

Caring Ambassadors Hepatitis C Program Newsletter
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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	1 - 10
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	10 - 13
HIV/HCV COINFECTION	13 - 15
COMPLEMENTARY AND ALTERNATIVE MEDICINE	15
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS	16 - 17

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Successful treatment of chronic hepatitis C virus infection in severely opioid-dependent patients under heroin maintenance.

Schulte B, Schütt S, Brack J, et al. Drug Alcohol Depend. 2010 Feb 16. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20167441?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: Severely opioid-dependent patients are at high risk of both acquiring and spreading the hepatitis C virus (HCV). It is uncertain, however, whether these patients are possible candidates for HCV treatment. We therefore explored treatment retention and adherence as well as sustained viral response in co-morbid severely opioid-dependent subjects under heroin maintenance, who previously failed in conventional substitution treatment or were not in any drug treatment. **METHODS:** All patients in heroin maintenance in the German heroin trial, who received standard antiviral HCV therapy with pegylated interferon and ribavirin, were included. Co-consumption of licit and illicit drugs was tolerated as long as it did not interfere with treatment. **RESULTS:** Twenty-six patients in heroin maintenance were treated for chronic HCV infection. Both the Global Severity Index of the Symptom Checklist 90-R (average score 65.9) and the Opiate Treatment Index (average score 16.6) indicated relevant co-morbidity. Twenty-one patients (81%) were retained in treatment; the adherence rate was 92%. Eighteen patients (69%) achieved a sustained viral response, with a 100% response rate for genotype 2, 90% for genotype 3, and 42% for genotype 1. **DISCUSSION:** This is the first study that investigates the feasibility of antiviral HCV treatment in a well-defined sample of co-morbid severely opioid-dependent subjects in heroin maintenance treatment. Viral response rates are comparable to non-drug-user populations. Within a need-adapted treatment setting, HCV treatment may even be extended to difficult-to-treat opioid-dependent patients.

Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. Bruno S, Shiffman ML, Roberts SK, et al. Hepatology. 2010 Feb;51(2):388-97.

http://www.ncbi.nlm.nih.gov/pubmed/19918980?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1

The objective of this study is to determine the efficacy and safety of peginterferon alfa-2a (40 KD)/ribavirin in patients with advanced fibrosis. Data from 341 genotype 1/4 patients (99 with bridging fibrosis/cirrhosis) treated for 48 weeks and 1547 genotype 2/3 patients (380 with bridging fibrosis/cirrhosis) treated for 16 or 24 weeks enrolled in three randomized international studies were analyzed. Sustained virological response (SVR) rates decreased progressively from

60% in genotype 1/4 patients without advanced fibrosis to 51% in those with bridging fibrosis and 33% in those with cirrhosis (trend test $P = 0.0028$); and from 76% to 61% and 57%, respectively, in genotype 2/3 patients treated for 24 weeks (trend test $P < 0.0001$). Irrespective of genotype, patients without advanced fibrosis were more likely to have an earlier response to treatment that was associated with higher SVR rates and lower relapse rates during untreated follow-up. Among patients with or without a diagnosis of advanced fibrosis, rates of SVR and relapse were similar for patients with similar responses in the first 12 weeks. **CONCLUSION:** Compared with patients with less severe disease, SVR rates are significantly lower in patients with advanced fibrosis. However, irrespective of genotype and degree of fibrosis, the time to become hepatitis C virus (HCV) RNA undetectable was the strongest predictor of SVR.

Efficacy and tolerability of peginterferon alfa-2a or alfa-2b plus ribavirin in the daily routine treatment of patients with chronic hepatitis C in Germany: The PRACTICE Study.

Witthoef T, Hueppe D, John C, et al. J Viral Hepat. 2010 Feb 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Witthoef%20T%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

In randomized clinical trials, treatment with peginterferon plus ribavirin (RBV) results in a sustained virological response (SVR) in around half of hepatitis C virus genotype 1-infected and 80% of genotype 2/3-infected individuals. This study aimed to evaluate efficacy and tolerability of peginterferon alfa-2a plus RBV compared with peginterferon alfa-2b plus RBV for the treatment of chronic hepatitis C in routine clinical practice. The intent-to-treat cohort consisted of 3414 patients treated with either peginterferon alfa-2a plus RBV (Group A) or peginterferon alfa-2b plus RBV (Group B) in 23 centres participating in the large, multicentre, observational PRACTICE study. Collected data included baseline characteristics, treatment regimen, RBV dose and outcome. Rates of early virological response, end of treatment response and SVR were 76.6%, 75.7% and 52.9% in Group A, and 70.2%, 65.6% and 50.5% in Group B, respectively. In patients matched by baseline parameters, 59.9% of patients in Group A and 55.9% in Group B achieved an SVR ($P \leq 0.051$). In genotype 1-infected patients matched by baseline parameters and cumulative RBV dose, SVR rates were 49.6% and 43.7% for Group A and Group B, respectively ($P \leq 0.047$); when matched by baseline parameters and RBV starting dose, SVR rates were 49.9% and 44.6%, respectively ($P = 0.068$). Overall, 21.8% of group A and 29.6% of group B patients discontinued treatment ($P \leq 0.0001$). The efficacy and tolerability of peginterferon plus RBV in this large cohort of patients treated in routine daily practice was similar to that in randomized clinical trials. In matched pairs analyses, more patients achieved an SVR with peginterferon alfa-2a compared with peginterferon alfa-2b.

Clinical trial: low- and standard-dose peginterferon alfa-2a for chronic hepatitis C, genotype 2 or 3 - efficacy, tolerability, viral kinetics and cytokine response. Rotman Y, Borg BB, Soza A, et al. Aliment Pharmacol Ther. 2010 Feb 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Rotman%20Y%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND/AIMS: Chronic infection with hepatitis C, genotype 2/3, responds better than other genotypes to peginterferon and ribavirin treatment. We hypothesized that a lower dose of peginterferon would be as effective, but less toxic than standard doses. **METHODS:** 30 patients were treated with low-dose peginterferon alfa-2a (90 mug/week) and 27 patients with standard doses (180 mug/week) for 24 weeks in combination with 800 mg/day of ribavirin. Patients who

failed treatment were offered 48 weeks of standard-dose treatment. Viral and serum IP-10 levels were measured and early viral kinetic parameters were calculated. **RESULTS:** Sustained virological response was achieved in 68% of the low-dose and 87% of the standard-dose patients (per-protocol, $p=0.79$ for non-inferiority). Retreatment was successful in all patients who tolerated full dose and duration. The standard-dose group had greater first phase declines of viral levels and faster time to negativity. The second phase slope was not dose-dependent. IP-10 induction was significantly greater with the standard dose. Although fatigue and general feeling during treatment were worse for standard dose, hematologic toxicity and depression did not differ between groups. **CONCLUSIONS:** A lower dose of peginterferon is associated with some symptomatic benefit but the response is not equivalent to standard dosing.

Clinical trial: efficacy and safety of oral PF-03491390, a pancaspase inhibitor - a randomized placebo-controlled study in patients with chronic hepatitis C. Shiffman ML, Pockros P, McHutchison JG, et al. *Aliment Pharmacol Ther.* 2010 Feb 16. [Epub ahead of print] Schiff ER, Morris M, Burgess G.

http://www.ncbi.nlm.nih.gov/pubmed/20163376?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2

BACKGROUND: Elevated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) reflect hepatocellular injury in patients with chronic hepatitis C virus (HCV). Increased apoptosis and activated caspases are present in these patients. PF-03491390 inhibits multiple caspases and lowers serum AST and ALT levels in patients with chronic liver diseases. Aim: To determine if treatment with an oral pancaspase inhibitor could reduce serum AST and ALT in patients with HCV. **METHODS:** Double-blind, randomized, placebo-controlled, parallel-dose study in 204 patients treated with placebo or PF-03491390 (5 mg, 25 mg or 50 mg) orally twice daily (BID) for up to 12 weeks. Serum AST and ALT were monitored weekly. **RESULTS:** Significant reductions in serum AST and ALT were observed within 1 week of initiating PF-03491390 in all treatment groups ($P<0.0001$). These reductions in AST and ALT were maintained throughout the 12 week treatment period and returned to baseline levels when PF-03491390 was discontinued. Increasing the dose did not further lower AST or ALT. The most frequently reported adverse events (AEs) were headache and fatigue. **CONCLUSION:** PF-03491390 significantly reduced serum AST and ALT levels in patients with chronic HCV and was well tolerated over 12 weeks.

Short versus standard treatment with Pegylated interferon alfa-2a plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the CLEO trial. Mecenate F, Pellicelli AM, Barbaro G, et al. *BMC Gastroenterol.* 2010 Feb 19;10(1):21. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Mecenate%20F%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: In patients with chronic hepatitis C virus (HCV) genotype 2 or 3, 24 weeks' treatment with pegylated interferon alfa (PEG-IFN- α) and ribavirin induces a sustained virological response (SVR) in [almost equal to]80% of cases. Evidence suggests that a similar response rate may be obtained with shorter treatment periods, especially in patients with a rapid virological response (RVR). The aim of this study was to compare the efficacy of 12 or 24 weeks of treatment in patients with chronic HCV genotype 2 or 3 and to identify patients suitable for 12 weeks treatment. **METHODS:** Two hundred and ten patients received PEG-IFN- α -2a (180 ug/week) and ribavirin (800-1200 mg/day) for 4 weeks. Patients with an RVR (HCV RNA not

detectable) were then randomized (1:1) to either 12 (group A1) or 24 (group A2) weeks of combination therapy. Patients without an RVR continued with 24-weeks' combination therapy (group B). HCV RNA was monitored at weeks 4, 8, 12, and 24, and at week 24 post-treatment.

RESULTS: At study end, end of treatment response (ETR) was observed in 62 (86%) patients of group A1 and in 55 (77%) patients of group A2 ($p < 0.05$). Relapse rate was 3% each in groups A1 and A2, and 6% in group B. Among patients with an HCVRNA test 24 weeks after the end of treatment, SVR was observed in 60 (83%) of group A1 patients and in 53 (75%) group A2 patients. Rapid virological response, low baseline HCV RNA levels, elevated alanine aminotransferase levels and low fibrosis score, were the strongest covariates associated with SVR, independent of HCV genotype. No baseline characteristic was associated with relapse.

CONCLUSION: In HCV patients with genotype 2 or 3, 12-week combination therapy is as efficacious as 24-week therapy and several independent covariates were predictive of SVR.

Farglitazar lacks antifibrotic activity in patients with chronic hepatitis c infection.

McHutchison J, Goodman Z, Patel K, et al. Gastroenterology. 2010 Feb 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22McHutchison%20J%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND & AIMS: Farglitazar (GI262570), an insulin-sensitizing agent, selectively binds and activates peroxisome proliferator-activated receptor gamma (PPARgamma) and inhibits stellate cell activation. We evaluated its antifibrotic effect in patients with chronic hepatitis C that did not respond to standard-of-care therapy. **METHODS:** Patients with fibrosis of Ishak stages 2-4 ($n = 265$), based on analysis of liver biopsy samples, were randomly assigned to groups given once-daily doses of 0.5 mg farglitazar, 1.0 mg farglitazar, or placebo for 52 weeks; repeat liver biopsy samples were then obtained. The primary end points were changes in levels of alpha-smooth muscle actin (SMA) expression and collagen, based on morphometry and ranked histologic assessments. **RESULTS:** Two hundred nine patients had paired biopsy specimens that were adequate for analysis (81.5% with pretreatment Ishak scores of stage 2 or 3). There was no overall difference in SMA ($P = .58$) or collagen ($P = .99$) levels at week 52. SMA levels increased by a median of 49% in samples from patients given placebo, 58% in patients given 0.5 mg farglitazar and 52% in patients given 1.0 mg farglitazar, respectively. Median levels of collagen increased by 27% in placebo samples and 31% in samples from patients given either dose of farglitazar. There were no significant differences between treatment groups in the ranked assessment of paired biopsy specimens or in the proportion of patients with a change in fibrosis score \geq Ishak stage. **CONCLUSIONS:** In patients with chronic hepatitis C and moderate fibrosis, 52 weeks of treatment with farglitazar does not affect stellate cell activation or fibrosis (measured by morphometry or comparison of paired biopsy specimens).

Replicated association between an il28b gene variant and a sustained response to pegylated interferon and ribavirin.

McCarthy JJ, Li JH, Thompson A, et al. Gastroenterology. 2010 Feb 19. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/20176026?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND & AIMS: Patients with chronic hepatitis C virus (HCV) infections are treated with pegylated interferon and ribavirin (PEG-IFN/RBV), which is effective in less than 50% of those infected with HCV genotype 1. Genome-wide association studies have linked response to

PEG-IFN/RBV with common single nucleotide polymorphisms in the vicinity of IFN-lambda genes on chromosome 19. We investigated the association between the polymorphism rs12979860 and treatment response in a diverse cohort of chronic HCV patients. **METHODS:** A cross-sectional study was performed using data from 1021 consecutive patients enrolled in the Duke Hepatology Clinic Research Database and Biorepository. We analyzed DNA, clinical, and demographic data, along with validated data of the response of 231 subjects to PEG-IFN/RBV. The study included Caucasians (n=178), African Americans (n=53), and HCV genotypes 1 (n=186) and 2/3 (n=45). The rs12979860 genotype was tested for an association with sustained virologic response, defined as undetectable levels of HCV RNA 24 weeks after treatment ended. **RESULTS:** The rs12979860 CC genotype (found in ~40% of Caucasians) predicted a sustained virologic response to therapy among Caucasians (odds ratio 5.79; 95% confidence interval 2.67-12.57; $p=9.0 \times 10^{-6}$), independent of HCV genotype and other covariates. Rs12979860 CC predicted a sustained response with 78% specificity and 65% sensitivity in patients infected with HCV genotype 1-better than HCV genotype (currently used to predict treatment response). **CONCLUSIONS:** rs12979860 genotype is a significant independent predictor of response to PEG-IFN/RBV in patients with chronic HCV infection; tests for this genotype might be used to determine the best course of treatment for patients considering antiviral therapy.

Prognostic value of Ishak fibrosis stage: findings from the hepatitis C antiviral long-term treatment against cirrhosis trial. Everhart JE, Wright EC, Goodman ZD, et al. Hepatology. 2010 Feb;51(2):585-94.

http://www.ncbi.nlm.nih.gov/pubmed/20101752?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2

Studies of the prognostic value of Ishak fibrosis stage are lacking. We used multi-year follow-up of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial to determine whether individual Ishak fibrosis stages predicted clinical outcomes in patients with chronic hepatitis C. Baseline liver biopsy specimens from 1050 patients with compensated chronic hepatitis C who had failed combination peginterferon and ribavirin were reviewed by a panel of expert hepatopathologists. Fibrosis was staged with the Ishak scale (ranging from 0 = no fibrosis to 6 = cirrhosis). Biopsy fragmentation and length as well as number of portal tracts were recorded. We compared rates of prespecified clinical outcomes of hepatic decompensation and hepatocellular carcinoma across individual Ishak fibrosis stages. Of 1050 biopsy specimens, 25% were fragmented, 63% longer than 1.5 cm, 69% larger than 10 mm(2), and 75% had 10 or more portal tracts. Baseline laboratory markers of liver disease severity were worse and the frequency of esophageal varices higher with increasing Ishak stage ($P < 0.0001$). The 6-year cumulative incidence of first clinical outcome was 5.6% for stage 2, 16.1% for stage 3, 19.3% for stage 4, 37.8% for stage 5, and 49.3% for stage 6. Among nonfragmented biopsy specimens, the predictive ability of Ishak staging was enhanced; however, no association was observed between Ishak stage and outcomes for fragmented biopsy specimens because of high rates of outcomes for patients with noncirrhotic stages. Similar results were observed with liver transplantation or liver-related death as the outcome. **CONCLUSION:** Ishak fibrosis stage predicts clinical outcomes, need for liver transplantation, and liver-related death in patients with chronic hepatitis C. Patients with fragmented biopsy specimens with low Ishak stage may be understaged

Reduction of insulin resistance with effective clearance of hepatitis C infection: Results from the Halt-C Trial. Delgado-Borrego A, Jordan SH, Negre B, et al. Clin Gastroenterol Hepatol. 2010 Feb 12. [Epub ahead of print]

BACKGROUND & AIMS: Hepatitis C virus (HCV) infection is associated with an increased prevalence of diabetes and insulin resistance (IR); whether this is a causal relationship has not been established. **METHODS:** We performed a longitudinal study within the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial to evaluate whether suppression of hepatitis C is associated with improvement in IR. Participants had advanced hepatic fibrosis and carried non-3 HCV genotypes (n=96). Patients underwent 24 weeks of pegylated interferon (PEG IFN) and ribavirin therapy and were categorized into HCV clearance groups at week 20 based on HCV RNA levels: null responders (NR) had < 1 log(10) decline (n=38); partial responders (PR) had ≥ 1 log(10) decline (n=37), but detectable HCV RNA, and complete responders (CR) had no detectable HCV RNA (n=21). The primary outcome was change (week 20 minus week 0) in IR using the homeostasis model assessment (HOMA2-IR). **RESULTS:** Adjusting only for baseline HOMA2-IR, mean HOMA2-IR differences were -2.23 (CR), -0.90 (PR), and +0.18 (NR) (p=0.036). The observed differences in mean HOMA2-IR scores were ordered in a linear fashion across response groups (p=0.01). The association between HCV clearance and improvement in HOMA2-IR could not be accounted for by adiponectin or tumor necrosis alfa, and was independent of potential confounders including age, gender, ethnicity, BMI, duration of infection, medications used, and fibrosis. **CONCLUSION:** HCV suppression correlates with improvement in insulin resistance. These data provide further support for a role of HCV in the development of insulin resistance.

Equally poor outcomes to pegylated interferon-based therapy in African Americans and Hispanics with chronic hepatitis C infection. Satapathy SK, Lingisetty CS, Proper S, Chaudhari S, Williams S. J Clin Gastroenterol. 2010 Feb;44(2):140-5.

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Satapathy%20SK%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: Treatment response to pegylated interferon based regimen is different between African Americans and Whites, but little comparable data is available comparing Hispanics and African Americans. **PATIENTS:** We retrospectively evaluated the rate of success in the treatment completion and response to peginterferon alpha-2a or alpha-2b plus ribavirin in 103 (male:female-69:34) hepatitis C virus (HCV)-polymerase chain reaction positive patients that included 68 Hispanic and 35 African Americans. **METHODS:** Patients were treated with peginterferon alpha-2a 180 mcg/wk (n=25) or peginterferon alpha-2b 1.5 mcg/kg/wk (N=78) and ribavirin 1000 to 1200 mg/d for 24 weeks (genotype 2 and 3) or 48 weeks (genotype 1 and 4) based on the genotype of the patient. Treatment was discontinued if the patients failed to have a 2-log drop in viral load after 12 weeks of treatment. Primary aim of the study was to evaluate success in completing a scheduled duration of pegylated interferon and ribavirin treatment in patients with chronic HCV infection and the reasons for discontinuation of the treatment. The secondary aim was to look for the end of treatment virologic response and sustained virologic response. The analysis was conducted by intention-to-treat. **RESULTS:** Of the 103 patients included in the study, 50 (48.5%) patients dropped out of the treatment because of side effects of the drug or noncompliance to the treatment protocol or alternate reasons; 44 (42.7%) of them could not continue beyond 12 weeks of therapy. There were no significant differences in the drop out rate between the African American [15 (43%)] and Hispanic [35 (51.5%)] patients (P=0.41).

Overall, 41% of the patients completed the scheduled 24 week or 48 week treatment. HCV genotype-1 was the most prevalent genotype in both African Americans and Hispanics (88.6% vs. 75%, P=0.10). Overall end of the treatment response (ETR) was 29.1% (30/103) and sustained virologic response (SVR) was 23.3% (24/103) in this population. No significant differences were noted in the ETR (20% vs. 34%, P=0.14) and the SVR (20% vs. 25%, P=0.57) between the African Americans and Hispanics. When data were analyzed by genotype, overall SVR rates were 14.6% (12/82) in genotype 1 versus 57% (12/21) in genotype 2/3/4 (P<0.0001). Both these ethnic groups had comparable response rates when only patients with genotype-1 were considered 5/31 (16.1%) versus 7/51 (13.7%, P=0.76). **CONCLUSIONS:** A significant proportion of the African Americans and Hispanics referred for HCV treatment with pegylated interferon dropped out early in the therapy, suggesting possible racial, socioeconomic, and cultural barriers in successful treatment for chronic HCV infection. Overall, both groups had similar poor response rates, well below those reported for White patients. As is true for the general population, patients with nongenotype 1 infection had a significantly better ETR and SVR.

Acute hepatitis C: analysis of a 126-case prospective, multicenter cohort. Morin T, Pariente A, Lahmek P, et al. Eur J Gastroenterol Hepatol. 2010 Feb;22(2):157-66.

http://www.ncbi.nlm.nih.gov/pubmed?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.

Causes and predictive factors of mortality in a cohort of patients with hepatitis c virus-related cryoglobulinemic vasculitis treated with antiviral therapy. Landau DA, Scerra S, Sene D, et al. J Rheumatol. 2010 Jan 28. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Landau%20DA%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVE: Hepatitis C virus (HCV)-associated mixed cryoglobulinemia (MC) vasculitis is an autoimmune disorder with significant morbidity and mortality. Renal involvement was associated with an increased mortality, and was the most common cause of death; these data were obtained before effective antiviral treatment was available. We studied causes of death and

predictive factors in patients with HCV-associated MC vasculitis treated with antivirals.

METHODS: Case histories of 85 patients with HCV-associated MC vasculitis treated in a single center between 1990 and 2006 were retrospectively reviewed. Prognostic factors affecting mortality were studied by comparing 23 patients who died with 62 survivors, using the Cox model regression analysis. **RESULTS:** The most common cause of death was infection, accounting for 34.7%, followed by end-stage liver disease in 30.4% (including 4 patients with hepatocellular carcinoma), and cardiovascular disease in 17.4% of patients. Endstage renal disease accounted for only 8.7% of deaths, as did central nervous system vasculitis and nonhepatic malignancy. Increased mortality was strongly associated with immunosuppressive treatment [hazard ratio (HR) 6.51, 95% CI 2.75-15.37], cutaneous ulcers (HR 5.37, 95% CI 1.79-16.14), and renal insufficiency (HR 3.25, 95% CI 1.37-7.72). A 2 log₁₀ decrease in HCV viral load at month 3 after starting antiviral treatment was associated with decreased mortality (HR 0.39, 95% CI 0.16-0.95). **CONCLUSION:** While renal involvement is still associated with poorer prognosis, infectious processes are now the most common cause of death in HCV cryoglobulinemia vasculitis. Immunosuppressive treatment is associated with an increased risk of death, independently from disease severity. Response to antiviral treatment is associated with significantly reduced mortality risk.

Knowledge of hepatitis C virus screening in long-term pediatric cancer survivors: a report from the Childhood Cancer Survivor Study. Lansdale M, Castellino S, Marina N, et al. *Cancer*. 2010 Feb 15;116(4):974-82.

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Lansdale%20M%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Pediatric cancer survivors who were treated before routine hepatitis C virus (HCV) screening of blood donors in 1992 have an elevated risk of transfusion-acquired HCV. **METHODS:** To assess long-term pediatric cancer survivors' knowledge of HCV testing and blood transfusion history, a questionnaire was administered to 9242 participants in the Childhood Cancer Survivor Study who are at risk for transfusion-acquired HCV after cancer therapy from 1970 to 1986. **RESULTS:** More than 70% of survivors reported either no prior HCV testing (41%) or uncertainty about testing (31%), with only 29% reporting prior testing. One half recalled having a treatment-related blood transfusion; those who recalled a transfusion were more likely to report HCV testing (39%) than those who did not (18%) or were unsure (20%). In multivariate models, survivors who reported no prior HCV testing were more likely to be older (odds ratio [OR] per 5-year increase, 1.1; 95% confidence interval [CI], 1.0-1.1) and to report no care at a cancer center within the past 2 years (OR, 1.2; 95% CI, 1.0-1.4), no cancer treatment summary (OR, 1.3; 95% CI, 1.2-1.5), and no transfusions (OR, 2.6; 95% CI, 2.3-3.0) or uncertainty about transfusions (OR, 2.2; 95% CI, 1.9-2.6), and less likely to be racial/ethnic minorities (OR, 0.9; 95% CI, 0.8-1.0) or survivors of acute myeloid leukemia (OR, 0.7; 95% CI, 0.5-1.0). **CONCLUSIONS:** Many pediatric cancer survivors at risk for transfusion-acquired HCV are unaware of their transfusion history and prior testing for HCV and would benefit from programs to increase HCV knowledge and screening.

Mutations in the interferon sensitivity determining region and virological response to combination therapy with pegylated-interferon alpha 2b plus ribavirin in patients with chronic hepatitis C-1b infection. Nakagawa M, Sakamoto N, Ueyama M, et al. *J Gastroenterol*. 2010 Jan 30. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/20112032?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=5

BACKGROUND: Pegylated-interferon-alpha 2b (PEG-IFN) plus ribavirin (RBV) therapy is currently the de-facto standard treatment for hepatitis C virus (HCV) infection. The aims of this study were to analyze the clinical and virological factors associated with a higher rate of response in patients with HCV genotype 1b infection treated with combination therapy.

METHODS: We analyzed, retrospectively, 239 patients with chronic hepatitis C-1b infection who received 48 weeks of combination therapy. We assessed clinical and laboratory parameters, including age, gender, pretreatment hemoglobin, platelet counts, HCV RNA titer, liver histology, the number of interferon sensitivity determining region (ISDR) mutations and substitutions of the core amino acids 70 and 91. Drug adherence was monitored in each patient. We carried out univariate and multivariate statistical analyses of these parameters and clinical responses.

RESULTS: On an intention-to-treat (ITT) analysis, 98 of the 239 patients (41%) had sustained virological responses (SVRs). Patients with more than two mutations in the ISDR had significantly higher SVR rates ($P < 0.01$). Univariate analyses showed that stage of fibrosis, hemoglobin, platelet counts, ISDR mutations, serum HCV RNA level, and adherence to PEG-IFN plus RBV were significantly correlated with SVR rates. Multivariate analysis in subjects with good drug adherence extracted the number of ISDR mutations (two or more: odds ratio [OR] 5.181). **CONCLUSIONS:** The number of mutations in the ISDR sequence of HCV-1b (≥ 2) is the most effective parameter predicting a favorable clinical outcome of 48-week PEG-IFN plus RBV therapy in patients with HCV genotype 1b infection.

Complete blood count, measures of iron status and inflammatory markers in inner-city African Americans with undiagnosed hepatitis C seropositivity. Ufearo H, Kambal K, Onojobi GO, et al. Clin Chim Acta. 2010 Feb 1. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Ufearo%20H%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Hepatitis C virus (HCV) infection may be associated with thrombocytopenia and increased iron stores in patients receiving medical care. We aimed to determine how often changes in hematologic, iron metabolic and inflammatory markers occur in individuals with undiagnosed HCV in the community. **METHODS:** Inner-city African Americans ($n=143$) were recruited from the community according to reported ingestion of alcohol. They were divided broadly into those who drank more or less than 56g alcohol/day as assessed by dietary questionnaire. HCV serology was determined and laboratory values were compared according to HCV seropositivity in analyses that adjusted for alcohol consumption. **RESULTS:** The prevalence of HCV seropositivity was 23% among men and 29% among women. Levels of hepatocellular enzymes were higher with HCV seropositivity ($P < 0.0001$) but hemoglobin concentrations, white blood cell and platelet counts and serum ferritin concentrations did not differ. The globulin fraction of the serum protein concentration ($P=0.002$) was increased with HCV seropositivity as expected with chronic inflammation. However, erythrocyte sedimentation rate and serum iron and haptoglobin levels did not differ significantly according to HCV status. Furthermore, multivariate analysis revealed that C-reactive protein was decreased and transferrin concentration was increased with both HCV and alcohol consumption ($P < 0.014$).

CONCLUSIONS: Previously undiagnosed HCV seropositivity has little effect on the complete blood count and body iron stores but appears to perturb the response to an inflammatory

stimulus, causing reduced rather than increased circulating CRP concentrations and increased rather than decreased transferrin concentrations.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Thermal stability and inactivation of hepatitis C virus grown in cell culture. Song H, Li J, Shi S, Yan L, Zhuang H, Li K. *Virol J.* 2010 Feb 18;7(1):40. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/20167059?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2

BACKGROUND: Hepatitis C virus (HCV) is a blood-borne flavivirus that infects many millions of people worldwide. Relatively little is known, however, concerning the stability of HCV and reliable procedures for inactivating this virus. **METHODS:** In the current study, the thermostability of cell culture-derived HCV (HCVcc, JFH-1 strain) under different environmental temperatures (37degreesC, room temperature, and 4degreesC) and the ability of heat, UVC light irradiation, and aldehyde and detergent treatments to inactivate HCVcc were evaluated. The infectious titers of treated viral samples were determined by focus-forming unit (FFU) assay using an indirect immunofluorescence assay for HCV NS3 in hepatoma Huh7-25-CD81 cells highly permissive for HCVcc infection. MTT cytotoxicity assay was performed to determine the concentrations of aldehydes or detergents at which they were no longer cytotoxic. **RESULTS:** HCVcc in culture medium was found to survive 37degreesC and room temperature (RT, 25 +/- 2degreesC) for 2 and 16 days, respectively, while the virus was relatively stable at 4degreesC without drastic loss of infectivity for at least 6 weeks. HCVcc in culture medium was sensitive to heat and could be inactivated in 8 and 4 min when incubated at 60degreesC and 65degreesC, respectively. However, at 56degreesC, 40 min were required to eliminate HCVcc infectivity. Addition of normal human serum to HCVcc did not significantly alter viral stability at RT or its susceptibility to heat. UVC light irradiation (wavelength = 253.7 nm) with an intensity of 450 muW/cm2 efficiently inactivated HCVcc within 2 min. Exposures to formaldehyde, glutaraldehyde, ionic or nonionic detergents all destroyed HCVcc infectivity effectively, regardless of whether the treatments were conducted in the presence of cell culture medium or human serum. **CONCLUSIONS:** The results provide quantitative evidence for the potential use of a variety of approaches for inactivating HCV. The ability of HCVcc to survive ambient temperatures warrants precautions in handling and disposing of objects and materials that may have been contaminated with HCV.

Human liver chimeric mice provide a model for hepatitis B and C virus infection and treatment. Bissig KD, Wieland SF, Tran P, et al. *J Clin Invest.* 2010 Feb 22. pii: 40094. doi: 10.1172/JCI40094. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed?term=%22Bissig%20KD%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

A paucity of versatile small animal models of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection has been an impediment to both furthering understanding of virus biology and testing antiviral therapies. We recently described a regulatable system for repopulating the liver of immunodeficient mice (specifically mice lacking fumaryl acetoacetate hydrolase [Fah], recombination activating gene 2 [Rag2], and the gamma-chain of the receptor for IL-2 [Il-2rgamma]) with human hepatocytes. Here we have shown that a high transplantation dose (3 x 10⁶ to 5 x 10⁶ human hepatocytes/mouse) generates a higher rate of liver chimerism than was

previously obtained in these mice, up to 95% human hepatocyte chimerism. Mice with a high level of human liver chimerism propagated both HBV and HCV, and the HCV-infected mice were responsive to antiviral treatment. This human liver chimeric mouse model will expand the experimental possibilities for studying HBV and HCV infection, and possibly other human hepatotropic pathogens, and prove useful for antiviral drug testing.

Practical evaluation of a mouse with chimeric human liver model for hepatitis c virus infection using an NS3-4A protease inhibitor. Kamiya N, Iwao E, Hiraga N, et al. J Gen Virol. 2010 Feb 17. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/20164258?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1

A small animal model for hepatitis C virus (HCV) infection was developed using severe combined immunodeficiency (SCID) mice encoding homozygous urokinase-type plasminogen activator (uPA) transplanted with human hepatocytes. Currently, limited information is available concerning the HCV clearance rate in the SCID mouse model and the virion production rate in engrafted hepatocytes. In this study, several cohorts of uPA^{+/+}/SCID^{+/+} mice with nearly half of their livers repopulated by human hepatocytes were infected with HCV genotype 1b and were used to evaluate HCV dynamics by pharmacokinetic and pharmacodynamic analyses of a specific NS3-4A protease inhibitor (telaprevir). A dose-dependent reduction in serum HCV RNA was observed. At telaprevir exposure equivalent to that in clinical studies, rapid turnover of serum HCV was also observed in this mouse model and the estimated slopes of viral decline were 0.11-0.17 log₁₀ h⁻¹. During the initial phase of treatment, the log₁₀ reduction level of HCV RNA was dependent on the drug concentration, which was about 4-fold higher in the liver than in plasma. HCV RNA levels in the liver relative to human endogenous gene expression were correlated with serum HCV RNA levels at the end of treatment for up to 10 days. A mathematical model analysis of viral kinetics suggested that 1 g of the chimeric human liver could produce at least 10⁸ virions per day and this may be comparable to HCV production in the human liver.

Selection-driven immune escape is not a significant factor in the failure of CD4 T cell responses in persistent hepatitis C virus infection. Fuller MJ, Shoukry NH, Gushima T, et al. Hepatology. 2010 Feb;51(2):378-87.

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Fuller%20MJ%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Immune escape driven by selection pressure from virus-specific CD8 T cells has been demonstrated in both chimpanzees and humans infected with the hepatitis C virus (HCV). Although escape mutations have also been characterized in major histocompatibility complex (MHC) class II-restricted HCV epitopes, it is unknown whether selection-driven immune escape by CD4 T cell epitopes is a significant factor in the failure of these responses or contributes to persistent infection. To address this issue, evolution of MHC class I- and class II-restricted HCV epitopes was compared in four chimpanzees persistently infected with the virus for more than 10 years. We identified an amino acid change in a CD4 epitope of the HCV NS3 protein in one of the chimpanzees 3 years after infection. This mutation resulted in diminished activation, cytokine production (interferon-gamma and interleukin-2), and proliferation by an epitope-specific CD4 T cell line. We expanded our analysis to determine if mutations were common in multiple CD4 versus CD8 T cell epitopes in the four chronically infected animals. Whereas we observed

mutations in over 75% of CD8 T cell epitopes analyzed in this study, only 18% of CD4 T cell epitopes analyzed showed amino acid changes. The frequency of changes in class II epitopes was not different from flanking regions, so CD4 T cells rarely exert selection pressure against the HCV genome. **CONCLUSION:** Apparent mutational escape can occur in MHC class II-restricted epitopes, but this is uncommon when compared with class I-restricted epitopes in the same individual. This indicates that other mechanisms for silencing CD4 T cells are dominant in persistent HCV infections.

Genetic diversity of NS5A protein from hepatitis C virus genotype 3a and its relationship to therapy response. Bittar C, Jardim AC, Yamasaki LH, et al. *BMC Infect Dis.* 2010 Feb 23;10(1):36. [Epub ahead of print]

BACKGROUND: The quasispecies nature of HCV may have important implications for viral persistence, pathogenicity and resistance to antiviral agents. The variability of one of the viral proteins, NS5A, is believed to be related to the response to IFN therapy, the standard treatment for infection. In this study we analyzed the quasispecies composition of NS5A protein in patients infected with HCV genotype 3a, before IFN therapy. **METHODS:** Viral RNA was isolated from samples of 12 patients: four sustained virological responders (SVR), four non-responders (NR), and four end-of-treatment responders (ETR). cDNA was synthesized, the NS5A region was amplified and the fragments obtained were cloned. Fifteen clones from each patient were sequenced with eight primers, generating 179 contigs. **RESULTS:** Higher values for substitution (either synonymous or non-synonymous) and for distance were found in the SVR group. However, the NR group showed relatively more non-synonymous mutations than the other groups, owing to the higher values of dN/dS in complete NS5A and most specific regions. Overall, NS5A protein is undergoing purifying selection, since all dN/dS ratios values are below 0.5. **CONCLUSIONS:** Our study provides an overview of the genetic variability of complete NS5A protein in HCV genotype 3a.

Hepatitis C virus core protein enhances Telomerase activity in Huh7 cells. Zhu Z, Wilson AT, Gopalakrishna K, et al. *J Med Virol.* 2010 Feb;82(2):239-48.

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Gopalakrishna%20K%22%5BAuthor%5D&itol=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Hepatitis C is an oncogenic virus although the mechanisms responsible for this behavior are not clear. We studied the effects of hepatitis C virus (HCV) core protein expression on Telomerase, an enzyme closely associated with cellular immortalization and neoplasia. The aim of this study was to investigate the effects of HCV core protein on the regulation of Telomerase activity in human hepatoma cells. Regulation and expression of human Telomerase reverse transcriptase (TERT) was compared in Huh7 cells stably transfected with HCV core protein or cells expressing vector alone. Telomerase activity was measured using Quantitative Telomerase Detection (QTD) and telomere length was measured by fluorescence in situ hybridization (FISH). Transient transfection and luciferase assay were used to evaluate TERT promoter activity. Telomerase activity was increased twofold in Huh7 cells expressing HCV core protein compared to controls ($P < 0.01$). This was accompanied by a 1.4-fold increase of TERT mRNA and 1.9-fold increase in TERT protein ($P < 0.01$ in either case). Cellular fractionation and immunocytochemical studies showed increased localization of TERT in the nucleus of core-expressing cells as compared to controls. FISH assay confirmed that telomeres of HCV core-expressing Huh7 cells were relatively longer than those of control cells (0.22 ± 0.05 vs. $0.12 \pm$

0.03, $P < 0.01$). TERT promoter activity was enhanced about 30% in HCV core-expressing Huh7 cells compared to control cells ($P < 0.02$). HCV core protein is associated with increased Telomerase activity in hepatoma cells. These findings suggest that enhancement of Telomerase activity by HCV core protein may contribute to the oncogenicity of HCV.

HIV/HCV COINFECTION

Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. Nunes D, Fleming C, Offner G, et al. Am J Gastroenterol. 2010 Feb 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Nunes%20D%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: Noninvasive markers of liver fibrosis correlate with the stage of liver fibrosis, but have not been widely applied to predict liver-related mortality. **METHODS:** We assessed the ability of two indices of liver fibrosis, aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and Fib-4, and two markers of extracellular matrix metabolism, hyaluronic acid (HA) and YKL40, to predict liver mortality in a prospective cohort of hepatitis C virus (HCV)-infected individuals with and without HIV coinfection. These were compared with two established prognostic scores, the Child-Pugh-Turcotte (CPT) and model of end-stage liver disease (MELD) scores. **RESULTS:** A total of 303 subjects, of whom 207 were HIV positive at study entry, were followed up for a mean period of 3.1 years. There were 33 deaths due to liver disease. The ability of each test and score to predict 3-year liver mortality was expressed as the area under the receiver operator curve. The area under the receiver operator curve 95% confidence intervals were: HA 0.92 (0.86-0.96), CPT 0.91 (0.79-0.96), APRI 0.88 (0.80-0.93), Fib-4 0.87 (0.77-0.92), MELD 0.84 (0.71-0.91). In multivariate analyses HA, APRI, and fib-4 were independent predictors of mortality when included in models with MELD or CPT.

CONCLUSION: Noninvasive markers of liver fibrosis are highly predictive of liver outcome in HCV-infected individuals with and without HIV coinfection. These markers seem to have a prognostic value independent of CPT and MELD.

Hepatitis C infection on immune recovery in HIV-positive patients on successful HAART: The role of genotype 3. Seminari E, Tinelli C, Ravasi G, et al. Curr HIV Res. 2010 Feb 18.

[Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Seminari%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVE: The primary objective of this study was to investigate the impact of HCV infection and of HCV genotypes on immune restoration in HIV-infected patients on a successful HAART regimen. **METHODS:** Patients from the MASTER Study were included in this current longitudinal study if they met the following criteria: being on any successful HAART, availability of CD4+ cell count and HIV RNA level before starting the suppressive HAART and 12 months after suppressive therapy, availability of HCV antibodies. The primary endpoints of the study were defined as achieving a difference above 100 cell/mm³ between CD4+ at baseline and at time of HIV RNA suppression while on therapy (DeltaCD4+early), or 12 month after a suppressive therapy (DeltaCD4+late). **RESULTS:** 844 HIV-positive patients were included in the analysis: 673 were HCV-negative and 171 were HCV-positive [92 (53.8%) subjects had HCV genotype 1; 58 (33.9%), genotype 3; 21 (12.3%), genotype 4]. Plasma HIV RNA (both

baseline as highest value), nadir CD4+, being naïve, time to reach undetectable plasma HIV RNA, treatment with PI vs NNRTI were associated with an early immunological recovery; the occurrence of previous AIDS event, a history of injection drug use, and HCV infection were associated with failure to achieve an early immunological recovery. Variables associated with DeltaCD4+late immune recovery were baseline CD4+ value, plasma HIV RNA (both baseline as highest value), being naïve and time to reach undetectable plasma HIV RNA. HCV infection per se was not associated with a worse probability to reach late immunologic response, although among HCV infected patients, having a genotype 3 was associated with a worse immune recovery. At multivariable analysis, factors that remained associated with failure to achieve an early immunological response were being HCV infected and history of injection drug use, while those associated with a failure to achieve a late immunological response were being infected with HCV genotype 3 and older age. **CONCLUSIONS:** A blunted early immune recovery was observed in HCV infected patients, compared with HCV negative subjects, while late immune recovery was not different among HCV infected as a whole and not infected subjects; only the subgroup of subjects infected with genotype 3 showed an impaired late immune recovery.

Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. Bedimo R, Westfall AO, Mugavero et al. HIV Med. 2010 Feb 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Bedimo%20R%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: Among HIV-infected patients, hepatitis C virus (HCV) coinfection is associated with lower cholesterol levels, but it remains unclear how it affects cardiovascular outcomes. **METHODS:** We performed logistic regression to evaluate acute myocardial infarction (AMI) and cerebrovascular disease (CVD) events by HCV status among HIV-infected US veterans in the highly active antiretroviral therapy (HAART) era (1996-2004). We then performed survival analyses to evaluate incident AMI and CVD, exploring antiretroviral therapy (ART) as a time-dependent variable. **RESULTS:** A total of 19 424 HIV-infected patients [31.6% of whom were HCV-coinfected (HIV/HCV)] contributed 76 376 patient-years of follow-up. HCV coinfection was associated with lower rates of hypercholesterolaemia (18.0% in HIV/HCV vs. 30.7% in HIV-only patients; $P<0.001$), but higher rates of hypertension (43.8% vs. 35.6%; $P<0.0001$), type 2 diabetes mellitus (16.2% vs. 11.1%; $P<0.0001$) and smoking (36.7% vs. 24.7%; $P=0.009$). Rates of AMI and CVD were significantly higher among HIV/HCV than HIV-only patients: 4.19 vs. 3.36 events/1000 patient-years, respectively ($P<0.001$), for AMI; and 12.47 vs. 11.12 events/1000 patient-years, respectively ($P<0.001$), for CVD. When analyses were controlled for diabetes mellitus, hypertension, age and duration of ART, hazard ratios (HRs) among those with HIV/HCV (vs. HIV only) were 1.25 [95% confidence interval (CI) 0.98-1.61; $P=0.072$] for AMI and 1.20 (CI 1.04-1.38; $P=0.013$) for CVD. Hypertension (HR 2.05; $P<0.001$), greater age (HR 1.79; $P<0.001$) and longer duration (cumulative years) of antiretroviral use (HR 1.12; $P=0.0411$) were also associated with increased risk of AMI in the adjusted model. **CONCLUSIONS:** In the HAART era, HCV coinfection was associated with a significantly increased risk of CVD and a trend towards an increased risk of AMI among HIV-infected patients.

Hepatitis C and the risk of kidney disease and mortality in veterans with HIV.

Fischer MJ, Wyatt CM, Gordon K, et al. J Acquir Immune Defic Syndr. 2010 Feb 1;53(2):222-6. http://www.ncbi.nlm.nih.gov/pubmed/20104121?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2

OBJECTIVES: To examine the effect of hepatitis C virus (HCV) on the prevalence of chronic kidney disease (CKD) among veterans with HIV and to evaluate independent associations of HCV and CKD with mortality. **METHODS:** We studied a national cohort of HIV-infected patients receiving care through the Veterans Healthcare Administration from 1998 to 2004. CKD was defined as an estimated glomerular filtration rate [eGFR (mL/min/1.73 m²)] < 60. Poisson regression was used to assess relationships between CKD, HCV, and mortality. **RESULTS:** Among 23,155 HIV-infected veterans, 12% had CKD. Forty percent of the cohort was coinfecting with HCV, and a higher proportion of coinfecting subjects had CKD compared with monoinfected subjects (14% vs 11%, P < 0.001). During the median follow-up of 7.6 years, 37% of subjects died and a graduated increase in adjusted mortality rates occurred with lower levels of eGFR (P < 0.001). Adjusted mortality rates were consistently higher in HCV-coinfecting subjects across all levels of eGFR (P < 0.001). HCV was independently associated with increased mortality (incidence rate ratio 1.23, 95% confidence interval 1.17-1.29). **CONCLUSIONS:** CKD is prevalent in HIV-infected veterans and associated with substantially higher mortality. Compared with their monoinfected counterparts, veterans coinfecting with HCV have significantly higher rates of CKD and mortality.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medicine use in chronic liver disease patients. Ferrucci LM, Bell BP, Dhotre KB, et al. J Clin Gastroenterol. 2010 Feb;44(2):e40-5. http://www.ncbi.nlm.nih.gov/pubmed?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.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Attribution of hepatitis C virus seroconversion risk in young injection drug users in 5 US cities. Hagan H, Pouget ER, Williams IT, et al. *J Infect Dis.* 2010 Feb 1;201(3):378-85.

http://www.ncbi.nlm.nih.gov/pubmed/20053137?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=3

BACKGROUND: In studies of hepatitis C virus (HCV) seroconversion in injection drug users (IDUs), some have questioned whether underreporting of syringe sharing, a stigmatized behavior, has led to misattribution of HCV risk to other injection-related behaviors.

METHODS: IDUs aged 15-30 years who were seronegative for human immunodeficiency virus and HCV antibodies were recruited into a prospective study in 5 US cities. Behavioral data were collected via computer-assisted self-interviewing to reduce socially desirable reporting. Hazard ratios (HRs) were estimated to assess associations between behavior and HCV seroconversion. Because the shared use of cookers, cottons, and rinse water was highly correlated, a summary variable was created to represent drug preparation equipment sharing. **RESULTS:.** Among 483 IDUs who injected during the period covered by the follow-up assessments, the incidence of HCV infection was 17.2 cases per 100 person years; no HIV seroconversions occurred.

Adjusting for confounders, the shared use of drug preparation equipment was significantly associated with HCV seroconversion (adjusted HR, 2.66; 95% confidence interval, 1.03-23.92), but syringe sharing was not (adjusted HR, 0.91). We estimated that 37% of HCV seroconversions in IDUs were due to the sharing of drug preparation equipment.

CONCLUSIONS: Associations between sharing drug preparation equipment and HCV seroconversion are not attributable to underascertainment of syringe sharing. Avoiding HCV infection will require substantial reductions in exposure to all sources of contaminated blood.

Hepatic steatosis in hepatitis C is a storage disease due to HCV interaction with microsomal triglyceride transfer protein (MTP). Mirandola S, Bowman D, Hussain MM, Alberti A. *Nutr Metab (Lond).* 2010 Feb 23;7(1):13. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Mirandola%20S%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

ABSTRACT: Liver steatosis is a frequent histological feature in patients chronically infected with hepatitis C virus (HCV). The relationship between HCV and hepatic steatosis seems to be the result of both epigenetic and genetic factors. In vivo and in vitro studies have shown that HCV can alter intrahepatic lipid metabolism by affecting lipid synthesis, oxidative stress, lipid peroxidation, insulin resistance and the assembly and secretion of VLDL. Many studies suggest that HCV-related steatosis might be the result of a direct interaction between the virus and MTP. It has been demonstrated that MTP is critical for the secretion of HCV particles and that inhibition of its lipid transfer activity reduces HCV production. However, higher degrees of hepatic steatosis were found in chronic hepatitis C patients carrying the T allele of MTP -493G/T polymorphism that seems to be associated with increased MTP transcription. We propose here that liver steatosis in hepatitis C could be a storage disease induced by the effects of the virus and of its proteins on the intracellular lipid machinery and on MTP. Available data support the hypothesis that HCV may modulate MTP expression and activity through a number of mechanisms such as inhibition of its activity and transcriptional control. Initial up regulation could favour propagation of HCV while down regulation in chronic phase could cause

impairment of triglyceride secretion and excessive lipid accumulation, with abnormal lipid droplets facilitating the "storage" of virus particles for persistent infection.

Monitoring peripheral blood CD4+ adenosine triphosphate activity in recurrent hepatitis C and its correlation to fibrosis progression. Alkhouri N, Hanouneh IA, Lopez R, Zein NN.

Liver Transpl. 2010 Feb;16(2):155-62.

http://www.ncbi.nlm.nih.gov/pubmed/20104483?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=3

The recurrence of hepatitis C virus (HCV) after orthotopic liver transplantation (OLT) is often associated with rapid fibrosis progression attributed to the state of impaired cellular immunity. At present, there are no means to predict those at risk for progression. Peripheral blood CD4+ adenosine triphosphate (ATP) release (the ImmuKnow assay) correlates with immunoreactivity and has been used to monitor global cellular immune function in transplant recipients. The aim of this study was to assess the relationship between cellular immune function measured by the ImmuKnow assay and fibrosis progression in patients with HCV recurrence after OLT. The ImmuKnow assay was prospectively performed in adult HCV patients at 4 and 12 months post-OLT. Protocol liver biopsies were performed (on day 7, in month 4, and yearly) after OLT. The first biopsy that showed fibrosis post-OLT was used to determine the time interval for developing fibrosis. Sixty-two patients met the inclusion criteria. The median follow-up time was 12 (6.5-12.1) months. Fibrosis progression was observed in 61.3% of the patients. ATP levels were lower in patients with fibrosis progression in comparison with patients without progression at 4 months (145 versus 259 ng/mL, $P < 0.001$) and at 12 months (152 versus 264 ng/mL, $P = 0.008$). ATP levels at 4 and 12 months post-OLT were found to be significantly associated with a higher hazard of progression. For each 25-unit increase in ATP levels at 4 and 12 months after transplantation, the hazard of fibrosis progression decreased by 22% ($P = 0.001$) and 12% ($P = 0.015$), respectively. In conclusion, greater suppression of cellular immunity, as measured by the ImmuKnow assay, is associated with more rapid progression of fibrosis in patients with recurrent HCV post-OLT. Post-OLT monitoring of CD4+ ATP activity may identify a subset of patients at greatest risk for early fibrosis progression.

Management of acute hepatitis C. Maheshwari A, Thuluvath PJ. Clin Liver Dis. 2010

Feb;14(1):169-76; x.

http://www.ncbi.nlm.nih.gov/pubmed/20123448?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=4

The World Health Organization estimates that about 170 million people are infected with hepatitis C virus (HCV). Blood transfusions from unscreened donors and unsafe therapeutic procedures are the major modes of HCV transmission in the developing world, and injection drug use accounts for most newly diagnosed HCV infections in the developed countries. Acute infection with HCV leads to symptomatic hepatitis in only a minority of patients, and recent studies suggest that spontaneous clearance of virus is higher in symptomatic acute hepatitis C infection. Pooled data from various studies suggest that higher sustained viral clearance rates could be achieved with a shorter course of antiviral treatment in the early stages of chronic HCV infection. This article examines the diagnosis of acute infection and critically appraises the various treatment regimens.