

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

Lack of association between hepatitis C infection and chronic kidney disease. Asrani SK, Buchanan P, Pinsky B, Rey LR, Schnitzler M, Kanwal F. Clin Gastroenterol Hepatol. 2009 Sep 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Asrani%20SK%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND & AIMS: Chronic kidney disease (CKD) can have a negative impact on the natural history of hepatitis C virus infection (HCV); patients with HCV and CKD often have adverse outcomes. We evaluated a large and geographically diverse group of patients to determine whether HCV status has an independent effect on the risk of developing CKD. **METHODS:** We conducted a cohort study of 167,569 patients included in a national healthcare claims database from January 1, 2003 to December 31, 2006, with a mean follow up of 25.3 months. We used multivariable logistic regression analyses to measure the independent effect of HCV status on the baseline prevalence of and progression to CKD (estimated glomerular filtration rate <60 ml/min/1.73m²). **RESULTS:** The baseline prevalence of CKD was similar in patients with vs those without HCV (5.3% vs 5.1%, p=0.3). Similarly, among patients with preserved renal function at baseline (n=82,629), there was no difference in the overall progression to CKD in patients with vs those without HCV (3.8% vs 3.5%, p=0.1). HCV status was not associated with progression to CKD even after adjusting for patient demographics, co-morbidities, and use of relevant medications (odds ratio = 0.92, 95% confidence interval 0.79-1.08). **CONCLUSION:** We found no association between HCV and risk of development of CKD. These data are relevant in counseling HCV patients regarding the impact of HCV on renal function.

Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. Osburn WO, Fisher BE, Dowd KA, et al. Gastroenterology. 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Osburn%20WO%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND & AIMS: We followed persons with ongoing hepatitis C virus (HCV) exposure following control of an initial HCV infection to determine whether primary control conferred protection against future persistent infections. **METHODS:** Twenty-two active injection drug users (IDU) who had cleared a primary hepatitis C viremia for at least 60 days were monitored monthly. Reinfection was defined as the detection of a new hepatitis C virus infection. Protection was assessed based on the magnitude and duration of viremia following reinfection and generation of T-cell and neutralizing antibody (nAb) responses **RESULTS:** Reinfection occurred in 11 IDUs (50%)

who previously spontaneously controlled primary HCV infection. Although viral clearance occurs in approximately 25% of patients with primary infections, spontaneous viral clearance was observed in 83% of reinfected patients. The duration and maximum level of viremia during subsequent episodes of reinfection were significantly decreased, compared with those of the primary infection in the same subjects. In contrast to chronic infection, reinfection was associated with a significant increase in the breadth of T-cell responses. During acute infection, nAbs against heterologous viral pseudoparticles were detected in 60% of reinfected subjects; cross-reactive nAbs are rarely detected in patients who progress to chronic infection. **CONCLUSIONS:** HCV reinfection is associated with a reduction in the magnitude and duration of viremia (compared with the initial infection), broadened cellular immune responses, and the generation of cross-reactive humoral responses. These findings are consistent with the development of adaptive immunity that is not sterilizing but protects against chronic disease.

Randomized study of peginterferon-alpha2a plus ribavirin versus peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Rumi M, Aghemo A, Prati GM, et al. *Gastroenterology*. 2009 Sep 17. [Epub ahead of print]

2009 Sep 17. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Rumi%20M%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Ribavirin (RBV) combined with either Pegylated interferons (PegIFN)alpha2a or PegIFNalpha2b is the standard of care for chronic hepatitis C virus (HCV) infection. Head-to-head studies comparing efficacy and safety of the 2 regimens, are needed. **AIM:** The endpoints were safety and antiviral efficacy. **METHODS:** Treatment-naïve patients with chronic hepatitis C were randomly (1:1) assigned after stratification for HCV genotype to either regimen for 24 or 48 weeks according to virus genotype. RBV was weight dosed in all genotype patients receiving 1.5 mcg/Kg/week PegIFNalpha2b (800-1200 mg/day) and in HCV-1 and HCV-4 patients treated with 180 mcg/week PegIFNalpha2a (1000-1200 mg/day). Patients with HCV-2 and HCV-3 on PegIFNalpha2a received a fixed dose of 800 mg/day RBV. The study was powered to detect a difference of at least 10% in safety and efficacy of the two regimens. **RESULTS:** The 212 on PegIFNalpha2a and the 219 on PegIFNalpha2b had similar baseline characteristics, including cirrhosis (20% vs 18%). By intention to treat, the two groups showed similar rates of treatment related serious adverse events (1% vs 1%) and drop out rates for side effects (7% vs 6%). Overall, sustained virological response (SVR) rate was higher in PegIFNalpha2a than in PegIFNalpha2b (66% vs 54%, $p=0.02$), being 48% vs 32% in the 222 HCV 1-4 ($p=0.02$) and 96% vs 82% in the 143 HCV-2 ($p=0.01$). PegIFNalpha2a independently predicted SVR in the logistic regression analysis (OR 1.88; 95%-CI 1.20-2.96) **CONCLUSIONS:** While the two regimens showed a similar safety profile, the PegIFNalpha2a based treatment yielded significantly more SVR than PegIFNalpha2b.

Acute hepatitis C: analysis of a 126-case prospective, multicenter cohort. Morin T, Pariente A, Lahmek P, et al. *Eur J Gastroenterol Hepatol*. 2009 Sep 3. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Morin%20T%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: To analyze the data (epidemiology, mode of transmission, course, and outcome) of a large series of patients with acute hepatitis C (AHC) in France. **METHODS:** Prospective multicenter register, observational study. **RESULTS:** A cohort of 126 patients with AHC was prospectively enrolled between 1999 and 2007. Fifteen (12%) were HIV coinfecting. Suspected modes of hepatitis C virus transmission were drug use (38%), sexual contact (21%), nosocomial transmission (18%), and occupational exposure (12%). For 40% of the patients, AHC was revealed by jaundice. Spontaneous viral clearance occurred in 40% of the 72 patients observed for 3 months

without treatment. Only jaundice and nosocomial/occupational transmission were predictive of spontaneous viral clearance. Ninety patients were treated with standard or pegylated interferon-alpha alone (58%) or in combination with ribavirin (42%), for 24 weeks or less in 90%. In intention-to-treat, a sustained viral response was obtained in 58 of 78 (74%) hepatitis C virus monoinfected patients [19 of 22 (86%) with 24 weeks of pegylated interferon-alpha alone], but only six of 12 (50%) of HIV coinfecting patients. **CONCLUSION:** AHC remains rare, and drug and sexual transmission are predominant. A 3-month follow-up after diagnosis avoids treatment for four out of 10 patients. Antiviral treatment is highly effective, 24 weeks of pegylated interferon-alpha alone being a good option.

Induction pegylated interferon Alfa-2b in combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: A prospective, randomized, multi-center, open-label study. Brady DE, Torres DM, An JW, et al. Clin Gastroenterol Hepatol. 2009 Sep 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Brady%20DE%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND & AIMS: Standard of care (SOC) treatment for chronic hepatitis C (CHC) involves weekly PEG interferon plus weight based ribavirin with resultant sustained virologic response (SVR) rates at or near 50% for genotypes 1 and 4 virus. Induction therapy with higher doses of PEG interferon may improve first phase viral kinetics and thus improve the overall SVR in genotype 1 and 4 patients. **METHODS:** This multi-center, randomized, open-label trial enrolled treatment naïve genotype 1 and 4-infected CHC patients to either initial induction therapy versus SOC. The induction group received PEG interferon alfa-2b 3.0 mcg/kg weekly for 12 weeks followed by PEG interferon alfa-2b 1.5 mcg/kg weekly for 36 weeks and 13 +/- 2 mg/kg ribavirin daily for 48 weeks. SOC patients received PEG interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks and 13 +/- 2 mg/kg ribavirin daily for 48 weeks. The primary endpoint was SVR. **RESULTS:** 610 patients were enrolled throughout the United States. Complete early virologic response (cEVR) was 62.6% vs. 57.7% in induction vs. SOC (NS). Overall SVR was 32% in induction versus 29% in SOC group (NS). Dose reduction of either PEG interferon (24.1 versus 23.8%) or ribavirin (26.8% versus 25.1%) was similar between the two groups. There was a trend towards a significant difference when comparing the SVR in induction therapy in patients >85 kg versus those receiving SOC, 38% versus 28% (p=0.08). **CONCLUSIONS:** Induction therapy does not enhance cEVR or SVR rates in a predominantly genotype 1 CHC population compared to SOC therapy.

Retrospective, observational, multicentre study on an Italian population affected by chronic hepatitis C who failed to clear HCV-RNA after the combined therapy (PEG-IFN and ribavirin): NADIR study. Morisco F, Stroffolini T, Medda E, et al. J Viral Hepat. 2009 Sep 25. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Morisco%20F%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

There is a lack of information on the characteristics of patients with chronic hepatitis C virus infection (HCV) who fail to respond to antiviral treatment. We studied HCV-positive subjects with chronic liver diseases treated with pegylated-interferon (PEG-IFN) and ribavirin (RBV) who failed to clear HCV in routine clinical practice. A total of 2150 consecutive adult patients treated with PEG-IFN plus RBV therapy in 46 Italian centres between 1 July 2004, and 30 June 2005, were studied. Of the 2150 patients, 923 (42.9%) (M/F 585/335, mean age 54.8 years) failed to achieve a serum HCV-RNA clearance. Of these 923 patients, 429 (46.5%) were nonresponders, 298 (32.3%) relapsers, 168 (18.2%) drop-outs for noncompliance or adverse events and 28 (3.0%) were lost

during follow-up. Overall, 642 (70.6%) patients received adequate therapy (defined as more than 80% of the drug doses for >80% of the time). Genotypes 1-4 were observed in 76.9% of cases; genotypes 2-3 in 21.2% and mixed in 1.9%, respectively. Multiple logistic regression analysis identified genotypes 1 and 4 as the sole independent predictors of the likelihood of nonresponse to therapy compared with relapse (OR: 4.38; 95% CI = 2.28-8.4). Age older than 65 years was the sole independent factor associated with no adherence to therapy (OR: 2.22; 95% CI = 1.36-3.62). Patients who fail to respond to treatment are a nonhomogeneous population with different features, and the sole factor that discriminates nonresponse from relapse is the distribution of genotypes 1-4. Co-morbidities are unable to determine the type of treatment failure and inadequate adherence to therapy mostly affects patients older than 65 years of age.

Pilot study of postexposure prophylaxis for hepatitis C virus in healthcare workers. Corey KE, Servoss JC, Casson DR, et al. *Infect Control Hosp Epidemiol.* 2009 Oct;30(10):1000-5.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Corey%20KE%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND AND OBJECTIVE: Hepatitis C virus (HCV) transmission occurs in 0.2%-10% of people after accidental needlestick exposures. However, postexposure prophylaxis is not currently recommended. We sought to determine the safety, tolerability, and acceptance of postexposure prophylaxis with peginterferon alfa-2b in healthcare workers (HCWs) exposed to blood from HCV-infected patients. **DESIGN:** Open-label pilot trial of peginterferon alfa-2b for HCV postexposure prophylaxis. **SETTING:** Two academic tertiary-referral centers. **METHODS:** HCWs exposed to blood from HCV-infected patients were informed of the availability of postexposure prophylaxis. Persons who elected postexposure prophylaxis were given weekly doses of peginterferon alfa-2b for 4 weeks. **RESULTS:** Among 2,702 HCWs identified with potential exposures to bloodborne pathogens, 213 (7.9%) were exposed to an HCV antibody-positive source. Of 51 HCWs who enrolled in the study, 44 (86%) elected to undergo postexposure prophylaxis (treated group). Seven subjects elected not to undergo postexposure prophylaxis (untreated group). No cases of HCV transmission were observed in either the treated or untreated group, and no cases occurred in the remaining 162 HCWs who did not enroll in this study. No serious adverse events related to a peginterferon alfa-2b regimen were recorded, but minor adverse events were frequent. **CONCLUSION:** In this pilot study, there was a lower than expected frequency of HCV transmission after accidental occupational exposure. Although peginterferon alfa-2b was safe, because of the lack of HCV transmission in either the treated or untreated groups there is little evidence to support routine postexposure prophylaxis against HCV in HCWs.

Effect of HCV RNA suppression during peginterferon Alfa-2A maintenance therapy on clinical outcomes in the HALT-C Trial. Shiffman ML, Morishima C, Dienstag JL, et al.

Gastroenterology. 2009 Sep 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Shiffman%20ML%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND AND AIMS: The HALT-C trial demonstrated that low-dose peginterferon maintenance therapy was ineffective in preventing clinical outcomes in patients with chronic hepatitis C, advanced fibrosis and failure to achieve a sustained virologic response during lead-in phase treatment with standard dose peginterferon/ribavirin. This analysis was performed to determine if suppressing HCV RNA during the trial was associated with a reduction in clinical outcomes. **METHODS:** 764 patients treated during the lead-in phase of HALT-C were randomized to either peginterferon alfa-2a (90 mcg/week) maintenance therapy or no treatment (control) for 3.5 years. Clinical outcomes included an increase in Child-Turcotte-Pugh score, ascites, spontaneous

bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, hepatocellular carcinoma and mortality. **RESULTS:** During the lead-in, $\geq 4 \log(10)$ decline in serum HCV RNA occurred in 178 patients; 82% of whom lost detectable HCV RNA and later broke through or relapsed. These patients had significantly ($p=0.003$) fewer clinical outcomes whether randomized to maintenance therapy or control. Following randomization serum HCV RNA increased significantly in all 90 control patients and 58/88 receiving maintenance therapy. Only 30 patients had persistent suppression of HCV RNA by $\geq 4 \log(10)$ during maintenance therapy. No significant reduction in clinical outcomes was observed in these patients. **CONCLUSIONS:** Viral suppression by $\geq 4 \log(10)$ with full dose peginterferon/ribavirin is associated with a significant reduction in clinical outcomes. Continuing low dose peginterferon maintenance therapy, even in patients with persistent viral suppression, does not lead to a further decline in clinical outcomes.

Natural killer cells are polarized towards cytotoxicity in chronic hepatitis C in an interferon-alpha-dependent manner. Ahlenstiel G, Titerence RH, Koh C, et al. *Gastroenterology*. 2009 Sep 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19747917?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND AND AIMS: Patients with chronic hepatitis C virus (HCV) infection display great variability in disease activity and progression. While virus-specific adaptive immune responses have been extensively characterized and found to be impaired in chronic hepatitis C, the role of innate immune responses in disease activity and progression of chronic hepatitis C is not well understood. **METHODS AND RESULTS:** Studying 42 HCV-infected patients and 12 healthy uninfected controls, we found an increased frequency of NK cells expressing TRAIL, NKp44, NKG2C and CD122 in chronic hepatitis C as compared to healthy controls ($p<0.05$ for all markers) and stronger activation of NK cells in the liver than in the blood ($p<0.05$). This NK cell phenotype was associated with polarization of NK cell function towards CD107a expression as a marker of degranulation, but with not increased interferon (IFN)-gamma -production of CD56 (dim) NK cells. The polarized NK cell phenotype correlated with alanine aminotransferase levels ($r(2)=0.312$, $p=0.03$). To investigate whether in vivo exposure of NK cells to HCV-induced type I IFN was causing this NK cell phenotype, peripheral blood mononuclear cells from 10 healthy controls and 8 HCV-infected patients were stimulated in the presence of IFN-alpha, which resulted in increased NK cell expression of TRAIL and CD107a ($p<0.001$), but not IFN-gamma. **CONCLUSIONS:** Collectively, these results describe a polarized NK cell phenotype induced by chronic exposure to HCV-induced IFN-alpha. This phenotype may contribute to liver injury through TRAIL expression and cytotoxicity whereas the lacking increase in IFN-gamma production may facilitate the inability to clear HCV.

Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. Dore GJ, Hellard M, Matthews G, et al. *Gastroenterology*. 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19782085?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND & AIMS: Patients with acute hepatitis C virus (HCV) infection that receive treatment achieve high rates of sustained virological response (SVR), but few studies have examined outcomes among injecting drug users (IDUs). We evaluated the efficacy of treatment of recent HCV infection in IDUs with acute and early chronic HCV. **METHODS:** We analyzed data from the Australian Trial in Acute Hepatitis C (ATAHC)-a prospective study of the natural history and treatment outcomes of patients with recent HCV infection. Participants eligible for the study had their first anti-HCV antibody positive test result within the past 6 months and either acute clinical

HCV within the past 12 months or documented anti-HCV seroconversion within 24 months. Participants with HCV received pegylated interferon (PEG-IFN)alpha-2a (180 mug/week, n=74); those with HCV/HIV co-infection received PEG-IFNalpha-2a (180 mug/week) with ribavirin (n=35) for 24 weeks. **RESULTS:** From June 2004 to February 2008, 167 participants were enrolled in the ATAC; 79% had injected drugs in the previous 6 months. Among 74 with only HCV, the SVRs were 55% and 72% by intention-to-treat and per protocol analysis, respectively. In multivariate analyses, baseline factors independently associated with lower SVR included decreased social functioning and current opiate pharmacotherapy. Adherent participants had higher SVR rates (63% vs 29%, P=0.025). Of the 35 participants with HCV/HIV co-infection, the SVRs were 74% and 75% by intention-to-treat and per protocol analysis, respectively. **CONCLUSION:** Treatment of recent HCV infection among IDUs, including those with HIV co-infection, is effective. Strategies to engage socially marginalized individuals and increase adherence should improve treatment outcomes in this population.

Reduction in neutrophil count during hepatitis C treatment: Drug toxicity or predictor of good response? Alvarez-Uria G, Day JN, Nasir AJ, Russell SK, Vilar FJ. Dig Dis Sci. 2009 Sep 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Alvarez-Uria%20G%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Bone marrow suppression is a well-recognized toxicity of the treatment of hepatitis C virus (HCV). Reduction of the peginterferon dose because of neutropenia is common in clinical practice. However, reduction of peginterferon dose during the first weeks of HCV treatment is associated with failure to achieve sustained virological response. **AIMS:** The objective of this study is to investigate whether the fall of neutrophil count during hepatitis C treatment is associated with achieving sustained virological response. **METHODS:** We performed an observational study of patients who completed peginterferon and ribavirin treatment in an Infectious Diseases Department in Manchester, UK. **RESULTS:** Of the 74 patients included in the analysis, 78% had genotype 2 or 3 hepatitis C and 15% had liver cirrhosis. Sustained virological response was achieved in 78% of patients. On univariate analysis, factors related to achieving sustained virological response were younger age, genotype 2 or 3, baseline neutrophil count, and fall of neutrophil count during treatment. Multivariate analysis showed baseline neutrophil count $>3.5 \times 10^3$ cells/mm³ [odds ratio (OR) 5.7; 95% confidence interval (CI) 1.24-26.3] and a reduction of neutrophil count $>60\%$ (OR 4.5; 95% CI 1.03-19.9) to be independently associated with achieving sustained virological response. Neutropenia was not associated with an increased risk of infections. **CONCLUSIONS:** In this observational study, higher baseline neutrophil count and fall of neutrophil count during the treatment of hepatitis C was associated with achieving sustained virological response. These findings could have important implications for the monitoring and management of HCV treatment with peginterferon if they are confirmed in other studies.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Full length characterisation of hepatitis C Virus subtype 3a reveals novel hypervariable regions under positive selection during acute infection. Humphreys I, Fleming V, Fabris P, et al. J Virol. 2009 Sep 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Humphreys%20I%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Hepatitis C virus subtype-3a is a highly prevalent and globally distributed strain that is often associated with infection by injecting drug use. This subtype exhibits particular phenotypic characteristics. In spite of this, detailed genetic analysis of this subtype has rarely been performed. We performed full-length viral sequence analysis in 18 patients with chronic HCV subtype-3a infection and assessed genomic viral variability in comparison to other HCV subtypes. Two novel regions of intra-genotypic hypervariability within the envelope protein E2, of HCV genotype-3a, were identified. We have named these HVR495 and HVR575. These consisted of flanking conserved hydrophobic amino acids and central variable residues. A 5 amino-acid insertion found only in genotype-3a and a putative glycosylation site is contained within HVR575. Evolutionary analysis of E2 showed that positively selected sites within genotype-3a infection were largely restricted to HVR1, HVR495 and HVR575. Further analysis of clonal viral populations within single hosts showed that viral variation within HVR495 and HVR575 were subject to intra-host positive selecting forces. Longitudinal analysis of 4 patients with acute HCV subtype-3a infection sampled at multiple time points showed that positively selected mutations within HVR495 and HVR575 arose early during primary infection. HVR495 and HVR575 were not present in HCV subtypes-1a, -1b, -2a or -6a. Some variability, that was not subject to positive selection was present in subtype-4a HVR575. Further defining the functional significance of these regions may have important implications for genotype-3a E2 virus/receptor interactions and for vaccine studies that aim to induce cross-reactive anti-E2 antibodies.

A novel HCV NS3 protease mutation selected by combination treatment of the protease inhibitor boceprevir and NS5B polymerase inhibitors. Chase R, Skelton A, Xia E, et al.

Antiviral Res. 2009 Sep 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Chase%20R%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Boceprevir (SCH 503034) is an orally active novel inhibitor of the hepatitis C virus (HCV) NS3 protease currently in clinical development for the treatment of hepatitis C. In this in vitro study, we demonstrate that combination of boceprevir with a nucleoside analog or a non-nucleoside HCV NS5B polymerase inhibitor was superior to treatment by single agents in inhibiting viral RNA replication in replicon cells. In the presence of boceprevir (at 5xEC(90)), the addition of 2'-C-methyl-adenosine or an indole-N-acetamide targeting the polymerase finger-loop site (at 1xEC(90)) significantly reduced the emergence of resistant replicon colonies. A higher dose (5xEC(90)) of either of the polymerase inhibitors in combination with boceprevir suppressed replicon resistance further to below detectable levels. Sequencing analysis of replicon cells selected by the combination treatment revealed known resistance mutations to the two polymerase inhibitors but no previously reported resistance mutations to boceprevir. Interestingly, a novel mutation (M175L) in the protease domain was identified. The dually resistant replicon cells were monitored for over 30 passages and sensitivity to polymerase inhibitors was found to decrease over time in a manner that correlated with the increasing prevalence of specific resistance mutations. Importantly, these cells remained sensitive to interferon-alpha and different classes of polymerase inhibitors. These findings support the rationale for clinical evaluation of combination treatment of HCV protease and polymerase inhibitors.

Modulation of hepatic fibrosis by c-Jun-N-terminal kinase inhibition. Kluwe J, Pradere JP, Gwak GY, et al. Gastroenterology. 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kluwe%20J%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND & AIMS: c-Jun N-terminal kinase (JNK) is activated by multiple profibrogenic mediators; JNK activation occurs during toxic, metabolic, and autoimmune liver injury. However, its role in hepatic fibrogenesis is unknown. **METHODS:** JNK phosphorylation was detected by immunoblot analysis and confocal immunofluorescent microscopy in fibrotic livers from mice after bile duct ligation (BDL) or CCl(4) administration and in liver samples from patients with chronic hepatitis C and non-alcoholic steatohepatitis. Fibrogenesis was investigated in mice given the JNK inhibitor SP600125 and in JNK1- and JNK2-deficient mice following BDL or CCl(4) administration. Hepatic stellate cell (HSC) activation was determined in primary mouse HSCs incubated with pan-JNK inhibitors SP600125 and VIII. **RESULTS:** JNK phosphorylation was strongly increased in livers of mice following BDL or CCl(4) administration as well as in human fibrotic livers, occurring predominantly in myofibroblasts. In vitro, pan-JNK inhibitors prevented transforming growth factor (TGF)beta-, platelet-derived growth factor (PDGF)-, and angiotensin II-induced murine HSC activation and decreased PDGF and TGFbeta signaling in human HSCs. In vivo, pan-JNK inhibition did not affect liver injury but significantly reduced fibrosis after BDL or CCl(4). JNK1-deficient mice had decreased fibrosis after BDL or CCl(4) whereas JNK2-deficient mice displayed increased fibrosis after BDL but fibrosis was not changed after CCl(4). Moreover, patients with chronic hepatitis C who displayed decreased fibrosis in response to the angiotensin receptor type 1 blocker losartan showed decreased JNK phosphorylation. **CONCLUSION:** JNK is involved in HSC activation and fibrogenesis and represents a potential target for antifibrotic treatment approaches.

Mutagenesis of the fusion peptide-like domain of hepatitis C virus E1 glycoprotein: involvement in cell fusion and virus entry. Li HF, Huang CH, Ai LS, Chuang CK, Chen SS. J

Biomed Sci. 2009 Sep 24;16(1):89. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Li%20HF%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Envelope (E) glycoprotein E2 of the hepatitis C virus (HCV) mediates binding of the virus to target cell receptors. Nevertheless, the precise role of E1 in viral entry remains elusive. **METHODS:** To understand the involvement of the fusion peptide-like domain positioned at residues 264 to 290 within envelope glycoprotein E1 in HCV infection, mutants with Ala and Asn substitutions for residues conserved between HCV and E proteins of flaviviruses or the fusion proteins of paramyxoviruses were constructed by site-directed mutagenesis and their effects on membrane fusion and viral infectivity were examined. **RESULTS:** None of these mutations affected the synthesis or cell surface expression of envelope proteins, nor did they alter the formation of a non-covalent E1-E2 heterodimer or E2 binding to the large extracellular loop of CD81. The Cys residues located at positions 272 and 281 were unlikely involved in intra- or intermolecular disulfide bond formation. With the exception of the G267A mutant, which showed increased cell fusion, other mutants displayed reduced or marginally inhibited cell fusion capacities compared to the wild-type (WT) E1E2. The G267A mutant was also an exception in human immunodeficiency virus type 1 (HIV-1)/HCV E1E2 pseudotyping analyses, in that it showed higher one-cycle infectivity; all other mutants exhibited greatly or partially reduced viral entry versus the WT pseudotype. All but the G278A and D279N mutants showed a WT-like profile of E1E2 incorporation into HIV-1 particles. Since C272A, C281A, G282A, and G288A pseudotypes bound to Huh7 cells as effectively as did the WT pseudotype, the reduced infectivity of these pseudotypes was due to their ability to inhibit cell fusion. **CONCLUSION:** Our results indicate that specific residues, but not the structure, of this fusion peptide-like domain are required for mediating cell fusion and viral entry.

Abnormal B-cell activation associated with TALL-1 over-expression and SOCS-1 suppression during chronic hepatitis C virus infection. Moorman J, Dong ZP, Ni L, Zhang C, Borthwick T, Yao ZQ. Immunology. 2009 Oct;128(2):227-35.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Moorman%20J%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Chronic hepatitis C virus (HCV) infection is associated with cirrhosis, autoimmunity and lymphoproliferative disorders. We have previously reported a differential regulation of T and B lymphocytes by HCV core protein in vitro. In this report, we employed a translational approach to characterize the activation status of peripheral B cells from individuals with chronic HCV infection and to explore potential mechanisms for B-cell dysregulation in the setting of HCV infection. In contrast to the T-cell suppression observed in HCV-infected individuals, B cells exhibit a non-specific polyclonal activation phenotype, characterized by significantly higher levels of (1) the early activation marker, CD69, (2) the costimulatory molecule, CD86, and (3) the CCR5 chemokine receptor, CD195, when compared with B cells from healthy donors in response to phytohaemagglutinin (PHA) stimulation. Importantly, tumour necrosis factor- and Apo-L-related leucocyte-expressed ligand-1 (TALL-1), also known as B-lymphocyte stimulator (BLYS), was found to be up-regulated on the surface of B cells from HCV patients in response to PHA as well as HCV core antigen stimulation. This up-regulation of TALL-1 was associated with vigorous memory B-cell responses to viral antigenic stimulation. Additionally, suppressor of cytokine signalling-1 (SOCS-1), a negative feedback immunoregulator that is inhibited in B lymphocytes by HCV core in vitro, was also inhibited in B cells from HCV patients when compared with healthy donors. **These findings suggest** that TALL-1 over-expression and SOCS-1 suppression are associated with aberrant B-cell activation, providing a plausible basis for the B-cell clonal expansion underlying the lymphoproliferative disorders and autoimmune phenomena observed during chronic HCV infection.

Structural and functional analysis of hepatitis C virus strain JFH1 polymerase. Simister P, Schmitt M, Geitmann M, et al. J Virol. 2009 Sep 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Simister%20P%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

The hepatitis C virus (HCV) isolate JFH1 represents the only cloned wild-type sequence capable of efficient replication in cell culture as well as in chimpanzees. Previous reports have pointed to the viral polymerase NS5B as a major determinant for efficient replication of this isolate. To understand the underlying mechanisms we have expressed and purified NS5B of JFH1 and of the closely related isolate J6, which replicates below the limit of detection in cell culture. The JFH1 enzyme exhibited a 5 to 10fold higher specific activity in vitro, consistent with the polymerase activity itself contributing to efficient replication of JFH1. The higher in vitro activity of the JFH1 enzyme was not due to increased RNA binding, elongation rate or processivity of the polymerase, but to a higher initiation efficiency. By using homopolymeric and heteropolymeric templates we found that purified JFH1 NS5B was significantly more efficient in de novo initiation of RNA synthesis than the J6 counterpart, particularly at low GTP concentrations, probably representing an important prerequisite for the rapid replication kinetics of JFH1. Furthermore, we solved the crystal structure of JFH1 NS5B, which displays a very closed conformation that is expected to facilitate de novo initiation. Structural analysis shows that this closed conformation is stabilized by a sprinkle of substitutions that together promote extra hydrophobic interactions between the "thumb" and "fingers" subdomains. **These analyses provide** deeper insights into the initiation of HCV RNA synthesis and might help to establish more efficient cell culture models for HCV using alternative isolates.

Tacrolimus ameliorates metabolic disturbance and oxidative stress caused by hepatitis C virus core protein. Analysis using mouse model and cultured cells. Moriya K, Miyoshi H, Tsutsumi T, et al. Am J Pathol. 2009 Sep 3. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Moriya%20K%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Hepatic steatosis and insulin resistance are factors that aggravate the progression of liver disease caused by hepatitis C virus (HCV) infection. In the pathogenesis of liver disease and metabolic disorders in HCV infection, oxidative stress due to mitochondrial respiratory chain dysfunction plays a pivotal role. Tacrolimus (FK506) is supposed to protect mitochondrial respiratory function. We studied whether tacrolimus affects the development of HCV-associated liver disease using HCV core gene transgenic mice, which develop hepatic steatosis, insulin resistance, and hepatocellular carcinoma. Administration of tacrolimus to HCV core gene transgenic mice three times per week for 3 months led to a significant reduction in the amounts of lipid in the liver as well as in serum insulin. Tacrolimus treatment also ameliorated oxidative stress and DNA damage in the liver of the core gene transgenic mice. Tacrolimus administration reproduced these effects in a dose-dependent manner in HepG2 cells expressing the core protein. The intrahepatic level of tumor necrosis factor- α , which may be a key molecule for the pathogenesis in HCV infection, was significantly decreased in tacrolimus-treated core gene transgenic mice. Tacrolimus thus reversed the effect of the core protein in the pathogenesis of HCV-associated liver disease. **These results may provide** new therapeutic tools for chronic hepatitis C, in which oxidative stress and abnormalities in lipid and glucose metabolism contribute to liver pathogenesis.

Screening for hepatitis C virus non-nucleotide resistance mutations in treatment-naive women. Dryer PD, Limketkai BN, Martin CM, et al. J Antimicrob Chemother. 2009 Sep 18. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Dryer%20PD%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_RVAbstractPlus

OBJECTIVES: Hepatitis C virus (HCV) non-nucleoside inhibitors (NNIs) target the viral RNA-dependent RNA polymerase encoded by the NS5B gene. Several NNIs share a similar allosteric binding site, and their antiviral efficacy is attenuated by a cysteine-to-tyrosine mutation at amino acid 316 (C316Y). In the current study, we assessed NS5B resistance mutations in treatment-naive individuals from a prospective natural history study of viral infections in women. **METHODS:** Partial NS5B sequences from HCV-positive women were amplified by RT-PCR. Additionally, subcloning was performed to evaluate inpatient variability in selected samples. **RESULTS:** HCV NS5B genotypes were 45 genotype 1a (57.0%), 11 genotype 1b (13.9%), 5 genotype 2a (6.3%), 3 genotype 2b (3.8%), 9 genotype 3a (11.4%) and 6 genotype 4a (7.6%). One HCV genotype 1a-infected patient was found to have the C316Y mutation (1.3%). Clonal analysis further revealed that all NS5B sequences from this individual-representing three serum samples collected 4 years apart-contained the C316Y mutation. In contrast, the S282T resistance mutation was not found in any samples. **CONCLUSIONS:** The C316Y polymerase resistance mutation was found in 1.3% of samples from HCV-infected women. The presence of this mutation over time suggests significant replicative fitness of this variant and has implications for development of new specifically targeted antiviral therapies against HCV (STAT-C) targeting this region.

Trends in hepatitis C virus infection among patients in the HIV Outpatient Study, 1996-2007. Spradling PR, Richardson JT, Buchacz K, et al. *J Acquir Immune Defic Syndr.* 2009 Sep 4. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Spradling%20PR%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Coinfection with hepatitis C virus (HCV) contributes increasingly to the morbidity and mortality of persons infected with HIV. We assessed HCV infection screening practices and determined trends in the prevalence of HCV infection in the HIV Outpatient Study (HOPS) from 1996 to 2007. **METHODS:** We calculated the proportion of patients eligible to be tested for HCV infection (i.e., never tested or previously tested negative) and the prevalence of HCV infection annually from 1996 to 2007 by sociodemographic, clinical, and HIV risk category characteristics. We used multiple logistic regression analyses to evaluate factors independently associated with HCV testing. **RESULTS:** A total of 7618 patients were active in the HOPS from 1996 through 2007. The proportion of eligible patients tested for HCV infection increased from 10.7% in 1996 to 76.6% in 2007 and increased among all demographic and risk groups. Overall HCV prevalence decreased from 36.7% in 1996 to 19.7% in 2007; decreases in prevalence occurred among all groups except for injection drug users (IDUs). In multivariate analysis, age older than 35 years, nonwhite race, Hispanic ethnicity, high-risk heterosexual and IDU risk categories, and at least 3 years of enrollment in the HOPS were associated with increased odds of having been tested for HCV infection. **CONCLUSIONS:** Screening for HCV infection in the HOPS has improved, although a sizable fraction of patients remain unscreened. The decline in overall HCV infection prevalence from 1996 to 2007 resulted primarily from a decline in the fraction of all prevalent infections in the cohort attributable to IDU patients.

Risk factors for thrombocytopenia in HIV-infected persons in the era of potent antiretroviral therapy. Marks KM, Clarke RM, Bussell JB, Talal AH, Glesby MJ. *J Acquir Immune Defic Syndr.* 2009 Sep 3. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Marks%20KM%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVE: Before potent antiretroviral therapy, thrombocytopenia was observed frequently. Little is known about risk factors for or severity and consequences of thrombocytopenia since establishment of highly effective therapy for HIV. **METHODS:** We conducted a retrospective-matched case-control study of HIV-infected adult outpatients with and without thrombocytopenia to elucidate the contribution of HIV viremia, hepatitis C infection, and other potential risk factors for thrombocytopenia. Seventy-three cases with thrombocytopenia (platelet count $<100 \times 10^9/L$ persistent for >3 months) were matched by age, sex, and first clinic visit with 73 nonthrombocytopenic controls. Risk factors and outcomes were assessed using conditional logistic regression. **RESULTS:** Nadir platelet counts in cases were $\leq 50 \times 10^9/L$ in 58% and $\leq 30 \times 10^9/L$ in 38%. In multivariate modeling, HIV RNA >400 copies/ml, hepatitis C virus infection, and cirrhosis were significantly associated with thrombocytopenia with adjusted odds ratios of 5.3 [confidence interval (CI) 1.6-17.1, $P = 0.006$], 6.1 (CI 1.6-22.6, $P = 0.007$), and 24.0 (CI 1.7-338, $P = 0.019$), respectively. Thrombocytopenia was significantly associated with major bleeding events and nonbleeding-related death. **CONCLUSIONS:** Thrombocytopenia in the era of potent antiretroviral therapy is associated with hepatitis C virus infection, cirrhosis, and uncontrolled HIV replication, and serious complications including major bleeding and death.

Efficacy and safety of pegylated interferon plus ribavirin in HIV and hepatitis C virus-coinfected patients with advanced immunosuppression. Mira JA, Gutiérrez-Valencia A, Gil Ide L, et al. Clin Infect Dis. 2009 Oct 15;49(8):e84-91.

http://www.ncbi.nlm.nih.gov/pubmed/19772388?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: The aim of this study was to assess the efficacy and safety of pegylated interferon (IFN) plus ribavirin (RBV) in human immunodeficiency virus (HIV) and hepatitis C virus (HCV)-coinfected patients with severe immunodeficiency in a clinical cohort. **METHODS:** A total of 542 HIV-infected patients receiving treatment with pegylated IFN plus RBV from June 2001 through April 2007 were included in this study. The outcome variables were sustained virologic response (SVR) rate and the emergence of AIDS-defining events during HCV infection therapy. SVR rates among patients with a CD4 cell count ≤ 250 cells/mm³ at baseline were compared with those among patients with CD4 cell counts >250 cells/mm³. The association between SVR and potential predictors was analyzed. **RESULTS:** Ten (26%) of 39 individuals with a baseline CD4 cell count ≤ 250 cells/mm³ and 198 (39%) of 503 with baseline CD4 cell counts ≥ 250 CD4 cells/mm³ achieved SVR ($P = .09$). In a nested case-control study with populations matched at a 1:2 ratio, the SVR rate was 26% in the CD4 cell count ≤ 250 cells/mm³ group and 32% in the CD4 cell count >250 cells/mm³ group ($P = .5$). Baseline CD4 cell count (≤ 250 cells/mm³ vs >250 cells/mm³) was not associated with SVR in the multivariate analysis. Two (5%) individuals in the CD4 cell count ≤ 250 cells/mm³ group experienced opportunistic events during follow-up. In the CD4 cell count ≤ 250 cells/mm³ group, severe hematological toxicity and pegylated IFN or RBV dosage reductions occurred in 16 (41%) and 12 (31%) patients, respectively. In the CD4 cell count >250 cells/mm³ group, severe hematological toxicity and pegylated IFN or RBV dosage reductions occurred in 29% ($P = .1$) and 20% ($P = .1$) of patients, respectively. **CONCLUSIONS:** The efficacy of pegylated IFN plus RBV in HIV-HCV-coinfected patients with advanced immunosuppression is substantial and not significantly different to that observed in the overall coinfecting population. HCV therapy is generally safe in the population of coinfecting patients with advanced immunosuppression.

Natural history of compensated hepatitis C virus-related cirrhosis in HIV-infected patients.

Pineda JA, Aguilar-Guisado M, Rivero A, et al. Clin Infect Dis. 2009 Oct 15;49(8):1274-82.

http://www.ncbi.nlm.nih.gov/pubmed/19772387?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To provide information about the incidence and predictors of liver decompensation and death due to liver failure in human immunodeficiency virus (HIV)-infected patients with compensated hepatitis C virus (HCV)-related cirrhosis. **METHODS:** Prospective cohort study of 154 HIV-HCV-coinfected patients with a new diagnosis of Child-Pugh-Turcotte (CPT) class A compensated cirrhosis. We evaluated time from diagnosis to the first liver decompensation and death from liver disease, as well as predictors of these outcomes. **RESULTS:** Thirty-six patients (23.4%) developed liver decompensation. The incidence of liver decompensation was 6.40 cases per 100 person-years (95% confidence interval [CI], 4.18-9.38 cases per 100 person-years). Factors independently associated with liver decompensation were lack of HCV therapy (hazard ratio [HR], 3.38; 95% CI, 1.09-10.53; $P = .035$), baseline CD4 cell counts ≤ 300 cells/mm³ (HR, 2.12; 95% CI, 1.14-5.04; $P = .021$), CPT score 6 versus 5 (HR, 3.33; 95% CI, 1.39-7.69; $P = .007$), and a diagnosis of cirrhosis based on data other than biopsy or transient elastography (HR, 2.09; 95% CI, 1.05-4.16; $P = .036$). Fifteen patients (9.7%) died; 11 (73%) of these 15 died from liver disease (mortality due to liver failure, 2.44 deaths per 100 person-years; 95% CI, 1.21-4.36 deaths per 100 person-years). Hepatic encephalopathy as the first liver decompensation (HR, 20.67; 95% CI, 2.71-

157.57; P = .003), baseline CD4 count $\leq 300/\text{mm}^3$ (HR, 0.24; 95% CI, 0.07-0.78; P = 0.17), and baseline CPT score 6 (HR, 4.50; 95% CI, 1.63-12.37; P = .004) were independently associated with liver-related death. **CONCLUSIONS:** The incidence of clinical liver events in HIV-HCV-coinfected patients with CPT class A compensated cirrhosis is close to that previously reported in HCV-monoinfected patients. Lower baseline CD4 cell counts, lack of therapy against HCV, and higher CPT score are the factors related to the occurrence of clinical liver events. Minimal changes in CPT score have strong impact in the prognosis of this population.

Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers.

Sánchez-Conde M, Montes-Ramírez ML, Miralles P, et al. J Viral Hepat. 2009 Sep 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22S%C3%A1nchez-Conde%20M%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

SUMMARY: Transient elastography (FibroScan((R))) is a novel, rapid and noninvasive technique to assess liver fibrosis. Our objective was to compare transient elastography (TE) and other noninvasive serum indexes as alternatives to liver biopsy in HIV/hepatitis C virus (HCV)-coinfected patients. The fibrosis stage (METAVIR Score), TE, the aspartate aminotransferase-to-platelet ratio index, the Forns fibrosis index, FIB-4 and HGM-2 indexes were assessed in 100 patients between January 2007 and January 2008. The diagnostic values were compared by calculating the area under the receiver operating characteristic curves (AUROCs). Using TE, the AUROC (95% CI) of liver stiffness was 0.80 (0.72-0.89) when discriminating between $F \leq 1$ and $F > 2$, 0.93 (0.85-1.00) when discriminating between $F \leq 2$ and $F > 3$ and 0.99 (0.97-1.00) when discriminating between $F \leq 3$ and $F4$. For the diagnosis of $F \geq 3$, the AUROCs of TE were significantly higher than those obtained with the other four noninvasive indexes. Based on receiver operating characteristic curves, three cutoff values were chosen to identify $F \leq 1$ (< 7 kPa), $F \geq 3$ (≥ 11 kPa) and $F4$ (≥ 14 kPa). Using these best cutoff scores, the negative predictive value and positive predictive value were 81.1% and 70.2% for the diagnosis of $F \leq 1$, 96.3% and 60% for the diagnosis of $F \geq 3$ and 100% and 57.1% for the diagnosis of $F4$. Thus, Transient elastography accurately predicted liver fibrosis and outperformed other simple noninvasive indexes in HIV/HCV-coinfected patients. Our data suggest that TE is a helpful tool for guiding therapeutic decisions in clinical practice.

Does acute hepatitis C infection affect the central nervous system in HIV-1 infected individuals?

Winston A, Garvey L, Scotney E, et al. J Viral Hepat. 2009 Sep 25. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Winston%20A%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Central nervous system (CNS) manifestations of chronic hepatitis C virus (HCV) and chronic human immune deficiency virus-1 (HIV-1) infections have been reported, but the impact of acute HCV infection on the CNS is unknown. A total of 10 individuals with chronic stable HIV-1 with documented acute HCV (HCV-RNA polymerase chain reaction positive and HCV antibody negative, group 1) underwent cerebral proton magnetic resonance spectroscopy (MRS) using acquisition parameters to quantify myo-inositol/creatine (mI/Cr) ratio in the right basal ganglia (RBG). Two matched control groups also underwent MRS; group 2: ten with chronic HIV-1 and no evidence of HCV, and group 3: ten with no evidence of HIV or HCV. Subjects also underwent

computerized neurocognitive assessments (CogState). RBG mI/Cr ratio in group 1 (acute HCV in a background of HIV) was significantly lower than that in groups 2 and 3 [2.90 (+/-0.7) vs 3.34 (+/-0.4) and 3.43 (+/-0.4), mean (SD) for group 1 vs 2 and 3 respectively, P = 0.049], with 50% of subjects in group 1 having a mI/Cr ratio below the lowest observed ratio in either of the other groups. On neurocognitive testing, significant defects in the monitoring domain were observed in group-1, compared with matched controls (P = 0.021). Acute HCV in HIV-1 infected subjects is associated with CNS involvement. Clinicians should be vigilant of early CNS involvement when assessing subjects with acute HCV.

HIV-HCV co-infected patients with low CD4+ cell nadirs are at risk for faster fibrosis progression and portal hypertension. Reiberger T, Ferlitsch A, Sieghart W, et al. J Viral Hepat. 2009 Sep 25. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19780945?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Patients co-infected with the human immunodeficiency virus (HIV) and the hepatitis C virus (HCV) are fraught with a rapid fibrosis progression rate and with complications of portal hypertension (PHT) We aimed to assess the influence of immune function [Centers of Disease Control and Prevention (CDC) stage] on development of PHT and disease progression in HIV-HCV co-infection. Data of 74 interferon-naïve HIV-HCV co-infected patients undergoing liver biopsy, measurement of portal pressure and of liver stiffness and routine laboratory tests (including CD4+ cell count, HIV and HCV viral load) were analysed. Time of initial exposure (risk behaviour) was used to assess fibrosis progression. Fibrosis progression, time to cirrhosis and portal pressure were correlated with HIV status (CDC stage). HIV-HCV patients had rapid progression of fibrosis [0.201 +/- 0.088 METAVIR fibrosis units/year (FU/y)] and accelerated time to cirrhosis (24 +/- 13 years), high HCV viral loads (4.83 x 10⁶ IU/mL) and a mean HVPG at the upper limit of normal (5 mmHg). With moderate or severe immunodeficiency, fibrosis progression was even higher (CDC-2 = 0.177 FU/y; CDC-3 = 0.248 FU/y) compared with patients with higher CD4+ nadirs (CDC-1 = 0.120 FU/y; P = 0.0001). An indirect correlation between CD4+ cell count and rate of fibrosis progression (R = -0.6654; P < 0.001) could be demonstrated. Hepatic venous pressure gradient (HVPG) showed early elevation of portal pressure with median values of 4, 8 and 12 mmHg after 10, 15 and 20 years of HCV infection for CDC-3 patients. Patients treated with highly active anti-retroviral therapy (HAART) had similar rates of progression and portal pressure values than patients without HAART. Progression of HCV disease is accelerated in HIV-HCV co-infection, being more pronounced in patients with low CD4+ cell count. A history of a CD4+ cell nadir <200/μL is a risk factor for rapid development of cirrhosis and PHT. Thus, HCV treatment should be considered early in patients with HIV-HCV co-infection and largely preserved CD4+ cell counts.

Kupffer cells are depleted with HIV immunodeficiency and partially recovered with antiretroviral immune reconstitution. Balagopal A, Ray SC, De Oca RM, et al. AIDS. 2009 Sep 21. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Balagopal%20A%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: HIV-related enhancement of gut microbial translocation is associated with progression of hepatic fibrosis. Although hepatic macrophages (Kupffer cells) clear most microbial translocation products and can be infected by HIV, their fate in HIV progression has not been carefully investigated. **METHODS:** We studied Kupffer cell density (KCD) in 76 HIV-hepatitis C virus coinfecting patients investigated at various stages of liver disease and CD4 lymphocyte depletion (and restoration). **RESULTS:** KCD averaged 23 cells per high-powered field (range 4.4-

52.2) and was highest in portal and periportal regions as compared with centrilobular regions ($P < 0.001$). No differences were detected in KCD by age, liver fibrosis stage, or hepatic inflammatory score. Compared with individuals without apparent HIV-related immunosuppression, however, KCD was substantially lower in persons with lower peripheral blood CD4 lymphocyte counts ($P = 0.027$) and lowest among those with deepest CD4 lymphocyte nadir ($P = 0.006$). After the initial liver biopsy, eight patients began antiretroviral therapy and had immune restoration (≥ 2 -fold increase in peripheral CD4 lymphocyte count) and a second histologic evaluation with a median of 36.8 months later (range 28.1-58.4 months); KCD increased in all ($P = 0.007$). **CONCLUSION:** Given the central role of Kupffer cells in controlling microbial translocation, these data suggest Kupffer cell loss needs to be considered in the pathogenesis of liver fibrosis in HIV-hepatitis C virus coinfecting persons. The abundance of portal and periportal Kupffer cells is suggestive of their contribution to fibrosis in periportal regions in chronic viral hepatitis.

Interobserver concordance in the assessment of liver fibrosis in HIV/HCV-coinfecting patients using transient elastometry. Neukam K, Recio E, Camacho A, et al. Eur J Gastroenterol Hepatol. 2009 Sep 19. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19773664?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: Although the reproducibility of transient elastometry (TE) in hepatitis C virus (HCV)-monoinfected patients seems to be high, this may not be the case in HIV/HCV-coinfecting patients because of different degrees of steatosis and/or inflammation. This study was aimed to determine the interobserver concordance of TE measurements in HIV/HCV-coinfecting patients. **METHODS:** A total of 188 patients were evaluated in a cross-sectional, prospective study in two hospitals. The interobserver variability of TE results and the rate of unequal classification of significant fibrosis (cutoff value = 7.2 kPa) and cirrhosis (cutoff value = 14.6 kPa) for two observers were evaluated. **RESULTS:** The values of liver stiffness (LS) for two observers highly correlated [intraclass correlation index = 0.976; 95% confidence interval (CI): 0.968-0.982]. The kappa indexes for the concordance of patient classification were 0.60 for significant fibrosis and 0.89 for cirrhosis. Using two cutoff points to diagnose or rule out significant fibrosis ($LS \geq 9$ kPa or < 6 kPa) yielded a kappa index of 0.96, but 46% of patients were not classified. Covariables that influenced the interobserver agreement were a high interquartile range in the determination (adjusted odd ratio: 0.189; 95% CI: 0.087-0.411; $P = 0.001$) and elevated levels of triglycerides (adjusted odd ratio: 1.004; 95% CI: 1.000-1.008; $P = 0.031$). **CONCLUSION:** TE measurement is an observer-independent method to evaluate LS in HIV/HCV coinfecting patients. The concordance of the classification of mild-to-severe fibrosis is good and for the diagnosis of cirrhosis is excellent. Lower interquartile ranges and triglyceride levels lead to a higher interobserver agreement.

Inability to access addiction treatment and risk of HIV infection among injection drug users recruited from a supervised injection facility. Milloy MJ, Kerr T, Zhang R, Tyndall M, Montaner J, Wood E. J Public Health (Oxf). 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Milloy%20MJ%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Treatment for drug addiction is effective in reducing the harms of injection drug use, including infection with HIV and/or hepatitis C. We sought to examine the prevalence and correlates of being unable to access addiction treatment in a representative sample of injection drug users randomly recruited from a supervised injection facility. **METHODS:** Using generalized estimating equations, we determined the prevalence and factors associated with being unable to access addiction treatment. **RESULTS:** Between 1 July 2004 and 30 June 2006, 889 individuals

completed at least one interview and were included in this analysis. At each interview, approximately 20% of respondents reported trying but being unable to access any type of drug or alcohol treatment in the previous 6 months. Being unable to access treatment was independently associated with recent incarceration, daily use of heroin and borrowing used syringes. In a secondary question, the majority of individuals reported waiting lists were the reason for being unable to access treatment. **CONCLUSION:** Given the independent association between inability to access addiction treatment and elevated HIV risk behavior, these results suggest expanding addiction treatment may contribute significantly to HIV prevention efforts in this population.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Xanthohumol enhances antiviral effect of interferon alpha-2b against bovine viral diarrhea virus, a surrogate of hepatitis C virus. Zhang N, Liu Z, Han Q, Chen J, Lv Y. *Phytomedicine*. 2009 Sep 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19748253?ordinalpos=10&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Xanthohumol (XN) is a natural compound with multifunctional potentials, including antiviral activity. In this study, the antiviral activity of addition of XN to interferon (IFN)-alpha was examined and compared with each compound alone using bovine viral diarrhea virus (BVDV), a surrogate model of hepatitis C virus (HCV). BVDV E2 protein and the viral RNA level were determined by immunofluorescence and quantitative real-time RT-PCR, respectively. The addition of XN to IFN-alpha significantly improved CPEs induced by the virus and inhibited BVDV E2 protein and viral RNA levels. The interaction between XN and IFN-alpha was significant ($P < 0.001$). XN at 3.13 $\mu\text{g}/\text{ml}$ in combination with IFN-alpha at 50 IU/ml showed greater inhibitory effect on the viral RNA level than each compound used alone at 6.25 $\mu\text{g}/\text{ml}$ and 100 IU/ml, respectively, indicating synergistic effect on BVDV replication in this combination. The inhibitory activity in all the tested combinations of XN and IFN-alpha was stronger than that of each compound used alone at the corresponding concentration. **These results suggest** that XN in combination with IFN-alpha exhibited a greater in vitro antiviral effect compared with each compound used alone. Further studies are deserved to investigate the anti-HCV activity of XN and the potential of XN in formulating novel anti-HCV regimen.

Complementary and alternative medicine use in chronic liver disease patients. Ferrucci LM, Bell BP, Dhotre KB, et al. *J Clin Gastroenterol*. 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Ferrucci%20LM%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

GOALS: To examine a wide range of sociodemographic and clinical characteristics as potential predictors of complementary and alternative medicine (CAM) use among chronic liver disease (CLD) patients, with a focus on CAM therapies with the greatest potential for hepatotoxicity and interactions with conventional treatments. **BACKGROUND:** There is some evidence that patients with CLD commonly use CAM to address general and CLD-specific health concerns. **STUDY:** Patients enrolled in a population-based surveillance study of persons newly diagnosed with CLD between 1999 and 2001 were asked about current use of CAM specifically for CLD. Sociodemographic and clinical information was obtained from interviews and medical records. Predictors of CAM use were examined using univariate and multivariate logistic regression analysis. **RESULTS:** Of the 1040 participants, 284 (27.3%) reported current use of at least 1 of 3 CAM therapies of interest. Vitamins or other dietary supplements were the most commonly used therapy,

reported by 188 (18.1%) patients. This was followed by herbal medicine (175 patients, 16.8%) and homeopathy (16 patients, 1.5%). Several characteristics were found to be independent correlates of CAM use: higher education and family income, certain CLD etiologies (alcohol, hepatitis C, hepatitis C and alcohol, and hepatitis B), and prior hospitalization for CLD. **CONCLUSIONS:** Use of CAM therapies that have the potential to interact with conventional treatments for CLD was quite common among this population-based sample of patients with CLD. There is a need for patient and practitioner education and communication regarding CAM use in the context of CLD.

Silymarin inhibits in vitro T cell proliferation and cytokine production in hepatitis C virus infection. Morishima C, Shuhart MC, Wang CC, et al. *Gastroenterology*. 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19782083?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND AND AIMS: Silymarin, an extract from the seeds of the milk thistle plant *Silybum marianum*, has been used for centuries for the treatment of chronic liver diseases. Despite common use by patients with hepatitis C in the U.S., its clinical efficacy remains uncertain. The goal of this study was to determine if silymarin has in vitro effects on immune function that might have implications for its potential effect on HCV-induced liver disease. **METHODS:** Freshly isolated PBMC and T cells from HCV-infected and uninfected subjects were tested in vitro for responses to nonspecific and antigenic stimulation in the presence and absence of a standardized preparation of silymarin (MK001). **RESULTS:** Minimal MK001 toxicity on PBMC was found at concentrations between 5-40 µg/mL. MK001 dose-dependently inhibited the proliferation and secretion of TNF-α, IFN-γ, and IL-2 by PBMC stimulated with anti-CD3. In addition, MK001 inhibited proliferation by CD4+ T cells to HCV, *Candida* and Tetanus protein antigens, and by HLA-A2/HCV1406-1415-specific CD8+ T cells to allogeneic stimulation. MK001 inhibited T cell TNF-α and IFN-γ cytokine secretion to Tetanus and *Candida* protein antigens. Finally, MK001 inhibited NF-κB transcriptional activation after T cell receptor-mediated stimulation of Jurkat T cells, consistent with its ability to inhibit Jurkat T cell proliferation and secretion of IL-2.

CONCLUSION: Silymarin's ability to inhibit the proliferation and pro-inflammatory cytokine secretion of T cells, combined with its previously described anti-viral effect suggests a possible mechanism of action that could lead to clinical benefit during HCV infection.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Toxicology and biodistribution study of CIGB-230, a DNA vaccine against hepatitis C virus. Bacardí D, Amador-Cañizares Y, Cosme K, et al. *Hum Exp Toxicol*. 2009 Sep 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Bacard%C3%AD%20D%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

CIGB-230, a mixture of a DNA plasmid expressing hepatitis C virus (HCV) structural antigens and a HCV recombinant capsid protein, has demonstrated to elicit strong immune responses in animals. The present study evaluated the plasmid biodistribution after the administration of CIGB-230 in mice, as well as toxicity of this vaccine candidate in rats. In the biodistribution study, mice received single or repeated intramuscular injections of CIGB-230, 50 µg of plasmid DNA mixed with 5 µg of Co.120 protein. Plasmid presence was assessed in ovaries, kidney, liver, pancreas, mesenteric ganglion, blood, and muscle of the injection site by a qualitative polymerase chain

reaction. The toxicology evaluation included treatment groups receiving doses 5, 15, or 50 times higher, according to the body weight, than the expected therapeutic clinical dose. During the first hour after repeated inoculation, a promiscuous distribution was observed. However, 3 months later, plasmid could not be detected in any tissue. There was an absence of detectable adverse effects on key toxicology parameters and no damage evidenced in inspected organs and tissues. **These results indicate** that CIGB-230 is nontoxic at local and systemic levels and no concerns about persistence are observed, which support clinical testing of this vaccine candidate against HCV.

Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites and normal serum creatinine levels. Seo YS, Jung ES, An H, et al. [J38: Liver Int. 2009 Sep 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19725889?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

ABSTRACT BACKGROUND/AIMS: Serum creatinine (Cr) is not a reliable marker for early detection of renal dysfunction in patients with cirrhotic ascites. Several reports have suggested that cystatin C (CysC) is more sensitive than Cr for detecting reduced renal function in these patients. This study evaluated the clinical significance of CysC in patients with cirrhotic ascites and a normal serum Cr level. **METHODS:** We enrolled patients with ascites and a normal serum Cr level (<1.2 mg/dl). Liver function tests, international normalized ratio (INR) and serum Cr and CysC levels were measured on the same day for all patients. CysC levels were measured using the automated latex-enhanced immunonephelometric method. The endpoint of follow-up was the development of hepatorenal syndrome (HRS) or mortality. **RESULTS:** Seventy-eight patients with cirrhotic ascites were enrolled in the study (58 men and 30 women; age, 53+/-11 years). The underlying liver diseases in these patients were chronic hepatitis B (37%), chronic hepatitis C (4%), alcoholic liver disease (53%) and others (6%). Forty-six (59%) and 32 (41%) patients were in Child-Pugh classes B and C respectively. HRS developed in 14 patients during the follow-up period (349+/-241 days), with cumulative incidences of 10.2% and 20.4% at 6 and 12 months respectively. The CysC level was the only independent predictive factor for HRS. Twenty-three patients died during the follow-up period. CysC level and INR were independent factors for predicting mortality. **CONCLUSION:** Serum CysC level is a good marker for predicting HRS and survival in patients with cirrhotic ascites and a normal Cr level.

Clinical case registries: Simultaneous local and national disease registries for population quality management. Backus LI, Gavrilov S, Loomis TP, et al. J Am Med Inform Assoc. 2009 Aug 28. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Backus%20LI%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

The Department of Veterans Affairs (VA) has a system-wide, patient-centric electronic medical record system (EMR) within which we developed the Clinical Case Registries (CCR) to support population-centric delivery and evaluation of VA medical care. To date, we have applied the CCR to populations with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Local components use diagnosis codes and laboratory test results to identify patients who may have HIV or HCV and support queries on local care delivery with customizable reports. For each patient in a local registry, key EMR data are transferred via HL7 messaging to a single national registry. From 128 local registry systems, over 60,000 and 320,000 veterans in VA care have been identified as having HIV and HCV, respectively, and entered in the national database. Local and national reports covering demographics, resource utilization, quality of care metrics and medication safety issues have been generated.

Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. Page K, Hahn JA, Evans J, et al. *J Infect Dis.* 2009 Oct 15;200(8):1216-26.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Page%20K%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Hepatitis C virus (HCV) infection, clearance, and reinfection are best studied in injection drug users (IDUs), who have the highest incidence of HCV and are likely to represent most infections. **METHODS:** A prospective cohort of HCV-negative young IDUs was followed up from January 2000 to September 2007, to identify acute and incident HCV and prospectively study infection outcomes. **RESULTS:** Among 1,191 young IDUs screened, 731 (61.4%) were HCV negative, and 520 (71.1%) of the 731 were enrolled into follow-up. Cumulative HCV incidence was 26.7/100 person-years of observation (95% confidence interval [CI], 21.5-31.6). Of 135 acute/incident HCV infections, 95 (70.4%) were followed; 20 (21.1%) of the 95 infections cleared. Women had a significantly higher incidence of viral clearance than did men (age-adjusted hazard ratio, 2.91 [95% CI, 1.68-5.03]) and also showed a faster rate of early HCV viremia decline ([Formula: see text]). The estimated reinfection rate was 24.6/100 person-years of observation (95% CI, 11.7-51.6). Among 7 individuals, multiple episodes of HCV reinfection and reclearance were observed. **CONCLUSIONS:** In this large sample of young IDUs, females show demonstrative differences in their rates of viral clearance and kinetics of early viral decline. Recurring reinfection and reclearance suggest possible protection against persistent infection. These results should inform HCV clinical care and vaccine development.

Improving the diagnosis of acute hepatitis C virus infection with expanded viral load criteria. McGovern BH, Birch CE, Bowen MJ, et al. *Clin Infect Dis.* 2009 Oct 1;49(7):1051-60.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22McGovern%20BH%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: The diagnosis of acute hepatitis C virus (HCV) infection is imprecise because antibody testing does not differentiate between acute and chronic infection. Although virologic features, such as viral load fluctuations and low levels of viremia, have been noted to be characteristic of acute HCV infection, these parameters have not been used for diagnosis. **METHODS:** We validated the use of these novel parameters (ie, viral load fluctuations >1 log and HCV RNA levels <100,000 IU/mL) in a cohort of acute HCV seroconverters. We then applied standard diagnostic criteria for acute HCV infection in a cohort of high-risk injection drug users entering prison with suspected acute HCV infection (n=37). We subsequently assessed whether these novel virologic parameters, measured serially over a 10-week period, could enhance the diagnosis of acute infection. **RESULTS:** Low-level viremia and viral load fluctuations were highly prevalent in our cohort of acute seroconverters (81% and 86%, respectively), whereas low-level viremia occurred in only 13% of control patients with chronic infection. With use of standard criteria, 37 inmates received a diagnosis of acute HCV infection. Among the 35 patients with HCV RNA detectable at baseline, we found low-level viremia to be highly prevalent (n=27; 77%); among patients with a minimum of 2 HCV RNA samples, we demonstrated viral fluctuations in more than one-third (n=9; 36%). **CONCLUSIONS:** The diagnosis of acute infection in HCV-seropositive patients is strengthened by the use of virologic parameters that are uncommon in chronic disease. Viral load fluctuations and low levels of HCV RNA should be incorporated into standard diagnostic criteria.

The impact of the prevention programme of hepatitis C over more than a decade: the French experience. Delarocque-Astagneau E, Meffre C, Dubois F, Pioche C, et al. *J Viral Hepat.* 2009 Sep 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Delarocque-Astagneau%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

To assess the impact of the French national hepatitis C prevention programme initiated in 1999, we analysed trends in hepatitis C virus (HCV) prevalence, testing and characteristics of HCV-infected patient at first referral from 1994 to 2006. We used four data sources: Two national population-based sero-prevalence surveys carried out in 1994 and 2004; two surveillance networks, one based on public and private laboratories throughout France and the other on hepatology reference centres, which aim to monitor, respectively, trends of anti-HCV screening and of epidemiological-clinical characteristics of HCV patients at first referral. Between 1994 and 2004, the anti-HCV prevalence for adults aged 20-59 years decreased from 1.05 (95% confidence interval 0.75-1.34) to 0.71 (0.52-0.97). During the same period, those anti-HCV positive with detectable HCV RNA decreased from 81 to 57%, whereas, the proportion of anti-HCV positive persons aware of their status evolved from 24 to 56%. Anti-HCV screening activity increased by 45% from 2000 to 2005, but decreased in 2006 (-10%), while HCV positivity among those tested decreased from 4.3 to 2.9%. The proportion of cirrhosis at first referral remains around 10% between 2001 and 2006, with many patients with excessive alcohol consumption (34.7% among males) or viral co-infections (HIV seropositivity for 5.2% patients). Our analysis indicates that the national programme had a positive impact at the population level through improved prevention, screening and management. There is still a need to identify timely those at risk for earlier interventions, to assess co-morbidities better and for a multidisciplinary approach to HCV management.

Depression and protective factors of mental health in people with hepatitis C: A questionnaire survey. Erim Y, Tagay S, Beckmann M, et al. *Int J Nurs Stud.* 2009 Sep 18. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19766994?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Most studies investigating the effects of chronic hepatitis C (HCV) infection on the central nervous system have focused on cognitive impairment or on the health-related quality of life, but only few on depression. **OBJECTIVES:** This study investigated depression in HCV-infected people. Sense of coherence and social support were surveyed as protective factors of mental health. **METHODS:** In a cross-sectional study-design, 81 HCV-infected people with mild liver disease, who were not receiving antiviral therapy, were surveyed by validated measures. Anxiety (HADS), depression (BDI), psychopathological symptoms (SCL-90-R), social support (F-SozU) and resilience (SOC) were assessed. **RESULTS:** Higher levels of depression than normal controls ($p=.001$) and a wide range of psychological symptoms were associated with HCV infection. Women, single participants, and persons with a shorter interval after first diagnosis exhibited significantly higher scores of depression. Gender and sense of coherence predicted depression scores in HCV people ($R(2)=.42$, $p<.001$). **CONCLUSIONS:** The expression of depression in HCV-infected people is modulated not only by biological but also by psychological factors of mental health. Sense of coherence as a protective factor has a significant impact on the degree of depression. Furthermore, the high prevalence of depression and anxiety among persons not receiving antiviral therapy justifies psychosocial screening and support for HCV people independent of antiviral therapy.

Predicting clinical and histological outcomes based on standard laboratory tests in

advanced chronic hepatitis C. Ghany MG, Lok AS, Everhart JE, et al. *Gastroenterology*. 2009 Sep 17. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19766643?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND & AIMS: Predictors of clinical outcomes and histological progression among patients with chronic hepatitis C and advanced fibrosis are poorly defined. We developed statistical models to predict clinical and histological outcomes in such patients. **METHODS:** Baseline demographic, clinical, and histological data from Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial participants were subjected to multivariate analyses to determine their ability to predict clinical outcomes (ascites, spontaneous bacterial peritonitis, Child-Turcotte-Pugh score ≥ 7 on two consecutive visits, variceal bleeding, hepatic encephalopathy, and liver-related death) and histological outcome (≥ 2 -point increase in Ishak fibrosis stage) during the 3.5 years of the trial. **RESULTS:** Of 1,050 randomized patients, 135 had one or more clinical outcomes a median of 23 (range 1-45) months after randomization. Factors associated with a clinical outcome in multivariate analyses were higher AST/ALT ratio, lower albumin, lower platelet count, higher total bilirubin, and more advanced Ishak fibrosis score ($p < 0.0001$). The cumulative 3.5-year incidence of a clinical outcome was 2% in the lowest and 65% in the highest risk group. Of 547 patients without cirrhosis at baseline and at least one follow-up biopsy, 152 had a histological outcome. Independent variables associated with a histological outcome were higher body mass index, lower platelet count, and greater hepatic steatosis ($p < 0.0001$). **CONCLUSION:** In patients with chronic hepatitis C and advanced fibrosis, risk of clinical complications and fibrosis progression during 3.5 years can be predicted using baseline laboratory tests and histological data. Our models may be useful in counseling patients and determining the frequency of monitoring.

Combined effects of alcohol and hepatitis C: A secondary analysis of alcohol use biomarkers and high-risk behaviors from two medication trials for alcohol dependence.

Plebani JG, Tirado CF, Pettinati HM, et al. *Addict Behav*. 2009 Sep 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Plebani%20JG%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: The goal of this secondary analysis was to examine the combined effects of HCV infection and recent alcohol use on baseline biologic markers of alcohol consumption in two outpatient medication trials for alcohol dependence. In addition, the relationship between Hepatitis C virus (HCV) infection and behavioral risk factors for HCV infection in these clinical populations were examined. **METHODS:** Data ($n=345$) from two randomized, placebo-controlled trials of naltrexone and psychosocial treatment for alcohol dependence (Study I, $n=212$) and comorbid alcohol and cocaine dependence (Study II, $n=133$) were used to examine baseline measures of HCV risk behaviors (injection drug use, needle sharing), and biomarkers of alcohol use (AST, ALT, GGT and CDT) were compared by HCV serostatus first within each study and then across studies.

RESULTS: Although groups had differing sociodemographic profiles (as indicated by race, marital status, level of education) subjects in Study I exhibited no statistically significant differences from the Study II cohort in HCV prevalence (12.7 vs. 20.0%, $p=0.07$), lifetime history of injection drug use (13.8 vs. 22.0%, $p=0.74$), lifetime history of needle sharing (9.1 vs. 18.0%, $p=0.62$). As such, the data from both studies were analyzed together. Regardless of drinking status, HCV infection was significantly associated with an upward shift in the baseline level of ALT, AST, and GGT ($p < 0.006$ for all measures) and a downward shift in baseline CDT ($p=0.002$). When using standard laboratory cutoff values to determine clinically significant elevations, HCV seropositivity was significantly associated with elevations in ALT, AST, GGT ($p < 0.001$), and with decreases in CDT ($p=0.002$).

CONCLUSIONS: These data emphasize the importance of evaluating HCV infection and HCV risk behaviors at intake in medication trials for alcohol dependence and also raise questions regarding the use of cutoff scores for ALT, AST, GGT and CDT levels as biologic markers of alcohol use in subjects when HCV status is unknown.

Managing depression during hepatitis C treatment. Sockalingam S, Abbey SE. *Can J Psychiatry.* 2009 Sep;54(9):614-25.

http://www.ncbi.nlm.nih.gov/pubmed/19751550?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: The prevalence of hepatitis C virus (HCV) infection in Canada is estimated to be 1% and expected to increase during the next decade. Mental illness, particularly depression, is common among HCV-infected patients and remains an obstacle to interferon-alpha (IFN-alpha) treatment. We summarize the risk factors for interferon-alpha-induced major depressive disorder (IFN-alpha-MDD) in HCV patients and the evidence for antidepressant prophylaxis and symptomatic antidepressant treatment of depression. **METHODS:** We searched MEDLINE, EMBASE, and CINAHL for randomized controlled or quasi-experimental trials evaluating antidepressant prophylactic and symptomatic treatment approaches for depression emerging during IFN-alpha treatment. Manual searches of references listed in review articles, case series, and anecdotal reports supplemented our literature search. **RESULTS:** A total of 9 trials involving prophylactic and symptomatic treatment approaches for IFN-alpha-MDD are summarized in our review.

Antidepressant pretreatment is beneficial for patients with elevated baseline depressive symptoms and a preexisting history of IFN-alpha-MDD. Although limited evidence exists for several antidepressant agents, much of the evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are safe and efficacious in treating depressive symptoms secondary to IFN-alpha therapy.

CONCLUSION: Both antidepressant pretreatment and symptomatic treatment are viable strategies for treating IFN-alpha-MDD. Improved treatment outcomes and early identification of depression during HCV treatment can be achieved using an integrated medical and mental health treatment approach.