

Caring Ambassadors Hepatitis C Program Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Integrated internist - addiction medicine - hepatology model for hepatitis C management for individuals on methadone maintenance. Martinez AD, Dimova R, Marks KM, et al. J Viral Hepat. 2010 Dec 3. doi: 10.1111/j.1365-2893.2010.01411.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21129131>

Despite a high prevalence of hepatitis C virus (HCV) among drug users, HCV evaluation and treatment acceptance are extremely low among these patients when referred from drug treatment facilities for HCV management. We sought to increase HCV treatment effectiveness among patients from a methadone maintenance treatment program (MMTP) by maintaining continuity of care. We developed, instituted and retrospectively assessed the effectiveness of an integrated, co-localized care model in which an internist-addiction medicine specialist from MMTP was embedded in the hepatitis clinic. Methadone maintenance treatment program patients were referred, evaluated by the internist and hepatologist in hepatitis clinic and provided HCV treatment with integration between both sites. Of 401 evaluated patients, anti-HCV antibody was detected in 257, 86% of whom were older than 40 years. Hepatitis C virus RNA levels were measured in 222 patients, 65 of whom were aviremic. Of 157 patients with detectable HCV RNA, 125 were eligible for referral to the hepatitis clinic, 76 (61%) of whom accepted and adhered with the referral. Men engaged in MMTP <36 months were significantly less likely to be seen in hepatitis clinic than men in MMTP more than 36 months (odds ratio = 7.7; 95% confidence interval 2.6-22.9) or women. We evaluated liver histology in 63 patients, and 83% had moderate to advanced liver disease. Twenty-four patients initiated treatment with 19 completing and 13 (54%) achieving sustained response. In conclusion, integrated care between the MMTP and the hepatitis clinic improves adherence with HCV evaluation and treatment compared to standard referral practices.

Hepatitis C virus-related kidney disease: various histological patterns. Sumida K, Ubara Y, Hoshino J, et al. Clin Nephrol. 2010 Dec;74(6):446-56.

<http://www.ncbi.nlm.nih.gov/pubmed/21084048>

BACKGROUND: Although hepatitis C virus (HCV) infection is known to be associated with Type 2 cryoglobulinemic glomerulopathy (CG), only a few reports about other types of nephropathy have been published. **METHODS:** 68 HCV antibody positive patients in whom renal biopsy had been performed for persistent proteinuria, hematuria, and/or renal dysfunction

between 1992 and 2008 at our institute were included. The histological, clinical and laboratory characteristics including the age, gender, hypertension, diabetes mellitus, liver histology (chronic hepatitis or liver cirrhosis), HCV-RNA, HCV genotype, splenomegaly, gastroesophageal varices, serum creatinine, hemoglobin, platelet count, rheumatoid factor, cryoglobulin, IgG, IgA, IgM, CH50, C3, C4, creatinine clearance, 24-h protein excretion, and hematuria, between their nephropathy with and without immune deposition were compared. **RESULTS:** Nephropathy was classified into two groups based on the detection of immune deposits by immunofluorescence microscopy: i.e., a positive group (n = 39) and a negative group (n = 29). The former group was further classified into three types of nephropathy: IgG dominant group (n = 10) (including membranous nephropathy (MN)), IgA dominant group (n = 20) (including IgA nephropathy (IgAN)), membranoproliferative glomerulonephritis (MPGN) (IgA type)), and IgM dominant group (n = 9) (MPGN apart from the IgA type). The latter group included diabetic nephropathy (n = 13), focal glomerular sclerosis (n = 4), and benign nephrosclerosis (n = 3), malignant nephrosclerosis (n = 1), tubulointerstitial nephritis (TIN) (n = 2), minimal change nephrotic syndrome (n = 1), cast nephropathy (n = 1), granulomatous TIN (n = 1), and others (n = 3). An increased serum IgM level, hypocomplementemia, splenomegaly, thrombocytopenia, liver cirrhosis, hematuria, and a high HCV RNA level were features of patients with MPGN of IgM dominant group (consistent with "CG"). **CONCLUSIONS:** Our results showed various histological patterns of HCV-related kidney disease and the specificity of CG, and revealed that a minority of HCV patients (n = 7) presented typical CG, while IgAN, MN, and diabetic nephropathy were more frequent.

Early Menopause is Associated with Lack of Response to Antiviral Therapy in Women with Chronic Hepatitis C. Villa E, Karampatou A, Cammà C, et al. *Gastroenterology*. 2010 Dec 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21167831>

BACKGROUND & AIMS: Chronic hepatitis c (CHC) and liver fibrosis progress more rapidly in men and menopausal women than in women of reproductive age. We investigated the associations among menopause, sustained virological response (SVR), and liver damage in patients with CHC. **METHODS:** We performed a prospective study of 1000 consecutive, treatment-naïve patients ≥ 18 years old with compensated liver disease from CHC. Liver biopsy samples were analyzed (for fibrosis, inflammation, and steatosis) before patients received standard antiviral therapy. From women (n = 442), we collected data on the presence, type, and timing of menopause; associated hormone and metabolic features; serum levels of interleukin-6 (IL-6); and hepatic tumor necrosis factor- α (TNF- α). **RESULTS:** Post-menopausal women achieved SVRs less frequently than women of reproductive age (46.0% vs. 67.5%, $P < .0001$) but as frequently as men (51.1%, $P = .178$). By multivariate regression analysis, independent significant predictors for women to not achieve an SVR were early menopause (odds ratio [OR]=8.055; 95% confidence interval [CI], 1.834-25.350), levels of γ -glutamyl transpeptidase (OR=2.165, 95% CI, 1.3643-.436), infection with hepatitis C virus (HCV) genotypes 1 or 4 (OR=3.861; 95% CI, 2.433-6.134), and cholesterol levels (OR=0.967; 95% CI 0.943-0.991). Early menopause was the only independent factor that predicted lack of an SVR among women with genotype 1 HCV infection (OR=3.933; 95% CI, 1.274-12.142). Baseline levels of liver inflammation, fibrosis, steatosis, serum IL-6 ($P = .04$), and hepatic TNF- α ($P = .007$) were significantly higher among post-menopausal than women of reproductive age.

CONCLUSIONS: Among women with CHC, early menopause was associated with a low likelihood of SVR, probably because of inflammatory factors that change at menopause.

Increasing Prevalence of HCC and Cirrhosis in Patients with Chronic Hepatitis C Virus

Infection. Kanwal F, Hoang T, Kramer JR, et al. *Gastroenterology*. 2010 Dec 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21184757>

BACKGROUND & AIMS: Patients with hepatitis C virus (HCV) infection are at risk for developing additional liver disorders that are costly to treat and have high rates of morbidity, although the actual prevalence of these diseases is not known. We examined time trends in the prevalence of cirrhosis and its related complications, such as hepatic decompensation and hepatocellular cancer (HCC). **METHODS:** We calculated the annual prevalence of cirrhosis, decompensated cirrhosis, and HCC in a national sample of veterans diagnosed with HCV between 1996 and 2006. Patients with HCV who had at least 1 physician visit in a given calendar year were included in the analysis of prevalence for that year. We used direct standardization to adjust the prevalence of cirrhosis and related complications for increasing age of the cohort, as well as sex and changes in clinical characteristics. **RESULTS:** In this cohort, the number of individuals with HCV increased from 17,261 in 1996 to 106,242 in 2006. The prevalence of cirrhosis increased from 9% in 1996 to 18.5% in 2006. Similarly, the prevalence of patients with decompensated cirrhosis doubled, from 5% in 1996 to 11% in 2006, whereas the prevalence of HCC increased approximately 20-fold (0.07% in 1996 to 1.3% in 2006). After adjustment, the time trend in the prevalence of cirrhosis (and its complications) was lower than the crude trend, although it still increased significantly. **CONCLUSIONS:** The prevalence of cirrhosis and HCC in HCV-infected patients has increased significantly over the past 10 years, and could increase further. An aging cohort of HCV patients could partly explain our findings. Clinicians and healthcare systems should develop strategies to provide timely and effective care to this high-risk population of patients.

Hepatitis C virus and alcohol: Same mitotic targets but different signaling pathways.

Alisi A, Ghidinelli M, Zerbini A, Missale G, Balsano C. *J Hepatol*. 2010 Dec 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21145809>

BACKGROUND & AIMS: Chromosomal aberrations are frequently observed in hepatitis C virus (HCV)- and alcohol-related hepatocellular carcinomas (HCCs). The mechanisms by which chromosomal aberrations occur during hepatocarcinogenesis are still unknown. However, these aberrations are considered to be the result of deregulation of some mitotic proteins, including the alteration of Cyclin B1 and Aurora kinase A expression, and the phosphorylation of gamma-tubulin. Our study aims at investigating changes in expression of the above mentioned proteins and related intracellular pathways, in in vitro and in vivo models of both HCV- and alcohol-dependent HCCs. **METHODS:** In this study, the molecular defects and the mechanisms involved in deregulation of the mitotic machinery were analyzed in human hepatoma cells, expressing HCV proteins treated or not with ethanol, and in liver tissues from control subjects (n=10) and patients with HCV- (n=10) or alcohol-related (n=10) HCCs. **RESULTS:** Expression of Cyclin B1, Aurora kinase A, and tyrosine-phosphorylated gamma-tubulin was analyzed in models reproducing HCV infection and ethanol treatment in HCC cells. Interestingly, HCV and alcohol increased the expression of Cyclin B, Aurora kinase A, and tyrosine-phosphorylated

gamma-tubulin also in tissues from patients with HCV- or alcohol-related HCCs. In vitro models suggest that HCV requires the expression of PKR (RNA-activated protein kinase), as well as JNK (c-Jun N-terminal kinase) and p38MAPK (p38 mitogen-activated protein kinase) proteins; while, ethanol bypasses all these pathways. **CONCLUSIONS:** Our results support the idea that HCV and alcohol may promote oncogenesis by acting through the same mitotic proteins, but via different signaling pathways.

Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy.

Oze T, Hiramatsu N, Yakushijin T, et al. J Hepatol. 2010 Dec 8. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/21145907>

BACKGROUND & AIMS: This study investigated the efficacy and adverse effects of pegylated interferon (Peg-IFN) plus ribavirin therapy in aged patients with chronic hepatitis C (CH-C). **METHODS:** A total of 1040 naïve patients with CH-C (genotype 1, n=759; genotype 2, n=281), of whom 240 (23%) over 65years old (y.o.), were treated with Peg-IFN alfa-2b plus ribavirin and assessed after being classified into five categories, according to age. **RESULTS:** The discontinuance rate was higher for patients over 70 y.o. (36%), the most common reason being anemia. In the presence of genotype 1, the SVR rate was similar (42-46%) among patients under 65 y.o. and declined (26-29%) among patients over 65 y.o. For patients over 65 y.o., being male (Odds ratio, OR, 3.5, p=0.035) and EVR (OR, 83.3, p<0.001) were significant factors for SVR, in multivariate analysis. The Peg-IFN dose was related to EVR, and when EVR was attained, 76-86% of patients over 65 y.o. achieved SVR. SVR was not achieved (0/35, 0/38, respectively) if a 1-log decrease and a 2-log decrease were not attained at week 4 and week 8, respectively. In the presence of genotype 2, the SVR rate was similar (70-71%) among patients under 70 y.o. and declined among patients over 70 y.o. (43%). **CONCLUSIONS:** Aged patients up to 65 y.o. with genotype 1 and 70 y.o. with genotype 2 can be candidates for pegylated interferon (Peg-IFN) plus ribavirin therapy. The response-guided therapy can be applied for aged patients with genotype 1.

The Effects of Angiotensin Blocking Agents on the Progression of Liver Fibrosis in the HALT-C Trial Cohort. Abu Dayyeh BK, Yang M, Dienstag JL, Chung RT. Dig Dis Sci. 2010 Dec 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21136163>

BACKGROUND: Therapies that can slow the progression of liver fibrosis in chronic liver disease are needed. Evidence suggests that the renin-angiotensin system (RAS) contributes to inflammation and fibrosis in chronic liver disease. Both animal and limited human studies have shown that RAS inhibition with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor-1 [AT-1] blockers (ARBs) has antifibrogenic properties. **AIMS:** In this study, we evaluated the effects of continuous ACEi/ARB use for 3.5 years on histological liver fibrosis progression in the HALT-C Trial cohort. **METHODS:** In the HALT-C Trial, subjects with chronic hepatitis C and advanced hepatic fibrosis (Ishak stage ≥ 3) underwent serial liver biopsies at baseline, 1.5 years, and 3.5 years after randomization. The primary outcome was a ≥ 2 -point increase in Ishak fibrosis score in at least one of the two serial biopsies. Sixty-six subjects were continuously taking ACEi/ARBs over the observation period, 126 were taking other antihypertensive medications, and 343 subjects took no antihypertensive medications.

RESULTS: The three groups were similar in baseline fibrosis scores, and the two groups being treated with antihypertensives were taking a similar number of antihypertensive medications. Fibrosis progression occurred in 33.3% of the ACEi/ARB group, 32.5% of the other antihypertensive medications group, and in 25.7% of subjects taking no antihypertensive medications. No significant associations between ≥ 2 -point increases in fibrosis scores and continuous ACEi/ARB use were apparent at either 1.5 or 3.5 years in diabetes-adjusted and unadjusted odds ratios. **CONCLUSIONS:** ACEi/ARB therapy did not retard the progression of hepatic fibrosis.

Glucose control and lipid metabolism in African American patients with type 2 diabetes and chronic hepatitis C. Zambare S, Samantray J, Seyoum B, Abou-Samra AB. *Endocr Pract.* 2010 Dec 6:1-19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21134881>

OBJECTIVE: Metabolic abnormalities are common in chronic hepatitis C infection. Understanding the interaction between hepatitis C infection, serum lipids and glucose metabolism in African American population is important because of the high prevalence of hepatitis C in inner city populations. **The aim of this study** was to compare the lipid profile, glucose control in this population with type 2 diabetes with and without chronic hepatitis C infection (HCV). **METHODS:** Retrospective dataset analyses of 283 African American patients in an academic outpatient setting, of whom 111 patients had Type 2 diabetes and HCV, 68 patients had HCV, and 104 patients had type 2 diabetes. Serum total, LDL and HDL cholesterol, triglyceride were compared in all three patient groups. **RESULTS:** Chronic HCV was associated with lower total and LDL cholesterol levels in the patients with or without type 2 diabetes. In contrast, the elevated serum triglyceride levels associated with diabetes were not reduced in patients with chronic HCV, although diabetes control was better in the diabetes group with HCV than the diabetes group without HCV (A1C: $7.1 \pm 1.8\%$ vs $8.8 \pm 2.1\%$, $p < 0.001$). The HDL cholesterol level was higher in the patients with earlier stages of HCV when compared to the other two groups. **CONCLUSIONS:** Chronic HCV infection in type 2 diabetes patients decreases serum levels of total and LDL cholesterol, but has no such protective effect on triglyceride levels. HCV infection may differently alter the cellular pathways of cholesterol and triglyceride metabolism in patients with type 2 diabetes.

Neutralizing antibodies to interferon- α and circulating interferon in patients with chronic hepatitis C non-responding to pegylated interferon plus ribavirin re-treated by pegylated interferon- α -2a and ribavirin (ANRS HC16 GAMMATRI substudy). Halfon P, Pérusat S, Bourlière M, et al. *J Med Virol.* 2010 Dec;82(12):2027-31.

<http://www.ncbi.nlm.nih.gov/pubmed/20981789>

A lack of antiviral response in patients with chronic hepatitis C treated with pegylated (PEG)-interferon (IFN)- α -2a + ribavirin (RIBA) may be explained by neutralizing antibodies to IFN- α -2a. **The aim** of this study was to assess neutralizing antibodies to IFN- α -2a and IFN levels in non-responder patients who were re-treated by PEG IFN- α -2a and RIBA for 12 weeks. Non-responders to a first-line treatment of PEG IFN- α -2a + RIBA were included for treatment with PEG IFN- α -2a (180 μ g/week) + RIBA (1,000 mg/day if < 75 kg, 1,200 mg otherwise) for 48 weeks. HCV RNA was measured at week 12. IFN levels and neutralizing antibodies to IFN- α -2a were measured retrospectively on stored sera at baseline and weeks 4 and 12, using a quantitative sandwich ELISA for neutralizing antibodies to IFN- α -2a. Twenty-three patients were non-

responders and 19 patients were responders at week 12 of the initial phase of the second-line treatment. Non-responders and responders did not differ statistically: baseline age (median age 47 vs. 50 years), HCV RNA (median 6.8 vs. 6.4 log₁₀ copies/ml), gender (70% vs. 73% males), genotype (genotype 1: 91% vs. 80%). The median IFN- α -2a levels (pg/ml) at weeks 0, 4, and 12 (interquartile range) did not differ between the 19 responders to initial phase of second-line treatment and the 23 non-responders: <3.3 (<3.3-371.4), 1457.3 (106.8-3284.8), and 1,652 (90.8-5,000); 84.5 (3.3-277.4), 1407.4 (120.2-2443.4), and 1620.1 (120.2-2287.1), respectively. Among non-selected consecutive non-responder patients, re-treatment with PEG IFN- α -2a + RIBA is associated with virological response regardless of the presence of antibody-mediated resistance to conventional IFN treatment.

Hepatitis C virus infection and increased risk of cerebrovascular disease. Lee MH, Yang HI, Wang CH, et al. Stroke. 2010 Dec;41(12):2894-900. Epub 2010 Oct 21.

<http://www.ncbi.nlm.nih.gov/pubmed/20966408>

BACKGROUND AND PURPOSE: The association between hepatitis C virus (HCV) infection and cerebrovascular disease remains controversial. This study aimed to assess the risk of lethal cerebrovascular diseases associated with chronic HCV infection. **METHODS:** In this community-based prospective cohort study, 23 665 residents (aged 30 to 65 years) were enrolled in 1991 to 1992. They were personally interviewed using structured questionnaires and provided blood samples for various serological and biochemical tests at study entry. Serum HCV RNA level and HCV genotype were tested for participants seropositive for antibodies against HCV (anti-HCV). Deaths from cerebrovascular disease during follow-up were ascertained by computerized linkage with National Death Certification profiles from 1991 to 2008 (International Classification of Diseases, 9th Revision 430 to 438). Multivariate-adjusted hazard ratio with 95% CI was estimated for each risk predictor. **RESULTS:** There were 255 cerebrovascular deaths during 382 011 person-years of follow-up. The cumulative risk of cerebrovascular deaths was 1.0% and 2.7% for seronegatives and seropositives of anti-HCV, respectively (P<0.001). The hazard ratio (95% CI) of cerebrovascular death was 2.18 (1.50 to 3.16) for anti-HCV seropositives after adjustment for several conventional risk factors of cerebrovascular disease. Compared with participants seronegative for anti-HCV as the referent, the multivariate-adjusted hazard ratio (95% CI) was 1.40 (0.62 to 3.16), 2.36 (1.42 to 3.93), and 2.82 (1.25 to 6.37), respectively, for anti-HCV-seropositive participants with undetectable, low, and high serum levels of HCV RNA (P<0.001 for trend). However, no significant association was observed between HCV genotype and cerebrovascular death. **CONCLUSIONS:** Chronic HCV infection is an independent risk predictor of cerebrovascular deaths showing a biological gradient of cerebrovascular mortality with increasing serum HCV RNA level.

Development and Progression of Portal Hypertensive Gastropathy in Patients With Chronic Hepatitis C. Fontana RJ, Sanyal AJ, Ghany MG, et al. Am J Gastroenterol. 2010 Dec 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21139575>

OBJECTIVES: The objective of this study was to determine the incidence and risk factors associated with new-onset and worsening portal hypertensive gastropathy (PHG) in patients with chronic hepatitis C (CHC). **METHODS:** A total of 831 CHC patients with bridging fibrosis or cirrhosis at the time of entry were prospectively monitored for clinical and histological liver disease progression while receiving either low-dose peginterferon α 2a or no antiviral therapy in

the HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) trial. Upper endoscopy with grading of PHG was performed at baseline and at year 4 of the study. The presence and severity of PHG were determined using the NIEC (New Italian Endoscopy Conference) criteria, and worsening PHG was defined as a score increase of ≥ 1 point.

RESULTS: During a median follow-up of 3.85 years, 50% of 514 subjects without PHG developed new-onset PHG, whereas 26% of 317 patients with baseline PHG had worsening PHG. Independent predictors of new-onset PHG included higher alkaline phosphatase and being diabetic, whereas predictors of worsening PHG were Caucasian race, lower albumin, as well as higher serum aspartate transaminase/alanine transaminase ratio and homeostatic model assessment levels. New-onset and worsening PHG were significantly associated with clinical and histological progression. They were also associated with new-onset and worsening gastroesophageal varices. **CONCLUSIONS:** New-onset and worsening PHG develop at a rate of 12.9% per year and 6.7% per year, respectively, in non-responder CHC patients with advanced fibrosis. If confirmed in other studies, endoscopic surveillance for PHG may need to be tailored to individual patient risk factors.

Early proteomic analysis may allow noninvasive identification of hepatitis C response to treatment with pegylated interferon α -2b and ribavirin. Devitt EJ, Power KA, Lawless MW, et al. Eur J Gastroenterol Hepatol. 2010 Dec 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21164346>

BACKGROUND AND AIM: Chronic hepatitis C virus (HCV) infection represents a significant disease burden worldwide. Approximately 170 million people are chronically infected. HCV can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma. Current standard treatment with pegylated interferon and ribavirin is suboptimal and up to 60% of patients fail to respond. Week 4 and 12 HCV RNA is used as a marker of response with nonresponders at 12 weeks discontinuing treatment. Earlier identification of nonresponders using novel biomarkers would be beneficial in preventing unnecessary toxicities and cost. This study profiled the proteomic response to treatment in HCV patients within the first 24 h using surface-enhanced laser desorption-ionization time-of-flight mass spectrometry (SELDI-TOF MS). **METHODS:** Serum from 25 HCV infected individuals during the initial 24 h of treatment was profiled using SELDI-TOF MS. Arrays were analyzed on the ProteinChip Reader and time-of-flight spectra were generated. Peak detection was performed by Biomarker Wizard software and analyzed using BioConductor packages. **RESULTS:** Significant differences were seen between the proteomic profiles of responders and nonresponders to treatment. Overall 70 peaks differentiated responders from nonresponders. A random forest classifier identified a panel of 20 peaks, which differentiated responders from nonresponders with 87.4% accuracy. The CM10 chip revealed 16 peaks identifying genotype 1 responders from nonresponders. **CONCLUSION:** This study identifies early proteomic spectra as potential predictors of HCV treatment response using SELDI-TOF MS. This illustrates the importance of early biomarkers in the prediction of response within the first 24 h, which may aid in tailoring HCV treatment regimens.

Effects of multiple-dose pegylated interferon alfa-2b on the activity of drug-metabolizing enzymes in persons with chronic hepatitis C. Gupta SK, Kolz K, Cutler DL. Eur J Clin Pharmacol. 2010 Dec 16. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21161196>

PURPOSE: To examine the effect of pegylated interferon (PEG-IFN) alfa-2b on the activity of major drug-metabolizing enzymes. **METHODS:** This nonrandomized, open-label, multiple-dose study examined the effects of PEG-IFN alfa-2b on the activity of CYP450 1A2, 2C8/9, 2D6, and 3A4 enzymes and N-acetyltransferase in subjects with chronic hepatitis C. Eligible subjects received PEG-IFN alfa-2b 1.5 µg/kg subcutaneously once weekly for 4 weeks (days 3, 10, 17, and 24). Oral probe substrates (dextromethorphan hydrobromide 45 mg, caffeine 200 mg, tolbutamide 500 mg, and dapsons 100 mg) were administered after a 10-h fast on days 1 and 25. Midazolam 4 mg was administered orally on days 2 and 26. Enzyme activity for each CYP450 isozyme and for N-acetyltransferase was estimated based on the ratios of the observed concentrations of the substrates and metabolites in plasma or urine samples. **RESULTS:** Twenty-six subjects enrolled in the study. Mean age was 44.3 years, mean weight was 78.9 kg, and mean body mass index was 26.3 kg/m². Multiple doses of PEG-IFN alfa-2b inhibited CYP1A2 activity to a limited extent (point estimate = 84.2%, 90% confidence interval [CI] 79-90), increased CYP2C8/9 activity to a limited extent (point estimate = 127.6%, 90% CI 115-142), increased CYP2D6 activity (point estimate = 167%, 90% CI 125-223), and had no effect on the activity of CYP3A4 or N-acetyltransferase. **CONCLUSION:** Weekly administration of PEG-IFN alfa-2b to subjects with chronic hepatitis C increased CYP2C8/9 and CYP2D6 activity in some individuals.

A comparison of the natural history and outcome of treatment for Asian and non-Asian hepatitis C-infected patients. Lawson A; on behalf of the Trent Hepatitis C Study Group. J Viral Hepat. 2010 Dec 7. doi: 10.1111/j.1365-2893.2010.01406.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21138506>

Ethnicity is an important host variable, but its impact on disease progression and response to therapy in Hepatitis C infection is unclear. Here we compare the natural history and outcome of therapy in White and Asian (Indian subcontinent) Hepatitis C infected patients. A total of 2123 White and 120 Asian HCV infected patients were identified within the Trent HCV study. Response to therapy was assessed in 224 White and 46 Asian patients with genotype 3 infection who received Pegylated Interferon and Ribavirin. Asian patients were more likely to be older, female, infected with genotype 3 and to consume no alcohol. At time of first biopsy, fibrosis stage was significantly higher in Asian patients than in Whites (3.0 ± 2.3 vs 1.8 ± 2.0, P < 0.001), as were necro-inflammation and steatosis scores. However, in those patients where duration of infection could be estimated, fibrosis progression was similar for both groups (0.25 ± 0.31 vs 0.16 ± 0.54 Ishak points/year, P = 0.068). 78.3% of Asian and 67.9% of White genotype 3 patients had a sustained virological response following Pegylated Interferon and Ribavirin. Cirrhosis and increased levels of GGT, but not ethnicity were associated with a reduction in the likelihood of a sustained virological response on multivariate analysis. Asian patients with Hepatitis C are more likely to be female, less likely to give a history of risk factors, present to medical services at an older age, and have more severe liver disease at diagnosis, but disease progression and response to treatment are similar to White patients.

Dynamic coinfection with multiple viral subtypes in acute hepatitis C. Smith JA, Aberle JH, Fleming VM, et al. J Infect Dis. 2010 Dec 15;202(12):1770-9. Epub 2010 Nov 10.

<http://www.ncbi.nlm.nih.gov/pubmed/21067369>

INTRODUCTION: Acute hepatitis C virus (HCV) infection is rarely studied, but virus sequence evolution and host-virus dynamics during this early stage may influence the outcome of infection. Hypervariable region 1 (HVR1) is genetically diverse and under selective pressure from the host immune response. We analyzed HVR1 evolution by frequent sampling of an acutely infected HCV cohort. **METHODS:** Three or more pretreatment samples were obtained from each of 10 acutely infected subjects. Polymerase chain reaction amplification was performed with multiple primer combinations to identify the full range of sequences present. Positive samples were cloned and sequenced. Phylogenetic analyses were used to assess viral diversity. **RESULTS:** Eight of the 10 subjects were coinfecting with at least 2 HCV subtypes. Multiple subtypes were detected in individual samples, and their relative proportions changed through acute infection. The subjects with the most complex subtype structure also had a dynamic viral load; however, changes in viral load were not directly linked to changes in subtype. **CONCLUSIONS:** This well-sampled cohort with acute HCV infection was characterized by dynamic coinfection with multiple viral subtypes, representing a highly complex virologic landscape extremely early in infection.

Reactivation of Epstein-Barr virus in B cells of patients with chronic hepatitis C.

Shimozuma Y, Ito T, Inokuchi M, Uchikoshi M, et al. J Med Virol. 2010 Dec;82(12):2064-72.

<http://www.ncbi.nlm.nih.gov/pubmed/20981794>

Hepatitis C virus (HCV) infection is associated with lymphoproliferative disorders. HCV infection of B cells is a predictive factor for lymphoproliferative disorders in patients with chronic hepatitis C, although its molecular mechanisms remain unknown. Epstein-Barr virus (EBV) is a B cell-tropic virus with the potential to cause lymphoproliferative disorders, and its reactivation is induced by several viruses and cytokines. The possibility that HCV infection triggers reactivation of EBV and induces lymphoproliferative disorders were investigated. Expression of EBV mRNAs was analyzed by RT-PCR in patients infected with HCV and control subjects, and correlations between reactivation of EBV and markers for lymphoproliferative disorders were investigated. BZLF1 mRNA, a starter molecule of reactivation, was detected in peripheral blood mononuclear cells from 12 of 52 (23%), patients infected with HCV and the frequency was higher than in healthy subjects [3 of 43 (9%), $P = 0.032$]. But the presence of the BZLF1 mRNA was not associated with an abnormality of markers for lymphoproliferative disorders. This study on BZLF1 mRNA expression among lymphoid cell subsets showed that reactivation of EBV was observed specifically in B cells. The BZLF1 mRNA disappeared following anti-viral therapy and remained negative after eradication of HCV in patients with a sustained viral response, while the EBER1 RNA, a marker for persistence of EBV, was detected throughout the therapy. Infection with HCV induces reactivation of EBV in B cells, but this reactivation was not associated directly with lymphoproliferative disorders triggered by HCV.

Interferon- α suppressed granulocyte colony stimulating factor production is reversed by CL097, a TLR7/8 agonist. Tajuddin T, Ryan EJ, Norris S, Hegarty JE, O'Farrelly C. J Gastroenterol Hepatol. 2010 Dec;25(12):1883-90. doi: 10.1111/j.1440-1746.2010.06281.x. <http://www.ncbi.nlm.nih.gov/pubmed/21092001>

BACKGROUND AND AIM: Neutropenia, a major side-effect of interferon- α (IFN- α) therapy can be effectively treated by the recombinant form of granulocyte colony stimulating factor (G-CSF), an important growth factor for neutrophils. We hypothesized that IFN- α might suppress G-CSF production by peripheral blood mononuclear cells (PBMCs), contributing to the development of neutropenia, and that a toll-like receptor (TLR) agonist might overcome this suppression. **METHODS:** Fifty-five patients who were receiving IFN- α /ribavirin combination therapy for chronic hepatitis C virus (HCV) infection were recruited. Absolute neutrophil counts (ANC), monocyte counts and treatment outcome data were recorded. G-CSF levels in the supernatants of PBMCs isolated from the patients and healthy controls were assessed by enzyme-linked immunosorbent assay following 18 h of culture in the absence or presence of IFN- α or the TLR7/8 agonist, CL097. **RESULTS:** Therapeutic IFN- α caused a significant reduction in neutrophil counts in all patients, with 15 patients requiring therapeutic G-CSF. The reduction in ANC over the course of IFN- α treatment was paralleled by a decrease in the ability of PBMCs to produce G-CSF. In vitro G-CSF production by PBMCs was suppressed in the presence of IFN- α ; however, co-incubation with a TLR7/8 agonist significantly enhanced G-CSF secretion by cells obtained both from HCV patients and healthy controls. **CONCLUSIONS:** Suppressed G-CSF production in the presence of IFN- α may contribute to IFN- α -induced neutropenia. However, a TLR7/8 agonist elicits G-CSF secretion even in the presence of IFN- α , suggesting a possible therapeutic role for TLR agonists in treatment of IFN- α -induced neutropenia.

Characterization of the specific CD4+ T cell response against the F protein during chronic hepatitis C virus infection. Gao DY, Jin GD, Yao BL, et al. PLoS One. 2010 Dec 6;5(12):e14237.

<http://www.ncbi.nlm.nih.gov/pubmed/21151917>

BACKGROUND: The hepatitis C virus (HCV) Alternate Reading Frame Protein (ARFP or F protein) presents a double-frame shift product of the HCV core gene. We and others have previously reported that the specific antibodies against the F protein could be raised in the sera of HCV chronically infected patients. However, the specific CD4(+) T cell responses against the F protein during HCV infection and the pathological implications remained unclear. In the current study, we screened the MHC class II-presenting epitopes of the F protein through HLA-transgenic mouse models and eventually validated the specific CD4(+) T cell responses in HCV chronically infected patients. **METHODOLOGY:** DNA vaccination in HLA-DR1 and-DP4 transgenic mouse models, proliferation assay to test the F protein specific T cell response, genotyping of Chronic HCV patients and testing the F-peptide stimulated T cell response in the peripheral blood mononuclear cell (PBMC) by in vitro expansion and interferon (IFN)- γ intracellular staining. **PRINCIPAL FINDINGS:** At least three peptides within HCV F protein were identified as HLA-DR or HLA-DP4 presenting epitopes by the proliferation assays in mouse models. Further study with human PBMCs evidenced the specific CD4(+) T cell responses against HCV F protein as well in patients chronically infected with HCV. **CONCLUSION:** The current study provided the evidence for the first time that HCV F protein

could elicit specific CD4(+) T cell response, which may provide an insight into the immunopathogenesis during HCV chronic infection.

COINFECTION

Changing Rate of Non-B Subtypes and Coinfection with Hepatitis B/C Viruses in Newly Diagnosed HIV Type 1 Individuals in Spain. Treviño A, Soriano V, Rodríguez C, et al. AIDS Res Hum Retroviruses. 2010 Dec 6. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/21039316>

Immigration from developing regions to Western countries has resulted in an increased rate of non-B subtypes in the HIV population. However, it is unclear whether these HIV variants remain confined to foreigners or are already spreading among natives. Since many immigrants come from regions in which hepatitis B virus (HBV) and hepatitis C virus (HCV) are endemic, HIV-hepatitis coinfection might be more frequent in newly diagnosed HIV persons. Herein, we report changes in the prevalence and distribution of HIV-1 subtypes in Madrid, Spain over the past 10 years as well as the rate of chronic HBV and HCV coinfection in 1854 newly diagnosed HIV-1 individuals. Overall 18.2% carried HIV-1 non-B subtypes, although the prevalence increased over time reaching a peak of 19.4% in the last period (2007-2010). The most common non-B variants were CRF02_AG (37%), G (12%), A (9.9%), and C (7.8%). In native Spaniards the rate of non-B subtypes increased from 1.5% in 2000-2002 to 7.2% in 2003-2006 and to 11.4% in 2007-2010 ($p = 0.04$). Chronic hepatitis B and C were found, respectively, in 4.2% and 8.3% of the study population. While the prevalence of chronic hepatitis B has remained fairly stable over time across distinct populations, the rate of chronic HCV infection has experienced a significant decline, mainly in native Spaniards as a result of a reduction in intravenous drug use. **In summary**, the prevalence of HIV-1 non-B subtypes is rising in newly diagnosed HIV-1 individuals in Spain, including the native population. In contrast, the rate of HBV coinfection remains unchanged and the rate of HCV coinfection has declined.

Treatment for hepatitis C virus genotype 1 infection in HIV-infected individuals on methadone maintenance therapy. Taylor LE, Bowman SE, Chapman S, et al.
<http://www.ncbi.nlm.nih.gov/pubmed/21177046>

BACKGROUND: A minority of HIV/HCV coinfecting patients with opiate addiction undergo HCV treatment. HCV therapy for HCV-monoinfected methadone maintenance (MM) recipients is safe and effective. We evaluated treatment efficacy and adherence to pegylated interferon (pegIFN) among HIV/HCV coinfecting MM recipients. **METHODS:** HCV treatment-naïve, HIV-infected persons 18-65 years with chronic HCV genotype 1 on MM were prospectively enrolled in an HCV treatment study at two HIV clinics. At weekly visits pegIFN alfa-2a injections were directly administered. Daily MM recipients had morning ribavirin delivered with methadone at off-site methadone clinics. Weekly take-home MM recipients took ribavirin unsupervised. Target enrollment was 30 participants. **RESULTS:** During 18 recruitment months, 11 participants were enrolled, 6 of whom received daily methadone. Mean age was 46, 64% were female, 5 were Caucasian, 4 Black and 2 Hispanic. At baseline, 82% had high HCV RNA and 55% had stage 2 fibrosis or greater. The majority (91%) were on HAART, and 82% had undetectable HIV RNA with a median CD4(+) of 508cells/ μ L. All had polysubstance use history, non-substance-based psychiatric diagnoses and were on psychotropic medications pre-enrollment. Two (18%) participants achieved a Sustained Virologic Response (SVR). Two

completed 48 treatment weeks, 5 were withdrawn due to adverse events, 2 dropped out prematurely and 2 had treatment discontinued for virologic non-response. Of on-treatment weeks, adherence to pegIFN was >99%. **CONCLUSIONS:** SVR rate was comparable to historic controls for coinfecting genotype 1 patients, with optimal pegIFN adherence. Adverse effects often prevented therapy completion in this population.

Chronic immune activation in the T cell compartment of HCV/HIV-1 co-infected patients.

Sandberg JK, Falconer K, Gonzalez VD. *Virulence*. 2010 Dec 22;1(3):177-9.

<http://www.ncbi.nlm.nih.gov/pubmed/21178437>

Activation of innate and adaptive immune mechanisms in response to infection is necessary to control and clear infections. However, chronic immune activation in human immunodeficiency virus 1 (HIV-1) infection has a series of detrimental effects and is a major driving force in HIV-1 disease progression. We recently found that patients with chronic hepatitis C virus (HCV)/HIV-1 co-infection display sharply elevated immune activation as determined by expression of CD38 in T cells. High immune activation was observed despite that these patients were on effective antiretroviral therapy (ART), which usually brings down activation levels in HIV-infected people. HCV treatment with pegylated interferon- α (IFN α) and ribavirin reduced activation, and this was at first glance unexpected as IFN α is believed to be involved in driving activation. **Here, we briefly summarize** these findings and discuss them in context of the emerging roles of the gut barrier and the liver in chronic immune activation and viral disease progression.

Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning.

Cohen RA, de la Monte S, Gongvatana A, et al. *J Neuroimmunol*. 2010 Dec 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21146232>

Cytokine disturbances have been linked to brain dysfunction among HIV-infected people. Past studies have not simultaneously examined a large set of cytokine measures and their relationships to HIV-associated neurocognitive deficits. **We hypothesized** that performance on measures of attention and executive and psychomotor functions would be associated with plasma cytokine concentrations in HIV-infected individuals. Plasma samples drawn from 30 HIV-infected and 37 HIV seronegative individuals were analyzed via xMAP multiplexed bead array immunoassay to determine concentrations of 13 cytokines. Performance on Trail Making A/B, Stroop Test, Letter-Number Sequencing, Digit Symbol Coding, Symbol Search, and Grooved Pegboard tests was assessed. Statistical analyses were performed to examine group differences in cytokine concentrations, and associations between cytokine and HIV clinical variables and neurocognitive performance. Significant HIV effects were found on 7 of the 13 cytokines, primarily with respect to interleukins. HIV clinical factors (CD4 and HIV RNA levels, duration of illness, antiretroviral treatment) and hepatitis C status were associated with specific plasma cytokine concentrations. Neurocognitive measures were associated with cytokine concentrations, most consistently among the interleukins and IP-10. Generally, cytokine concentrations were among the strongest predictors of neurocognitive function relative to other clinical factors, which reinforces their potential importance in examining the neuropathological processes of HIV. The findings also point to the potential value of simultaneously examining a panel of biomarkers. **The current results suggest** that a complex relationship likely exists among cytokines [how?] and that these relationships are mediated not only by HIV infection but also by antiretroviral treatment and other comorbid conditions.

Pharmacodynamics of PEG-IFN alpha-2a and HCV response as a function of IL28B polymorphism in HIV/HCV co-infected patients. de Araújo ES, Dahari H, Cotler SJ, et al. J

Acquir Immune Defic Syndr. 2010 Dec 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21157362>

We examined the association between IL28B single-nucleotide-polymorphism rs12979860, hepatitis C virus (HCV) kinetic and pegylated-interferon-alpha-2a pharmacodynamic parameters in HIV/HCV-co-infected patients from South America. Twenty-six subjects received PEG-IFN-alpha-2a+ribavirin. Serum HCV-RNA and interferon concentrations were measured frequently during the first 12-weeks of therapy and analyzed using mathematical models. African Americans and Whites had a similar distribution of IL28B genotypes ($p=0.5$). The CC genotype was overrepresented ($p=0.015$) in patients infected with HCV genotype-3 compared to genotype-1. In both genotype-1 and genotype-3, the first-phase-viral decline and the average PEG-IFN-alpha-2a effectiveness during the first week of therapy were larger (trend $P\leq 0.12$) in genotype-CC compared with genotypes-TC/TT. In genotype-1 patients, the second-slower phase of viral decline (days 2-29) and infected-cells-loss rate, δ , were larger ($p=0.02$ and 0.11 , respectively) in genotype-CC than in genotypes-TC/TT. These associations were not observed in genotype-3 patients.

Incidence and risk factors for steatosis progression in adults coinfecting with HIV and hepatitis C virus. Woreta TA, Sutcliffe CG, Mehta SH, et al. Gastroenterology. 2010 Dec 3.

[Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21134375>

BACKGROUND AND AIMS: Hepatic steatosis is a common histological finding in patients that are co-infected with HIV and hepatitis C virus (HCV), although little is known about its natural history. We prospectively examined the natural history of steatosis in patients co-infected with HIV and HCV that attended an urban HIV clinic. **METHODS:** The study cohort consisted of 222 co-infected patients (87% African American, 94% with HCV genotype 1 infection) who had at least 2 liver biopsies performed between 1993 and 2008. Biopsies were scored by a single pathologist; samples were classified as having trivial (< 5% of hepatocytes affected) or significant (>5%) levels of fat (steatosis). We characterized progression to significant levels of fat among patients whose first biopsy samples had no or trivial levels of fat, and regression among those with significant fat, using logistic regression. **RESULTS:** Initial biopsies from most patients (88%) had no or trivial amounts of fat. Among second biopsy samples, 74% had no or trivial fat and 13% had significant amounts of fat. The strongest risk factors for steatosis progression were alcohol abuse and overweight/obesity; cumulative exposure to anti-retroviral therapy between biopsies and high counts of CD4+ T cells were associated with reduced progression of steatosis. Among the 28 patients whose initial biopsy had significant fat levels, most (75%) regressed. **CONCLUSIONS:** Antiretroviral therapy and high counts of CD4+ T cells are associated with reduced progression of steatosis in patients co-infected with HIV and HCV. Efforts to diagnose and prevent steatosis should focus on persons with high body mass index and excessive alcohol intake.

Acute hepatitis C in HIV-infected individuals - recommendations from the NEAT consensus conference. Rockstroh JK; The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel. AIDS. 2010 Dec 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21139491>

Hepatitis C virus (HCV) infection is a transmissible disease with potentially severe consequences on morbidity and mortality. Although there is increasing awareness of an ongoing epidemic of acute HCV infection in HIV-infected men who have sex with men (MSM), there exists no guidance on the best management of acute HCV infection in HIV-infected individuals. As data from clinical trials and cohort studies has become available, evidence based guidelines are timely to permit best management of these individuals. To address this issue, the European AIDS Treatment Network (NEAT) invited members of the European AIDS Clinical Society (EACS) Hepatitis Group, the European Association for the Study of the Liver (EASL), the European Study Group on Viral Hepatitis (ESGVH) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European AIDS Treatment group (EATG) and other experts to attend a consensus conference on acute HCV infection in HIV-infected individuals in Paris, France, on May 21, 2010. This review reports the results of the conference and recommendations issued on the diagnosis, epidemiology, natural course and treatment of HIV-infected patients with acute hepatitis C infection.

Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Thomson EC, Fleming VM, Main J, et al. Gut. 2010 Dec 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21139063>

OBJECTIVE: An epidemic of acute hepatitis C virus (HCV) infection in HIV-positive men-who-have-sex-with-men (MSM) is emerging in Europe, Australia and the USA. The aim of this study was to characterise the natural history of primary HCV in this setting and to assess host and viral factors which predict spontaneous clearance. **METHODS:** This prospective longitudinal cohort study was carried out in 112 HIV-positive patients who were followed in a single centre (the St Mary's Acute HCV Cohort). Plasma and peripheral blood mononuclear cells (PBMCs) were obtained at monthly intervals for 3 months and at 3-monthly intervals thereafter for a median of 45 months (IQR=29-69 months). The primary end point was spontaneous clearance of HCV. Cox regression was used to assess the impact of clinical and virological variables on outcome, including liver function, CD4 count, rate of HCV RNA decline, T cell response and clonal sequence evolution within the HCV E2 envelope gene. **RESULTS:** 15% of patients cleared HCV spontaneously, while 85% progressed towards chronicity. The latter group included a significant proportion of 'fluctuating' progressors (37.5%), in whom a fall followed by a rise (>1 log(10)) in viraemia was observed. This was associated with superinfection with new HCV strains and partially effective T cell responses. Spontaneous clearance was strongly associated with a 2.2 log(10) viral load drop within 100 days of infection (HR=1.78; p<0.0001), elevated bilirubin (≥ 40   $\mu\text{mol/l}$; HR=5.04; p=0.006), elevated alanine aminotransferase (ALT; ≥ 1000  IU/ml; HR=2.62; p=0.048) and baseline CD4 count $\geq 650 \times 10^6/\text{l}$ (HR=2.66; p=0.045), and only occurred in patients with genotype 1 infection. Evolution to spontaneous clearance occurred in patients with low viral diversity in the presence of an early multispecific T cell response. **CONCLUSIONS:** Spontaneous clearance of acute HCV in HIV-positive men can be predicted by a rapid decline in viral load, high CD4 count, elevated bilirubin and ALT, and is associated with low viral diversity and strong T cell responses.

Impact of liver steatosis on the correlation between liver stiffness and fibrosis measured by transient elastography in patients coinfecting with human immunodeficiency virus and hepatitis C virus. Sánchez-Conde M, Montes Ramírez ML, Bellón Cano JM, et al. *J Viral Hepat.* 2010 Dec 3. doi: 10.1111/j.1365-2893.2010.01407.x. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21129129>

We assessed the effect of different hepatic conditions such as fibrosis, steatosis and necroinflammatory activity on liver stiffness as measured by transient elastography in HIV/HCV-coinfecting patients. We studied all consecutive HIV/HCV-coinfecting patients who underwent liver biopsy and elastography between January 2007 and December 2008. Liver fibrosis was staged following METAVIR Cooperative Study Group criteria. Steatosis was categorized according to the percentage of affected hepatocytes as low ($\leq 10\%$), moderate ($< 25\%$) and severe ($\geq 25\%$). A total of 110 patients were included. Fibrosis was distributed by stage as follows: F0, n=13; F1, n=47; F2, n=29; F3, n=18; and F4, n=3. Liver biopsy revealed the presence of hepatic steatosis in 68 patients (low to moderate, n=53; and severe n=15). By univariate regression analysis, fibrosis, necroinflammatory activity, and the degree of steatosis were correlated with liver stiffness. However, in a multiple regression analysis, steatosis and fibrosis were the only independent variables significantly associated with liver stiffness. With a cut-off of 9.5 kPa to distinguish patients with $F \leq 2$ from $F \geq 3$, elastography led to a significantly higher number of misclassification errors (25% vs 5%; $P = 0.014$), most of which were false positives for $F \geq 3$. **Our study suggests** that the correlation between liver stiffness and fibrosis as estimated by transient elastography may be affected by the presence of hepatic steatosis in HIV/HCV-coinfecting patients.

Treatment for hepatitis C virus genotype 1 infection in HIV-infected individuals on methadone maintenance therapy. Taylor LE, Bowman SE, Chapman S, et al. *Drug Alcohol Depend.* 2010 Dec 20. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21177046>

BACKGROUND: A minority of HIV/HCV coinfecting patients with opiate addiction undergo HCV treatment. HCV therapy for HCV-monoinfected methadone maintenance (MM) recipients is safe and effective. We evaluated treatment efficacy and adherence to pegylated interferon (pegIFN) among HIV/HCV coinfecting MM recipients. **METHODS:** HCV treatment-naïve, HIV-infected persons 18-65 years with chronic HCV genotype 1 on MM were prospectively enrolled in an HCV treatment study at two HIV clinics. At weekly visits pegIFN alfa-2a injections were directly administered. Daily MM recipients had morning ribavirin delivered with methadone at off-site methadone clinics. Weekly take-home MM recipients took ribavirin unsupervised. Target enrollment was 30 participants. **RESULTS:** During 18 recruitment months, 11 participants were enrolled, 6 of whom received daily methadone. Mean age was 46, 64% were female, 5 were Caucasian, 4 Black and 2 Hispanic. At baseline, 82% had high HCV RNA and 55% had stage 2 fibrosis or greater. The majority (91%) were on HAART, and 82% had undetectable HIV RNA with a median CD4(+) of 508 cells/ μL . All had polysubstance use history, non-substance-based psychiatric diagnoses and were on psychotropic medications pre-enrollment. Two (18%) participants achieved a Sustained Virologic Response (SVR). Two completed 48 treatment weeks, 5 were withdrawn due to adverse events, 2 dropped out prematurely and 2 had treatment discontinued for virologic non-response. Of on-treatment weeks, adherence to pegIFN was $>99\%$. **CONCLUSIONS:** SVR rate was comparable to historic

controls for coinfecting genotype 1 patients, with optimal pegIFN adherence. Adverse effects often prevented therapy completion in this population.

An Interrupted Time Series Evaluation of a Hepatitis C Intervention for Persons with HIV.

Proeschold-Bell RJ, Hoepfner B, Taylor B, Cohen S, Blouin R, Stringfield B, Muir AJ. *AIDS Behav.* 2010 Dec 30. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21191643>

Accurate HCV knowledge is lacking among high-risk groups, including people with HIV/AIDS (PLWHA). Liver disease primarily due to HCV has emerged as a serious cause of mortality among PLWHA. We used an Interrupted Time Series design to evaluate a social-ecologically based intervention for PLWHA, where an infectious disease clinic serving a six-county intervention area was monitored before (7 months) and after (17 months) intervention onset. The intervention included education of PLWHA and medical providers, HIV/HCV support groups, and adaptation of the patient chart top sheet to include HCV test information. Clinic-level outcomes were assessed prospectively every other week for 2 years by interviewing patients (n = 259) with clinic appointments on assessment days. Abrupt, gradual and delayed intervention effects were tested. Weighted regression analyses showed higher average HCV knowledge and a higher prevalence of patients reporting HCV discussion with their medical providers after intervention onset. A delayed effect was found for HCV awareness, and a gradually increasing effect was found for knowing one's HCV status. Other communities may consider adopting this intervention. Additional HCV interventions for PLWHA with HIV are needed.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. Lange CM, Bojunga J, Ramos-Lopez E, et al. *J Hepatol.* 2010 Dec 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21145801>

AIMS: Vitamin D is an important immune modulator and preliminary data indicated an association between vitamin D deficiency and sustained virologic response (SVR) rates in hepatitis C virus (HCV) genotype 1 patients. We therefore performed a comprehensive analysis on the impact of vitamin D serum levels and of genetic polymorphisms with functional relevance within the vitamin D cascade on chronic hepatitis C and its treatment. **METHODS:** Vitamin D serum levels, genetic polymorphisms within the vitamin D receptor and 1 α -hydroxylase were determined in a cohort of 468 HCV genotype 1, 2 and 3 infected patients who were treated with interferon-alfa based regimens. **RESULTS:** Chronic hepatitis C was associated with a high incidence of severe vitamin D deficiency compared to controls (25(OH)D(3) < 10 ng/ml in 25% versus 12%, p < 0.00001). 25(OH)D(3) deficiency correlated with SVR in HCV genotype 2 and 3 patients (50% and 81% SVR for patients with and without severe vitamin D deficiency, respectively, p < 0.0001). In addition, the CYP27-1260 promoter polymorphism rs10877012 had substantial impact on 1-25-dihydroxyvitamin D serum levels (72, 61, and 60 pmol/ml for rs10877012 AA, AC, and CC, respectively, p = 0.04) and on SVR rates in HCV genotype 1, 2 and 3 infected patients (77% and 65% versus 42% for rs10877012 AA, AC, and CC, respectively, p = 0.02). **CONCLUSIONS:** Chronic hepatitis C virus infection is associated with vitamin D deficiency. Reduced 25-hydroxyvitamin D levels and CYP27-1260 promoter polymorphism

leading to reduced 1,25-dihydroxyvitamin D levels are associated with failure to achieve SVR in HCV genotype 1, 2, 3 infected patients.

Vitamins B status and antioxidative defense in patients with chronic hepatitis B or hepatitis C virus infection. Lin CC, Liu WH, Wang ZH, Yin MC. Eur J Nutr. 2010 Dec 24. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21184088>

BACKGROUND & AIMS: The impact of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection upon B vitamins status and antioxidative defense in infected patients was examined.

METHODS: Dietary record and blood levels of B vitamins and oxidative stress-associated biomarkers were determined for 195 healthy controls, 132 HBV, and 114 HCV patients.

RESULTS: HBV-infected patients had significantly higher levels of total cholesterol, free fatty acids (FFA), and lower ghrelin level ($p < 0.05$); and HCV-infected patients had significantly higher Ishak inflammation score and lactate dehydrogenase activity ($p < 0.05$). HBV patients had significantly lower red blood cell (RBC) vitamins B(2) and B(6) levels, and HCV infection significantly decreased vitamins B(2,) B(6) and folate levels in RBC and/or plasma ($p < 0.05$). Correlation coefficients of RBC vitamin B(2) versus serum FFA in HBV patients, RBC vitamins B(2) and B(6) versus HCV RNA and Ishak inflammation score, and plasma vitamin B(6) vs Ishak inflammation score in HCV patients were < -0.5 . HBV-infected patients had significantly higher oxidized glutathione level and lower glutathione peroxidase activity ($p < 0.05$), but HCV patients had significantly lower superoxide dismutase and catalase activities ($p < 0.05$).

CONCLUSION: HBV or HCV infection enhanced oxidative stress and lowered B vitamins in circulation. In order to avoid other healthy risk, nutrition status should be monitored and limitation or supplementation of certain nutrients might be helpful for HBV- or HCV-infected patients.

Interferon plus Chinese herbs are associated with higher sustained virological response than interferon alone in chronic Hepatitis C: A meta-analysis of randomised trials. Zhao S, Liu E, Wei K, et al. Antiviral Res. 2010 Dec 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21167210>

BACKGROUND/AIMS: Traditional Chinese herbal therapies are widely used for the treatment of chronic hepatitis C (CHC) in Asia. The aim of this study was to perform a meta-analysis of randomised controlled trials (RCTs) comparing interferon therapies with Chinese herbal therapies and/or interferon plus Chinese herb therapies for the treatment of CHC. **METHODS:** The Cochrane Central Register of Controlled Trials, Medline, Science Citation Index, EMBASE, China National Knowledge Infrastructure, Wanfang Database and China Biomedical Database were searched to identify RCTs that evaluated the virological response to interferon therapies, Chinese herbal therapies and interferon plus Chinese herb therapies in CHC patients. We statistically combined data using a random-effect meta-analysis according to the intention-to-treat principle. **RESULTS:** The literature search yielded 770 studies, and 26 RCTs comprising 1905 patients matched the selection criteria. Overall, the sustained virological response (SVR) was significantly higher in patients treated with interferon plus Chinese herbs than in patients treated with interferon alone (49% vs 33%, relative risk, 1.52; 95% confidence interval: 1.23-1.89; $p < 0.05$). Combined therapies of interferon plus Chinese herb therapies were also superior to interferon therapies alone in achieving the end-of-treatment viral response (ETVR), and resulted in fewer relapses, fewer adverse events and more rapid alanine transaminase

normalisation. Interferon therapies achieved higher ETVR than Chinese herbal therapies, but they yielded a similar SVR. **CONCLUSIONS:** The current evidence suggests that combined therapies of interferon plus Chinese herbs yielded a higher SVR, and resulted in fewer relapses and fewer adverse events than interferon therapies.

Association Of Caffeine Intake and Histological Features of Chronic Hepatitis C. Costentin CE, Roudot-Thoraval F, Zafrani ES, et al. J Hepatol. 2010 Dec 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21145804>

RATIONAL: The severity of chronic hepatitis C (CHC) is modulated by host and environmental factors. Several reports suggest that caffeine intake exerts hepatoprotective effects in patients with chronic liver disease. The aim of this study was to evaluate the impact of caffeine consumption on activity grade and fibrosis stage in patients with CHC. **METHODS:** 238 treatment-naïve patients with histologically-proven CHC were included. Demographic, epidemiological, environmental, virological and metabolic features were collected, including daily consumptions of alcohol, cannabis, tobacco and caffeine during the six month preceding liver biopsy. Daily caffeine consumption was estimated as the sum of mean intakes of caffeinated coffee, tea and caffeine-containing sodas. Histological activity grade and fibrosis stage were scored according to Metavir. Patients (154 men, 84 women, mean age: 45±11 years) were categorized according to caffeine consumption quartiles: group 1 (<225 mg/day, n=59), group 2 (225-407 mg/day, n=57), group 3 (408-678 mg/day, n=62) and group 4 (>678 mg/day, n=60). **RESULTS:** There was a significant inverse relationship between activity grade and daily caffeine consumption: Activity grade >A2 was present in 78%, 61%, 52% and 48% of patients in group 1, 2, 3 and 4, respectively (p<0.001). By multivariate analysis, daily caffeine consumption greater than 408 mg/day was associated with a lesser risk of activity grade >A2 (OR=0.32 (0.12-0.85)). Caffeine intake showed no relation with the fibrosis stage. **CONCLUSIONS:** Caffeine consumption greater than 408 mg/day (3 cups or more) is associated with reduced histological activity in patients with CHC. These findings support potential hepatoprotective properties of caffeine in chronic liver diseases.

Dietary History and Physical Activity and Risk of Advanced Liver Disease in Veterans with Chronic Hepatitis C Infection. White DL, Richardson PA, Al-Saadi M, et al. Dig Dis Sci. 2010 Dec 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21188525>

BACKGROUND: The role of customary diet and physical activity in development of advanced HCV-related liver disease is not well-established. **METHODS:** We conducted a retrospective association study in 91 male veterans with PCR-confirmed chronic HCV and biopsy-determined hepatic pathology. Respondents completed the Block Food Frequency and the International Physical Activity questionnaires. We conducted three independent assessments based on hepatic pathology: fibrosis (advanced = F3-F4 vs. mild = F1-F2), inflammation (advanced = A2-A3 vs. mild = A1) and steatosis (advanced = S2-S3 vs. mild = S1). Each assessment compared estimated dietary intake and physical activity in veterans with advanced disease to that in analogous veterans with mild disease. Multivariate models adjusted for total calories, age, race/ethnicity, biopsy-to-survey lag-time, BMI, pack-years smoking, and current alcohol use. **RESULTS:** Average veteran age was 52, with 48% African-American. Advanced fibrosis was more prevalent than advanced inflammation or steatosis (52.7% vs. 29.7% vs. 26.4%, respectively). The strongest multivariate association was the suggestive 14-fold significantly

decreased advanced fibrosis risk with lowest dietary copper intake (OR = 0.07, 95% CI 0.01-0.60). Other suggestive associations included the 6.5-fold significantly increased advanced inflammation risk with lower vitamin E intake and 6.2-fold significantly increased advanced steatosis risk with lower riboflavin intake. The only physical activity associated with degree of hepatic pathology was a two-fold greater weekly MET-minutes walking in veterans with mild compared to advanced steatosis (P = 0.02). **CONCLUSIONS:** Several dietary factors and walking may be associated with risk of advanced HCV-related liver disease in male veterans. However, given our modest sample size, our findings must be considered as provisional pending verification in larger prospective studies.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Injection practices among clinicians in United States health care settings. Pugliese G, Gosnell C, Bartley JM, Robinson S. Am J Infect Control. 2010 Dec;38(10):789-98. <http://www.ncbi.nlm.nih.gov/pubmed/21093696>

BACKGROUND: Improper use of syringes, needles, and medication vials has resulted in patient-to-patient transmission of bloodborne pathogens, including hepatitis C virus. This study examined the injection practices of health care providers to identify trends and target opportunities for education on safe practices. **METHODS:** An on-line survey was conducted in May and June 2010 of clinicians in US health care settings that prepare and/or administer parenteral medications. **RESULTS:** The majority of the 5446 eligible respondents reported injection practices consistent with current recommendations. However, the following unsafe practices were identified: 6.0% "sometimes or always" use single-dose/single-use vials for more than 1 patient; 0.9% "sometimes or always" reuse a syringe but change the needle for use on a second patient; 15.1% reuse a syringe to enter a multidose vial and then 6.5% save that vial for use on another patient (1.1% overall). **CONCLUSION:** Unsafe injection practices represent an ongoing threat to patient safety. Ensuring safe injection practices in all health care settings will require a multifaceted approach that focuses on surveillance, oversight, enforcement, and continuing education.

Evaluation of a New; Rapid Test for Detecting HCV Infection; Suitable for Use with Blood or Oral Fluid. Lee SR, Kardos KW, Schiff E, et al. J Virol Methods. 2010 Dec 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21182871>

The availability of a highly accurate, rapid, point-of-care test for hepatitis C virus (HCV) may be useful in addressing the problem of under-diagnosis of HCV, by increasing opportunities for testing outside of traditional clinical settings. A new HCV rapid test device (OraQuick® HCV Rapid Antibody Test), approved recently in Europe for use with venous blood, fingerstick blood, serum, plasma, or oral fluid was evaluated in a multi-center study and performance compared to established laboratory-based tests for detection of HCV. The HCV rapid test was evaluated in prospective testing of subjects with signs and/or symptoms of hepatitis, or who were at risk for hepatitis C using all 5 specimen types. Performance was assessed relative to HCV serostatus established by laboratory methods (EIA, RIBA and PCR) approved in Europe for diagnosis of hepatitis C infection. Sensitivity to antibody in early infection was also compared to EIA in 27 seroconversion panels. In addition, the reliability of the oral fluid sample for accurate detection of anti-HCV was assessed by studying the impact of various potentially interfering conditions of

oral health, use of oral care products and consumption of food and drink. In this large study of at-risk and symptomatic persons, the overall specificities of the OraQuick(®) HCV Rapid Antibody Test were equivalent (99.6-99.9%) for all 5 specimen types and the 95% CIs substantially overlapped. Overall sensitivities were virtually identical for venous blood, fingerstick blood, serum and plasma (99.7-99.9%). Observed sensitivity was slightly lower for oral fluid at 98.1% though the upper CI (99.0%) was equal to the lower CI for venous blood and fingerstick blood. Most of the HCV positive subjects which gave nonreactive results in oral fluid had serological and virological results consistent with resolved infection. Sensitivity for anti-HCV in early seroconversion was virtually identical between the HCV rapid test and EIA. Detection of anti-HCV in oral fluid appeared generally robust to conditions of oral health, consumption of food and drink and use of oral care products. The OraQuick(®) HCV Rapid Antibody Test demonstrated clinical performance that was equivalent to current laboratory-based EIA. This new, HCV rapid test appears suitable as an aid in the diagnosis of HCV infection and may increase testing opportunities due to its simplicity and flexibility to use multiple specimen types, including fingerstick blood and oral fluid.

Infectious disease comorbidities adversely affecting substance users with HIV: hepatitis C and tuberculosis. Friedland G. J Acquir Immune Defic Syndr. 2010 Dec 1;55 Suppl 1:S37-42. <http://www.ncbi.nlm.nih.gov/pubmed/21045598>

The linkage between drug use, particularly injection drug use, and HIV/AIDS, hepatitis C (HCV), and tuberculosis (TB) has been recognized since the beginning of the HIV pandemic. These comorbid conditions affect drug users worldwide and act synergistically, with resultant adverse biologic, epidemiologic, and clinical consequences. Prevention, care, and treatment of TB and HCV can be successful, and both diseases can be cured. Special clinical challenges among drug users, however, can result in increased morbidity, mortality, and decreased therapeutic success. Among these are limited disease screening, inadequate and insensitive diagnostics, difficult treatment regimens with varying toxicities, and complicated pharmacokinetic and pharmacodynamic drug interactions. These may result in delayed diagnosis, deferred treatment initiation, and low completion rates, with the potential for generation and transmission of drug resistant organisms. Strategies to address these challenges include outreach programs to engage substance abusers in nonmedical settings, such as prisons and the streets, active screening programs for HIV, HCV, and TB, increased and broadened clinician expertise, knowledge and avoidance of drug interactions, attention to infection control, use of isoniazid preventive therapy, and creative strategies to insure medication adherence. All of these require structural changes directed at comprehensive prevention and treatment programs and increased collaboration and integration of needed services for substance abusers.

Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. Swan D, Long J, Carr O, et al. AIDS Patient Care STDS. 2010 Dec;24(12):753-62. <http://www.ncbi.nlm.nih.gov/pubmed/21138381>

Hepatitis C (HCV) infection is common among injecting drug users (IDUs), yet accessing of HCV care, particularly HCV treatment, is suboptimal. There has been little in-depth study of IDUs experiences of what enables or prevents them engaging at every level of HCV care, including testing, follow-up, management and treatment processes. This qualitative study aimed to explore these issues with current and former IDUs in the greater Dublin area, Ireland. From

September 2007 to September 2008 in-depth interviews were conducted with 36 service-users across a range of primary and secondary care services, including: two addiction clinics, a general practice, a community drop-in center, two hepatology clinics, and an infectious diseases clinic. Interviews were analyzed using a grounded theory approach. Barriers to HCV care included perceptions of HCV infection as relatively benign, fear of investigations and treatment, and feeling well. Perceptions were shaped by the discourse about HCV and "horror stories" about the liver biopsy and treatment within their peer networks. Difficulties accessing HCV care included limited knowledge of testing sites, not being referred for specialist investigations and ineligibility for treatment. Employment, education, and addiction were priorities that competed with HCV care. Relationships with health care providers influenced engagement with care: Trust in providers, concern for the service-user, and continuity of care fostered engagement. Education on HCV infection, investigations, and treatment altered perceptions. Becoming symptomatic, responsibilities for children, and wanting to move on from drug use motivated HCV treatment. In conclusion, IDUs face multiple barriers to HCV care. A range of facilitators were identified that could inform future interventions.

Effects of recognizing depression with a standardized questionnaire (CES-D) versus patient reporting of depression after a single-standardized question on the outcomes of treatment for hepatitis C with pegylated interferon- α -2b and ribavirin. Phillips FH, Prebis M, Grumbeck C, Hale T, Cubillas R, Brown GR. *Eur J Gastroenterol Hepatol.* 2010 Dec;22(12):1435-42.

<http://www.ncbi.nlm.nih.gov/pubmed/20802340>

BACKGROUND: Depression may worsen during antiviral treatment for hepatitis C virus, resulting in noncompliance treatment. **AIM:** The aim was to compare the response and compliance rates between the groups of veteran patients using two different methods of identifying depression, either the Centers for Epidemiology Studies for Depression Scale (group A) questionnaire or the report of symptoms of depression after a single-standardized question by the health care provider (group B). **METHODS:** One hundred and twenty-nine patients were randomly assigned to the two groups before the treatment. **RESULTS:** No statistical differences were noted in baseline characteristics between the groups. Depression was common in both the groups. No difference between initial Centers for Epidemiologic Studies Depression Scale scores and diagnosis of depression between the two groups was noted. Furthermore, the number of patients diagnosed with depression during the treatment was similar in each group. There were no significant differences between the groups in rates of sustained viral response (30% group A, 35% group B) or in rates of overall compliance with patients receiving more than 90% of prescribed PegIntronA therapy (44% group A, 39% group B), and ribavirin (32% group A and 37% group B). **CONCLUSION:** The use of the Centers for Epidemiology Studies for Depression Scale questionnaire to recognize depression had no significant advantage over patient reporting of depression symptoms after a single-standardized question on the hepatitis C virus clearance and the treatment compliance rates in veteran populations.

LIVER CANCER

Increasing Prevalence of HCC and Cirrhosis in Patients with Chronic Hepatitis C Virus Infection. Kanwal F, Hoang T, Kramer JR, et al. *Gastroenterology.* 2010 Dec 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21184757>

BACKGROUND & AIMS: Patients with hepatitis C virus (HCV) infection are at risk for developing additional liver disorders that are costly to treat and have high rates of morbidity, although the actual prevalence of these diseases is not known. We examined time trends in the prevalence of cirrhosis and its related complications, such as hepatic decompensation and hepatocellular cancer (HCC). **METHODS:** We calculated the annual prevalence of cirrhosis, decompensated cirrhosis, and HCC in a national sample of veterans diagnosed with HCV between 1996 and 2006. Patients with HCV who had at least 1 physician visit in a given calendar year were included in the analysis of prevalence for that year. We used direct standardization to adjust the prevalence of cirrhosis and related complications for increasing age of the cohort, as well as sex and changes in clinical characteristics. **RESULTS:** In this cohort, the number of individuals with HCV increased from 17,261 in 1996 to 106,242 in 2006. The prevalence of cirrhosis increased from 9% in 1996 to 18.5% in 2006. Similarly, the prevalence of patients with decompensated cirrhosis doubled, from 5% in 1996 to 11% in 2006, whereas the prevalence of HCC increased approximately 20-fold (0.07% in 1996 to 1.3% in 2006). After adjustment, the time trend in the prevalence of cirrhosis (and its complications) was lower than the crude trend, although it still increased significantly. **CONCLUSIONS:** The prevalence of cirrhosis and HCC in HCV-infected patients has increased significantly over the past 10 years, and could increase further. An aging cohort of HCV patients could partly explain our findings. Clinicians and healthcare systems should develop strategies to provide timely and effective care to this high-risk population of patients.

Predictive value of tumor markers for hepatocarcinogenesis in patients with hepatitis C virus. Kumada T, Toyoda H, Kiriya S, et al. Gastroenterol. 2010 Dec 7. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21132575>

BACKGROUND: Increases in tumor markers are sometimes seen in patients with chronic liver disease without hepatocellular carcinoma (HCC). The aim of this study was to determine the relationship between the levels of three tumor markers [alpha-fetoprotein (AFP), Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3%), and des-gamma-carboxy prothrombin (DCP)] and hepatic carcinogenesis to identify hepatitis C virus (HCV) carriers at high risk for cancer development. **METHODS:** A total of 623 consecutive HCV carriers with follow-up periods of >3 years were included. The average integration values were calculated from biochemical tests, and tumor markers, including AFP, AFP-L3%, and DCP, and factors associated with the cumulative incidence of HCC were analyzed. **RESULTS:** HCC developed in 120 (19.3%) of the 623 patients. Age >65 years [adjusted relative risk, 2.303 (95% confidence interval, 1.551-3.418), P < 0.001], low platelet count [3.086 (1.997-4.768), P < 0.001], high aspartate aminotransferase value [3.001 (1.373-6.562), P < 0.001], high AFP level [≥ 10 , <20 ng/mL: 2.814 (1.686-4.697), P < 0.001; ≥ 20 ng/mL: 3.405 (2.087-5.557), P < 0.001] compared to <10 ng/mL, and high AFP-L3% level [≥ 5 , <10%: 2.494 (1.291-4.816), P = 0.007; ≥ 10 %: 3.555 (1.609-7.858), P < 0.001] compared to <5% were significantly associated with an increased incidence of HCC on multivariate analysis. **CONCLUSIONS:** Increased AFP or AFP-L3% levels were significantly associated with an increased incidence of HCC. Among HCV carriers, patients with ≥ 10 ng/mL AFP or patients with ≥ 5 % AFP-L3% are at very high risk for the development of HCC even if AFP is less than 20 ng/mL or AFP-L3% is less than 10%, which are the most commonly reported cutoff values.

Correlation between clinical characteristics, survival and genetic alterations in patients with hepatocellular carcinoma from Saudi Arabia. Al-Qahtani A, Al-Hazzani T, Al-Hussain T, et al. *Cancer Genet Cytogenet.* 2010 Dec;203(2):269-77.

<http://www.ncbi.nlm.nih.gov/pubmed/21156243>

Amplification of the two oncogenes ERBB2 and MYC and deletion of the tumor suppressor gene TP53 are frequently encountered in cancerous tissues. The purpose of this study was to use the fluorescence in situ hybridization (FISH) technique for the assessment of ERBB2 and MYC amplification and TP53 deletion, and to relate these molecular markers to clinical and pathologic factors in Saudi patients with hepatocellular carcinoma. The study was conducted on 40 paraffin-embedded tissue samples originally taken from either hepatitis C virus (HCV)- or HBV-infected patients using the FISH technique. The level of ERBB2, MYC, and TP53 in the malignant group was significantly increased as compared to the control group. Of the 40 patients, 3 (7.5%) had amplification of ERBB2 gene, 4 (10%) different patients had amplification of MYC, and 26 patients (65%) had evidence of deletion of at least one allele on chromosome 17 for the TP53 gene in a high proportion of cells. There was a significant correlation between amplification of MYC oncogene and the number of tumor masses. Moreover, significant correlation was observed between poorly differentiated tumors when compared with moderate or well-differentiated tumors when MYC was analyzed. On the other hand, MYC failed to reveal any significant association between oncogene amplification and other clinicopathologic variables examined. Univariate analysis revealed a strong association between deletion of TP53 and multiple tumor mass ($P < 0.001$). No statistical correlation could be detected between deletion of TP53 and tumor size, grade, stage, and tumor differentiation. No significant difference could be detected in the mean survival time of patients positive for the alteration of the genes compared to the patients who showed no alterations for the same genes. However, when the stage of the tumor was analyzed, there was a significant difference in the mean survival time between patients who showed gene alterations compared to patients with no changes in the studied genes. When overall survival was analyzed, only patients with MYC amplification had a lower median survival (20.75 months) than patients without MYC amplification (35.82, $P=0.009$). Genetic alterations of ERBB2 and TP53 genes had no effect on survival 2 (see Results). The combination of ERBB2, MYC, and TP53 could be useful markers to stratify patients into different risk groups.

Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma.

Hagihara H, Nouse K, Kobayashi Y, et al. *Int J Clin Oncol.* 2010 Dec 9. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21152943>

BACKGROUND: We wished to determine whether pegylated interferon (PEG-IFN) therapy after curative treatment of hepatocellular carcinoma (HCC) prevents a recurrence of HCC.

METHODS: Thirty-seven HCC patients with hepatitis C virus (HCV) infection who were treated with PEG-IFN after curative treatment (PEG-IFN group) and 145 controls without IFN therapy (non-IFN group) were enrolled. The overall survival and recurrence-free survival rates were compared between the groups, and the predisposing factors for recurrence and survival were analyzed. The rates were also examined by propensity score (PS) matched analysis that could minimize selection biases. **RESULTS:** The median follow-up period was 3.7 years. The 5-year survival rate in the PEG-IFN group (91%) was significantly higher than that in the non-IFN group (56%; $P < 0.01$). The rate of the second recurrence but not that of the first recurrence of

HCC in the sustained virological responder (SVR) group was lower than that in the non-IFN group ($P = 0.03$). Improvement of survival by PEG-IFN and low rate of second recurrence in the SVR group were also observed in PS matched analysis. Multivariate analysis revealed that PEG-IFN therapy and high serum albumin were good prognostic factors for survival. Although low serum albumin and large and multiple tumors were risk factors for the first recurrence, non-SVR and low serum albumin were risk factors for the second recurrence. **CONCLUSION:** PEG-IFN-therapy after curative treatment of HCC improved the rate of survival, and SVR was found to be closely correlated with the prevention of recurrence.

Hepatitis B and C virus hepatocarcinogenesis: Lessons learned and future challenges.

Bouchard MJ, Navas-Martin S. *Cancer Lett.* 2010 Dec 17. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21168955>

Worldwide, hepatocellular carcinoma (HCC) is one of the most common cancers. It is thought that 80% of hepatocellular carcinomas are linked to chronic infections with the hepatitis B (HBV) or hepatitis C (HCV) viruses. Chronic HBV and HCV infections can alter hepatocyte physiology in similar ways and may utilize similar mechanisms to influence the development of HCC. There has been significant progress towards understanding the molecular biology of HBV and HCV and identifying the cellular signal transduction pathways that are altered by HBV and HCV infections. Although the precise molecular mechanisms that link HBV and HCV infections to the development of HCC are not entirely understood, there is considerable evidence that both inflammatory responses to infections with these viruses, and associated destruction and regeneration of hepatocytes, as well as activities of HBV- or HCV-encoded proteins, contribute to hepatocyte transformation. **In this review**, we summarize progress in defining mechanisms that may link HBV and HCV infections to the development of HCC, discuss the challenges of directly defining the processes that underlie HBV- and HCV-associated HCC, and describe areas that remain to be explored.

Serum level of adiponectin and the risk of liver cancer development in chronic hepatitis C patients.

Arano T, Nakagawa H, Tateishi R, et al. *Int J Cancer.* 2010 Dec 17. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21170963>

Obesity and metabolic syndrome are recognized risk factors for development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC). Dysregulation of adipokines, particularly the decreased secretion of adiponectin, appears to play a key role. **To investigate** the association between adiponectin and hepatocarcinogenesis, we conducted a large-scale retrospective cohort study. We enrolled 325 patients with CHC (146 men, 179 women; mean age 58.0 ± 10.3 yr) whose serum samples were collected between January 1994 and December 2002. Subjects were divided into two groups according to their serum adiponectin levels. We evaluated the association between adiponectin level and the risk of subsequent HCC development using univariate and multivariate Cox proportional hazard regression. Because average serum adiponectin level was higher in females than males, each gender was analyzed separately. Patients with CHC had significantly higher adiponectin levels than healthy controls. During the follow-up period (mean: 9.0 years), HCC developed in 122 subjects. Unexpectedly, subjects with higher serum adiponectin levels had a higher incidence of HCC (males: $p=0.032$; females: $p=0.01$; log-rank test). Multivariate analysis revealed that a high serum adiponectin level was independently associated with HCC development (hazard ratio [HR]=2.07; $p=0.031$ in females

and HR=1.82; p=0.05 in males). Isoform analysis revealed that middle- and low-molecular-weight isoforms contributed to the risk of HCC. **In conclusion**, Patients who had CHC with high serum adiponectin levels had a higher risk of liver cancer development. Adiponectin may thus be tumorigenic or indicate a liver disease state independently of other clinical parameters.