized stem-loop IV and abolished translation and replication of JFH-1 almost completely. **RESULTS:** During JFH-1 replication, translation initiation factors required for HCV IRES activity, including La protein, polypyrimidine tract binding protein (PTB), PSMA7, and PCBP2, were significantly induced in Huh-7.5 cells. Interestingly, JFH-1 infection increased telomerase activity and induced the expression of human telomerase RNA (hTR) in Huh-7.5 cells. In 37 tissue specimens from patients with chronic hepatitis C, La protein

significantly correlated with the representative essential telomerase components hTR, p23, and HSP90 ([Formula: see text]). Recombinant adenovirus that expressed short-hairpin RNA against La protein successfully suppressed the levels of La protein and core protein of JFH-1 to 30% of that in the control cells. **CONCLUSIONS:** HCV infection might be strongly related to telomerase activity in the liver through La protein induction. Inhibition of La protein substantially repressed JFH-1 replication; therefore, La protein is a potential therapeutic target for HCV.

#### **Inhibition of hepatitis C virus replication by single-stranded RNA structural mimics.**

Smolic R, Smolic M, Andorfer JH, Wu CH, Smith RM, Wu GY. World J Gastroenterol. 2010 May 7;16(17):2100-8.

<http://www.ncbi.nlm.nih.gov/pubmed/20440850>

**AIM:** To examine the effect of hepatitis C virus (HCV) structural mimics of regulatory regions of the genome on HCV replication. **METHODS:** HCV RNA structural mimics were constructed and tested in a HCV genotype 1b aBB7 replicon, and a Japanese fulminant hepatitis-1 (JFH-1) HCV genotype 2a infection model. All sequences were computer-predicted to adopt stem-loop structures identical to the corresponding elements in full-length viral RNA. Huh7.5 cells bearing the BB7 replicon or infected with JFH-1 virus were transfected with expression vectors generating HCV mimics and controls. Cellular HCV RNA and protein levels were quantified by real-time polymerase chain reaction and Western blotting, respectively. To evaluate possible antisense effects, complementary RNAs spanning a mimic were prepared. **RESULTS:** In the BB7 genotype 1b replicon system, mimics of the polymerase (NS-5B), X and BA regions inhibited replication by more than 90%, 50%, and 60%, respectively. In the JFH-1 genotype 2 infection system, mimics that were only 74% and 46% identical in sequence relative to the corresponding region in JFH-1 inhibited HCV replication by 91.5% and 91.2%, respectively, as effectively as a mimic with complete identity to HCV genotype 2a. The inhibitory effects were confirmed by NS3 protein levels. Antisense RNA molecules spanning the 74% identical mimic had no significant effects. **CONCLUSION:** HCV RNA structural mimics can inhibit HCV RNA replication in replicon and infectious HCV systems and do so independent of close sequence identity with the target.

#### **Regulation of PKR by HCV IRES RNA: Importance of Domain II and NS5A.** Toroney R, Nallagatla SR, Boyer JA, Cameron CE, Bevilacqua PC. J Mol Biol. 2010 May 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20447405>

Protein kinase R (PKR) is an essential component of the innate immune response. In the presence of double-stranded RNA (dsRNA), PKR is autophosphorylated, which enables it to phosphorylate its substrate, eukaryotic initiation factor 2alpha, leading to translation cessation. Typical activators of PKR are long dsRNAs produced during viral infection, although certain other RNAs can also activate. A recent study indicated that full-length internal ribosome entry site (IRES), present in the 5'-untranslated region of hepatitis C virus (HCV) RNA, inhibits PKR, while another showed that it activates. We show here that both activation and inhibition by full-length IRES are possible. The HCV IRES has a complex secondary structure comprising four domains. While it has been demonstrated that domains III-IV activate PKR, we report here that domain II of the IRES also potently activates. Structure mapping and mutational analysis of domain II indicate that while the double-stranded regions of the RNA are important for

activation, loop regions contribute as well. Structural comparison reveals that domain II has multiple, non-Watson-Crick features that mimic A-form dsRNA. The canonical and noncanonical features of domain II cumulate to a total of approximately 33 unbranched base pairs, the minimum length of dsRNA required for PKR activation. These results provide further insight into the structural basis of PKR activation by a diverse array of RNA structural motifs that deviate from the long helical stretches found in traditional PKR activators. Activation of PKR by domain II of the HCV IRES has implications for the innate immune response when the other domains of the IRES may be inaccessible. We also study the ability of the HCV nonstructural protein 5a to bind various domains of the IRES and alter activation. A model is presented for how domain II of the IRES and NS5A operate to control host and viral translation during HCV infection.

**HCV NS5A activates the mammalian target of rapamycin (mTOR) pathway contributing to cell survival via disrupting the interaction between FK506-binding protein 38 (FKBP38) and mTOR.** Lu P, Liang D, Tong W, Li J, Yuan Z. J Biol Chem. 2010 May 3. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20439463>

Hepatitis C virus (HCV) often establishes a persistent infection which most likely involves complex host-virus interplay. We previously reported that the HCV nonstructural protein 5A (NS5A) binds to cellular protein FKBP38 and results in apoptosis suppression in human hepatoma cell line Huh7. In the present research, we further find that NS5A in Huh7 deprived of serum increases phosphorylation levels of two mTOR-targeted substrates, S6K1 and 4EBP1; mTOR inhibitor rapamycin, or NS5A knockdown blocks S6K1 and 4EBP1 phosphorylation increase in NS5A stably expressing Huh7 and HCV replicon cells, suggesting that NS5A specifically regulates mTOR activation. Overexpression of deleted mutants of NS5A in Huh7, and FKBP38 knockdown or PI3K inhibitor LY294002 treatment in NS5A-Huh7 and HCV replicon cells reveal this mTOR activation is dependent on NS5A-FKBP38 interaction, but independent of PI3K. Moreover, NS5A suppresses caspase 3 and PARP activation, which is abolished by NS5A knockdown or rapamycin, indicating NS5A inhibits apoptosis specifically through the mTOR pathway; further analyses suggest that apoptotic inhibition exerted by NS5A via mTOR also require NS5A-FKBP38 interaction. GST-pull down and coimmunoprecipitation show that NS5A disrupts the mTOR-FKBP38 association. Additionally, mutants of NS5A or FKBP38 does not affect the mTOR-FKBP38 interaction, which indicates the impairment of mTOR-FKBP38 association relays on NS5A-FKBP38 binding. Collectively, our data show that HCV NS5A activates mTOR pathway to inhibits apoptosis through impairing the interaction between mTOR and FKBP38, which may represent a pivotal mechanism for HCV persistence and pathogenesis.

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## **HIV/HCV COINFECTION**

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**Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients.** Rallón NI, Naggie S, Benito JM, et al. AIDS. 2010 May 15;24(8):F23-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20389235>

**BACKGROUND:** Given that peginterferon-ribavirin treatment is poorly tolerated, there is interest in the identification of predictors of response, particularly in HIV/hepatitis C virus

(HCV)-coinfecting patients that respond less than HCV-monoinfecting individuals. A single nucleotide polymorphism (SNP) near the IL28B gene (rs12979860) has been shown to predict treatment response in HCV-monoinfecting patients carrying genotype 1. Information is lacking for HIV/HCV-coinfecting individuals and/or other HCV genotypes. **METHODS:** From 650 HIV/HCV-coinfecting patients, we identified those who had completed a course of peginterferon-ribavirin therapy with a validated outcome and available repository DNA. The rs12979860 SNP was examined in a blinded fashion. **RESULTS:** A total of 164 patients were included in the final IL28B genotyping analysis, 90 (55%) of whom achieved sustained virological response (SVR). HCV genotype distribution was as follows: HCV-1 58%, HCV-3 31% and HCV-4 11%. Overall, the SVR rate was higher in patients with CC than in those CT/TT genotypes: 56 of 75 (75%) versus 34 of 89 (38%) ( $P < 0.0001$ ). The effect of the SNP was seen in HCV genotypes 1 and 4 but not in HCV genotype 3 carriers. In the multivariable analysis (odds ratio; 95% confidence interval;  $P$  value), the rs12979860 CC genotype was a strong predictor of SVR (3.7; 1.6-8.5; 0.002), independent of HCV genotype 3 (8.0; 3.1-21.0;  $<0.001$ ), serum HCV-RNA less than 600,000 IU/ml (11.9; 3.8-37.4;  $<0.001$ ) and lack of advanced liver fibrosis (3.5; 1.4-8.9; 0.009). **CONCLUSION:** The rs12979860 SNP located near the IL28B gene is associated with HCV treatment response in HIV-infected patients with chronic hepatitis C due to genotypes 1 or 4. Thus, IL28B genotyping should be considered as part of the treatment decision algorithm in this difficult-to-treat population.

**Hepatitis C seropositivity is not a risk factor for sensory neuropathy among patients with HIV.** Cherry CL, Affandi JS, Brew BJ, et al. *Neurology*. 2010 May 11;74(19):1538-42.

<http://www.ncbi.nlm.nih.gov/pubmed/20458071>

**BACKGROUND:** Sensory neuropathy (SN) is common in patients with HIV. Hepatitis C (HCV) coinfection is often cited as an HIV-SN risk factor, but data to support this are lacking. This collaboration aimed to examine the association between HCV serostatus and SN risk among ambulatory HIV-positive patients. **METHODS:** Patients with HIV were assessed in cross-sectional studies in Baltimore, Jakarta, Johannesburg, Kuala Lumpur, Melbourne, and Sydney for SN (defined by both supportive symptoms and signs). HCV seropositivity was assessed as an SN risk using a chi(2) test, followed by logistic regression modeling to correct for treatment exposures and demographics. **RESULTS:** A total of 837 patients of African, Asian, and Caucasian descent were studied. HCV seroprevalence varied by site (Baltimore  $n = 104$ , 61% HCV+; Jakarta 96, 51%; Johannesburg 300, 1%; Kuala Lumpur 97, 10%; Melbourne 206, 16%; Sydney 34, 18%). HCV seropositivity was not associated with increased SN risk at any site, but was associated with reduced SN risk in Melbourne ( $p = 0.003$ ). On multivariate analyses, the independent associations with SN were increasing age, height, and stavudine exposure. HCV seropositivity was not independently associated with an increased SN risk at any site, but associated independently with reduced SN risk in Baltimore ( $p = 0.04$ ) and Melbourne ( $p = 0.06$ ). **CONCLUSIONS:** Hepatitis C (HCV) seropositivity was not associated with increased sensory neuropathy risk among HIV-positive patients at any site. While we were unable to assess HCV RNA or liver damage, the data suggest that HCV coinfection is not a major contributor to HIV-SN. HCV = hepatitis C; SN = sensory neuropathy.

**Coinfection with hepatitis C virus, oxidative stress and antioxidant status in HIV-positive drug users in Miami.** Baum MK, Sales S, Jayaweera DT, et al. HIV Med. 2010 May 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20500231>

**BACKGROUND:** The pathogenesis of HIV/hepatitis C virus (HCV) coinfection is poorly understood. We examined markers of oxidative stress, plasma antioxidants and liver disease in HIV/HCV-coinfected and HIV-monoinfected adults. **METHODS:** Demographics, medical history, and proof of infection with HIV, hepatitis A virus (HAV), hepatitis B virus (HBV) and HCV were obtained. HIV viral load, CD4 cell count, complete blood count (CBC), complete metabolic panel, lipid profile, and plasma concentrations of zinc, selenium, and vitamins A and E were determined. Malondialdehyde (MDA) and glutathione peroxidase concentrations were obtained as measures of oxidative stress. Aminotransferase to platelet ratio index (APRI) and fibrosis index (FIB-4) markers were calculated. **RESULTS:** Significant differences were found between HIV/HCV-coinfected and HIV-monoinfected participants in levels of alanine aminotransferase (ALT) (mean $\pm$ standard deviation: 51.4 $\pm$ 50.6 vs. 31.9 $\pm$ 43.1 U/L, respectively; P=0.014), aspartate aminotransferase (AST) (56.2 $\pm$ 40.9 vs. 34.4 $\pm$ 30.2 U/L; P<0.001), APRI (0.52 $\pm$ 0.37 vs. 0.255 $\pm$ 0.145; P=0.0001), FIB-4 (1.64 $\pm$ 0.91 vs. 1.03 $\pm$ 0.11; P=0.0015) and plasma albumin (3.74 $\pm$ 0.65 vs. 3.94 $\pm$ 0.52 g/dL; P=0.038). There were no significant differences in CD4 cell count, HIV viral load or antiretroviral therapy (ART) between groups. Mean MDA was significantly higher (1.897 $\pm$ 0.835 vs. 1.344 $\pm$ 0.223 nmol/mL, respectively; P=0.006) and plasma antioxidant concentrations were significantly lower [vitamin A, 39.5  $\pm$  14.1 vs. 52.4 $\pm$ 16.2 mug/dL, respectively (P=0.0004); vitamin E, 8.29 $\pm$ 2.1 vs. 9.89 $\pm$ 4.5 mug/mL (P=0.043); zinc, 0.61 $\pm$ 0.14 vs. 0.67 $\pm$ 0.15 mg/L (P=0.016)] in the HIV/HCV-coinfected participants than in the HIV-monoinfected participants, and these differences remained significant after adjusting for age, gender, CD4 cell count, HIV viral load, injecting drug use and race. There were no significant differences in glutathione peroxidase concentration, selenium concentration, body mass index (BMI), alcohol use or tobacco use between groups. Glutathione peroxidase concentration significantly increased as liver disease advanced, as measured by APRI (beta=0.00118; P=0.0082) and FIB-4 (beta=0.0029; P=0.0177). Vitamin A concentration significantly decreased (beta=-0.00581; P=0.0417) as APRI increased. **CONCLUSION:** HIV/HCV coinfection is associated with increased oxidative stress and decreased plasma antioxidant concentrations compared with HIV monoinfection. Research is needed to determine whether antioxidant supplementation delays liver disease in HIV/HCV coinfection.

**Impact of highly active antiretroviral therapy on hepatitis C virus protease quasispecies diversity in HIV co-infected patients.** Winters MA, Chary A, Eison R, Asmuth D, Holodniy M. J Med Virol. 2010 May;82(5):791-8.

<http://www.ncbi.nlm.nih.gov/pubmed/20336744>

Many hepatitis C virus (HCV)-infected patients are also infected with HIV, and undergo antiretroviral (ARV) treatment for their human immunodeficiency virus (HIV) infection. Due to changes in HIV burden and immunologic status, HIV ARV treatment may have indirect effects on the HCV population, which could impact the effectiveness of subsequent HCV protease inhibitor (PI) treatment. The genetic variability of the protease-encoding HCV NS3 gene was evaluated in 10 co-infected patients initiating ARVs (both before and after ARV initiation), and compared to the genetic variability in 10 patients on stable ARV therapy. After RT-PCR of

plasma-derived HCV RNA, a mean of 20 clones per patient time-point were sequenced and analyzed for changes in the HCV quasispecies population. No significant differences in sequence diversity or complexity at the nucleic acid or amino acid levels were seen at baseline between groups or between the two time points in either group. HCV protease diversity in the pre- and post-ARV treatment samples was not significantly different than samples from patients on stable ARV therapy. There was no significant development of amino acid substitutions known to confer HCV PI resistance in either group. Initiation of ARV for HIV infection does not significantly alter the genetic diversity or complexity of the HCV NS3 gene or result in increased number of HCV PI-associated amino acid changes. **These results suggest** ARV treatment for HIV would not affect the efficacy of HCV PI treatment.

**Stronger hepatitis C virus-specific CD8(+) T-cell responses in HIV coinfection.** Barrett L, Gallant M, Howley C, Ian Bowmer M, Hirsch G, Peltekian K, Grant M. J Viral Hepat. 2010 May 20. [Epub ahead of print]

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

**SUMMARY:** Hepatitis C virus (HCV) is a widespread chronic infection that shares routes of transmission with human immunodeficiency virus (HIV). Thus, coinfection with these viruses is a relatively common and growing problem. In general, liver disease develops over years with HIV coinfection, when compared to decades in HCV mono-infection. The role of the immune system in the accelerated pathogenesis of liver disease in HIV/HCV coinfection is not clear. In this study, we compared the frequency, magnitude, breadth and specificity of peripheral blood CD4(+) and CD8(+) T-cell responses between HCV-mono-infected and HCV/HIV-coinfected individuals and between HIV/HCV-coinfected subgroups distinguished by anti-HCV antibody and HCV RNA status. While HIV coinfection tended to reduce the frequency and breadth of anti-HCV CD8(+) T-cell responses in general, responses that were present were substantially stronger than in mono-infection. In all groups, HCV-specific CD4(+) T-cell responses were rare and weak, independent of either nadir or concurrent CD4(+) T-cell counts of HIV-infected individuals. Subgroup analysis demonstrated restricted breadth of CD8(+) HCV-specific T-cell responses and lower B-cell counts in HIV/HCV-coinfected individuals without anti-HCV antibodies. The greatest difference between HIV/HCV-coinfected and HCV-mono-infected groups was substantially stronger HCV-specific CD8(+) T-cell responses in the HIV-coinfected group, which may relate to accelerated liver disease in this setting.

**Combined use of aspartate aminotransferase, platelet count and matrix metalloproteinase 2 measurements to predict liver fibrosis in HIV/hepatitis C virus-coinfected patients.**

Macías J, Mira JA, Gilabert I, et al. HIV Med. 2010 May 17. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20497249>

**OBJECTIVE:** Noninvasive tests that can be used in place of liver biopsy to diagnose fibrosis have major limitations. They either leave a significant proportion of patients without a definitive diagnosis or produce inaccurate results. Moreover, the performance of these tests is lower in HIV/hepatitis C virus (HCV) coinfection. Against this background, we examined the utility of serum matrix metalloproteinase 2 (MMP-2) and tissue inhibitor of metalloproteinase 1 (TIMP-1) measurements in combination with routine clinical data to predict fibrosis in HIV/HCV-coinfected patients. **METHODS:** Patients with a liver biopsy who had not received anti-HCV therapy were included in the study. A model including variables independently associated with fibrosis was constructed. Diagnostic accuracy was determined by measuring the area under the

receiver operating characteristic curve (AUROC). Positive (PPV) and negative (NPV) predictive values were calculated. **RESULTS:** Ninety patients were included in the study. Aspartate aminotransferase (AST), platelet count and MMP-2 were predictors of significant fibrosis (F $\geq$ 2) and cirrhosis (F4). A score constructed using these variables yielded an AUROC of 0.76 for F $\geq$ 2 and 0.88 for F4. Score cut-offs detected (value  $\geq$ 3.5) and excluded (value  $\leq$ 1.5) F $\geq$ 2 with a PPV of 87% and an NPV of 88%. Thirty-one patients (34%) were correctly diagnosed using these cut-offs, with four (13%) incorrect classifications. Cirrhosis was excluded with a certainty of 98% and diagnosed with a probability of 83%. Two (17%) of 12 patients were misclassified as having cirrhosis. The AST to platelet count index and MMP-2 levels were sequentially applied to detect F $\geq$ 2. Forty-one patients (46%) were identified with this approach, with six (15%) misclassifications. **CONCLUSION:** MMP-2 levels can be used in combination with AST and platelet count to aid the diagnosis of liver fibrosis in HIV/HCV-coinfected patients.

**Mitochondrial toxicity is associated with virological response in patients with HIV and hepatitis C Virus coinfection treated with ribavirin and highly active antiretroviral therapy.** Reiberger T, Kosi L, Maresch J, et al. J Infect Dis. 2010 May 20. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20486858>

The combination of highly active antiretroviral therapy (HAART) plus ribavirin (RBV) in patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection has been reported to cause mitochondrial toxicity (MT). Sixty-four patients with HIV-HCV coinfection who were receiving antiviral therapy were evaluated for MT. Patients with concomitant HAART showed greater increases in lactate levels than did patients without HAART, and this difference was more pronounced in patients who received higher dosages of RBV. The incidence of pancreatic enzyme elevations and symptomatic pancreatitis was higher among patients who received HAART and high-dose RBV. Hepatic steatosis increased in patients who received HAART and high-dose RBV. Patients who showed signs of MT achieved higher rates of sustained virologic response than did patients without MT (73% vs 44%).

**Impact of hepatitis C viral replication on CD4+ T-lymphocyte progression in HIV-HCV coinfection before and after antiretroviral therapy.** Potter M, Oduyungbo A, Yang H, et al. AIDS. 2010 May 14. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/sites/entrez>

**OBJECTIVE:** HIV is known to have a negative impact on the progression of hepatitis C virus (HCV) infection, whereas the reverse remains unclear. We examined the impact of spontaneous clearance of HCV on CD4 T-lymphocyte count progression before and after initiation of antiretroviral therapy (ART) in HIV-HCV coinfecting adults. **METHODS:** Data were analysed from participants in a Canadian, multisite prospective cohort of HIV-infected adults with serologic evidence of HCV infection. The rate of CD4 T-lymphocyte change was determined using multivariate mixed linear regression comparing chronically HCV RNA+ with spontaneous clearers (persistently HCV RNA- without HCV therapy). **RESULTS:** Baseline characteristics of the 271 participants analysed did not differ between individuals whose HCV RNA cleared (n = 35) and those whose HCV RNA persisted (n = 236) except with respect to markers of liver disease. HCV RNA+ individuals had on average seven-times slower recovery of CD4 T-cells on chronic ART compared with HCV RNA-: (adjusted change in absolute CD4 cell T-lymphocyte count per year: 4 (95% confidence interval, -0.6 to 8) cells/ $\mu$ l vs. 26 (95% confidence interval,

12 to 41) cells/mul;  $P < 0.001$ . Analyses restricted to individuals initiating ART showed similar results. There was also a trend to greater CD4 decline prior to ART initiation among those HCV RNA+, although this did not reach statistical significance. **CONCLUSION:** We found that CD4 cell progression is negatively affected by the presence of ongoing HCV replication in coinfecting individuals initiating ART which persisted throughout stable ART suggesting active HCV infection affects immune restoration even after years of ART exposure.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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**Nutrigenomics Therapy of Hepatitis C Virus Hepatosteatosis.** Qing L, Bengmark S, Shen Q. BMC Gastroenterol. 2010 May 20;10(1):49. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20487553>

Nutrigenomics is a relatively new branch of nutrition science, which aim is to study the impact of the foods we eat on the function of our genes. Hepatosteatosis is strongly associated with hepatitis C virus infection, which is known to increase the risk of the disease progression and reduce the likelihood of responding to anti-virus treatment. It is well documented that hepatitis C virus can directly alter host cell lipid metabolism through nuclear transcription factors. To date, only a limited number of studies have been on the effect of human foods on the nuclear transcription factors of hepatitis C virus-induced hepatosteatosis. Three nutrients, selected among 46 different nutrients: beta-carotene, vitamin D2, and linoleic acid were found in a cell culture system to inhibit hepatitis C virus RNA replication. In addition, polyunsaturated fatty acids (PUFAs) especially arachidonic acid (AA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) have been demonstrated to inhibit hepatitis C virus RNA replication. These PUFAs, in particular the highly unsaturated n-3 fatty acids change the gene expression of PPAR $\alpha$  and SREBP, suppress the expression of mRNAs encoding key metabolic enzymes and hereby suppress hepatic lipogenesis and triglyceride synthesis, as well as secretion and accumulation in tissues. A recent prospective clinical trial of 1,084 chronic hepatitis C patients compared to 2,326 healthy subjects suggests that chronic hepatitis C patients may benefit from strict dietary instructions. Increasing evidence suggest that some crucial nuclear transcription factors related to hepatitis C virus-associated hepatosteatosis and hepatitis C virus RNA itself can be controlled by specific anti-hepatitis C virus nutrition. It seems important that these findings are taken into account and specific nutritional supplements developed to be used in combination with interferon as adjunctive therapy with the aim to improve both the early as well as the sustained virological response.

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Hepatocellular carcinoma - United States, 2001-2006.** Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 2010 May 7;59(17):517-20.

<http://www.ncbi.nlm.nih.gov/pubmed/20448528>

Liver cancer, primarily hepatocellular carcinoma (HCC), is the third leading cause of death from cancer worldwide and the ninth leading cause of cancer deaths in the United States. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections account for an estimated 78% of global HCC cases. To determine trends in HCC incidence in the United States, CDC analyzed data for the period 2001-2006 (the most recent data available) from CDC's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and

End Results (SEER) surveillance system. This report summarizes the results of that analysis, which determined that the average annual incidence rate of HCC for 2001-2006 was 3.0 per 100,000 persons and increased significantly from 2.7 per 100,000 persons in 2001 to 3.2 in 2006, with an average annual percentage change in incidence rate (APC) of 3.5%. The largest increases in HCC incidence rates were among whites (APC = 3.8), blacks (APC = 4.8), and persons aged 50-59 years (APC = 9.1). Among states, HCC incidence rates varied widely, ranging from 1.4 per 100,000 in South Dakota to 5.5 in Hawaii. The results demonstrate a continuation of long-term increases in HCC incidence and persistent HCC racial/ethnic disparities. Development of viral hepatitis services, including screening with care referral for persons chronically infected with HBV or HCV, full implementation of vaccine-based strategies to eliminate hepatitis B, and improved public health surveillance are needed to help reverse the trend in HCC.

### **Challenge pools of hepatitis C virus genotypes 1-6 prototype strains: replication fitness and pathogenicity in chimpanzees and human liver-chimeric mouse models.**

Bukh J, Meuleman P, Tellier R, et al. *J Infect Dis.* 2010 May 1;201(9):1381-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20353362>

Chimpanzees represent the only animal model for studies of the natural history of hepatitis C virus (HCV). To generate virus stocks of important HCV variants, we infected chimpanzees with HCV strains of genotypes 1-6 and determined the infectivity titer of acute-phase plasma pools in additional animals. The courses of first- and second-passage infections were similar, with early appearance of viremia, HCV RNA titers of >10(4.7) IU/mL, and development of acute hepatitis; the chronicity rate was 56%. The challenge pools had titers of 10(3)-10(5) chimpanzee infectious doses/mL. Human liver-chimeric mice developed high-titer infections after inoculation with the challenge viruses of genotypes 1-6. Inoculation studies with different doses of the genotype 1b pool suggested that a relatively high virus dose is required to consistently infect chimeric mice. The challenge pools represent a unique resource for studies of HCV molecular virology and for studies of pathogenesis, protective immunity, and vaccine efficacy *in vivo*.

**Prospective follow-up of patients with acute hepatitis C virus infection in Brazil.** Lewis-Ximenez LL, Lauer GM, Schulze Zur Wiesch J, et al. *Clin Infect Dis.* 2010 May 1;50(9):1222-30.

<http://www.ncbi.nlm.nih.gov/pubmed/20235831>

**BACKGROUND:** The natural outcome of infection with hepatitis C virus (HCV) varies substantially among individuals. However, little is known about host and viral factors associated with a self-limiting or chronic evolution of HCV infection. **METHODS:** From 1 January 2001 through 31 December 2008, a consecutive series of 65 patients from Rio de Janeiro, Brazil, with a well-documented diagnosis of acute HCV infection, acquired via various routes, were enrolled in this study. Patients were prospectively followed up for a median of 40 months after the estimated date of HCV infection with serial measurements of serum alanine aminotransferase, HCV RNA, and anti-HCV antibodies. Spontaneous viral clearance (SVC) was defined as undetectable levels of HCV RNA in serum, in the absence of treatment, for 3 consecutive HCV polymerase chain reaction tests within the first 6 months of follow-up. Cox proportional hazards regression was used to identify host and viral predictors of SVC. **RESULTS:** The cumulative rate of SVC was 44.6% (95% confidence interval, 32.3%-57.5%). Compared with chronic HCV evolution, patients with self-limiting disease had significantly lower peak levels of anti-HCV antibodies (median, 109.0 vs 86.7 optical density-to-cutoff ratio [od/co];  $P < .02$ ), experienced

disease symptoms more frequently (69.4% vs 100%;  $P < .001$ ), and had lower viral load at first clinical presentation (median, 4.3 vs 0.0 log copies;  $P = .01$ ). In multivariate analyses, low peak anti-HCV level ( $< 93.5$  od/co) was the only independent predictor for SVC; the hazard ratio compared with high anti-HCV levels ( $>$  or  $= 93.5$  od/co) was 2.62 (95% confidence interval, 1.11-6.19;  $P = .03$ ). **CONCLUSION:** Our data suggest that low levels of anti-HCV antibodies during the acute phase of HCV infection are independently related to spontaneous viral clearance.

### **Hepatitis C testing practices and prevalence in a high-risk urban ambulatory care setting.**

Southern WN, Drainoni ML, Smith BD, et al. J Viral Hepat. 2010 May 20. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20497311>

**SUMMARY:** Approximately 3.2 million persons are chronically infected with the hepatitis C virus (HCV) in the U.S.; most are not aware of their infection. Our objectives were to examine HCV testing practices to determine which patient characteristics are associated with HCV testing and positivity, and to estimate the prevalence of HCV infection in a high-risk urban population. The study subjects were all patients included in the baseline phase of the Hepatitis C Assessment and Testing Project (HepCAT), a serial cross-sectional study of HCV screening strategies. We examined all patients with a clinic visit to Montefiore Medical Center from 1/1/08 to 2/29/08. Demographic information, laboratory data and ICD-9 diagnostic codes from 3/1/97-2/29/08 were extracted from the electronic medical record. Risk factors for HCV were defined based on birth date, ICD-9 codes and laboratory data. The prevalence of HCV infection was estimated assuming that untested subjects would test positive at the same rate as tested subjects, based on risk-factors. Of 9579 subjects examined, 3803 (39.7%) had been tested for HCV and 438 (11.5%) were positive. The overall prevalence of HCV infection was estimated to be 7.7%. Risk factors associated with being tested and anti-HCV positivity included: born in the high-prevalence birth-cohort (1945-64), substance abuse, HIV infection, alcohol abuse, diagnosis of cirrhosis, end-stage renal disease, and alanine transaminase elevation. In a high-risk urban population, a significant proportion of patients were tested for HCV and the prevalence of HCV infection was high. Physicians appear to use a risk-based screening strategy to identify HCV infection.

### **Hepatitis C virus risk behaviors within the partnerships of young injecting drug users.**

Hahn JA, Evans JL, Davidson PJ, Lum PJ, Page K. Addiction. 2010 May 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20491725>

**AIMS:** Young injection drug users (IDU) are at high risk for hepatitis C virus (HCV). We sought to determine whether perceiving one's injecting partner to be HCV positive was associated with decreased odds of engaging in receptive needle/syringe sharing (RNS) or ancillary equipment sharing (AES) with that partner. **DESIGN:** Cross sectional study. Setting 2003 to 2007 in San Francisco. Participants 212 young (under age 30) IDU who were HCV antibody negative reported on 492 injecting partnerships. Measurements Self-reported RNS and AES within injecting partnerships. **FINDINGS:** RNS and AES (in the absence of RNS) occurred in 23% and 64% of injecting partnerships in the prior month. The odds of engaging in RNS were significantly lower for relationships in which the participant reported that his/her partner was HCV positive (odds ratio [OR] 0.49; 95% confidence interval [CI] 0.25-0.95). This association was attenuated when adjusted for reusing one's own needle/syringe (adjusted OR 0.57; 95% CI

0.28-1.15). The odds of engaging in AES were lower for participants who did not know the HCV status of their partner, only among non-sexual partnerships (OR 0.47; 95% CI 0.29-0.76).

**CONCLUSIONS:** Because perceiving one's partner to be HCV positive was associated with decreased RNS, increased HCV testing and partner disclosure may be warranted. AES was common and was decreased only among non-sexual partnerships in which the HCV status of the partner was not known. This suggests that interventions to reduce AES in young IDU must be widespread.

**Socio-behavioral and geographic correlates of prevalent hepatitis C virus infection among young injection drug users in metropolitan Baltimore and Chicago.** Boodram B, Golub ET, Ouellet LJ. Drug Alcohol Depend. 2010 May 14. [Epub ahead of print]

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**BACKGROUND:** Hepatitis C virus (HCV) infection prevalence among young injection drug users (IDUs) differs substantially between cities in the United States (U.S.). **METHODS:** Between 2002 and 2004, IDUs aged 15-30 were recruited for the Third Collaborative Injection Drug User Study in five U.S. cities using respondent-driven methods. Our cross-sectional study examined correlates and geographic distribution of prevalent HCV infection (HCV+) from the Baltimore (n=736) and Chicago (n=586) study sites. We evaluated baseline socio-demographic and behavioral data collected from computer-assisted self-interviews and serological antibody testing for human immunodeficiency virus (HIV) and hepatitis A, B, and C. **RESULTS:** HCV prevalence was 53.0% in Baltimore and 13.7% in Chicago ( $p<0.0001$ ). Baltimore compared to Chicago participants were significantly ( $p<0.05$ ) more likely to be older, co-infected with HIV and other hepatitis viruses, reside in an urban area, inject primarily cocaine, inject in public settings, inject with used syringes and paraphernalia, and have been injecting longer; they were less likely to utilize syringe exchange programs. However, after accounting for socio-demographic and behavioral risk factors in multivariable logistic regression, city was the strongest predictor of HCV prevalence (Baltimore versus Chicago adjusted odds ratio=3.5 [95% confidence interval, 2.2-5.6]). Geospatial analyses showed that almost half of all HCV+ participants in Baltimore resided within a 5-mile urban area, while Chicago participants were dispersed across the metropolitan area. **CONCLUSIONS:** The disparate HCV prevalence between the two cities is only partially explained by individual-level factors. Future studies should examine the network configurations and injection partners' characteristics of young IDUs.