

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

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**Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C type 1 and 4 patients with slow virological response.** Ferenci P, Laferl H, Scherzer TM, et al. Gastroenterology. 2009 Nov 9. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19909752?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19909752?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND & AIMS:** This randomized multicentre trial evaluated individualization of treatment duration with peginterferon alfa-2a 180 microg/week plus ribavirin 1000/1200 mg/day in patients with chronic hepatitis C genotype 1/4 based on the rapidity of virologic response (VR) **METHODS:** Patients with a rapid VR (RVR; undetectable HCV-RNA [ $<50$  IU/mL] at week 4) were treated for 24 weeks, those with an early VR (EVR; no RVR but undetectable HCV-RNA or  $\geq 2$ -log<sub>10</sub> drop at week 12) were randomized to 48 (Group A) or 72 weeks (Group B; peginterferon alfa-2a was reduced to 135 mug/week after week 48) of treatment. Patients without an EVR continued treatment until week 72 if they had undetectable HCV-RNA at week 24. The primary endpoint was relapse; sustained VR (SVR; undetectable HCV-RNA after 24 weeks' follow-up) was a secondary endpoint. **RESULTS:** Of 551 genotype 1/4 patients starting treatment, 289 were randomized to Group A (N=139), or Group B (N=150). The relapse rate was 33.6% in Group A (95% CI 24.8-43.4%), and 18.5% in Group B, (95% CI 11.9-27.6%;  $p=0.0115$  vs. Group A) and the SVR rate was 51.1% (95% CI 42.5%-59.6%) and 58.6% (95% CI 50.3%-66.6%;  $p>0.1$ ), respectively. The overall SVR rate was 50.4% (278/551; 95% CI: 46.2-54.7%) including 115/150 patients with an RVR treated for 24 weeks and 4/78 patients without an EVR. **CONCLUSIONS:** Extending therapy with peginterferon alfa-2a/ribavirin to 72 weeks decreases the probability of relapse in patients with an EVR. If they can be maintained on extended duration therapy, SVR rates may also improve.

**Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection.** Mederacke I, Wursthorn K, Kirschner J, et al. Liver Int. 2009 Nov;29(10):1500-6. Epub 2009 Sep 3.

[http://www.ncbi.nlm.nih.gov/pubmed/19732330?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19732330?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**BACKGROUND AND AIMS:** Transient elastography is increasingly being used in patients with chronic liver disease. It has proven particularly useful to identify patients with advanced fibrosis or cirrhosis, while classification of no or little fibrosis appears to be difficult. In general, stiffness values  $<6$  kPa are considered normal, whereas patients with higher levels are candidates for a disease-specific treatment or further diagnostic evaluation. Parameters influencing liver stiffness may include

food intake that increases liver blood flow. **METHODS:** In a pilot study, transient elastography was performed in eight patients with chronic hepatitis C at fasting and serially for 180 min after intake of a standardized breakfast. Confirmatory, 56 patients and 19 controls underwent liver stiffness determination at fasting, directly after meal intake and 1 h after breakfast. **RESULTS:** Liver stiffness significantly increased immediately after food intake for up to 60 min ( $P=0.01$ ) before normalizing after 180 min. An intraindividual analysis showed a significant increase in 22 out of 43 patients with an initial liver stiffness  $\leq 10$  kPa. An increase of at least 1 kPa after food intake was found in 24 out of 43 (56%) patients with initial stiffness  $\leq 10$  kPa. Notably, nine out of 23 (39%) patients with normal initial liver stiffness ( $< 6$  kPa) had a value of  $> 6$  kPa after food intake, potentially leading to unnecessary treatment or diagnostic procedures. **CONCLUSION:** Food intake increases liver stiffness in patients with hepatitis C virus infection and healthy controls. To standardize liver stiffness evaluation, we suggest measurement in the fasting condition.

**Similar treatment response to peginterferon and ribavirin in Asian and Caucasian patients with chronic hepatitis C.** Vutien P, Nguyen NH, Trinh HN, et al. *J Gastroenterol.* 2009 Nov 10. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19904247?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19904247?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**OBJECTIVES:** Previous studies have found ethnicity to be an important predictor of outcomes of treatment with peginterferon (PEG-IFN) and ribavirin (RBV) in chronic hepatitis C. Although the expected sustained virological response (SVR) rates of Hispanics and African Americans are lower than those of Caucasians, SVR rates in Asians appear to be more favorable. However, in some of these studies, hepatitis C virus (HCV) genotype was identified by INNO-LiPA assay, which can mistype the easier-to-treat HCV genotype 6 as genotype 1. Our goal was to compare SVR rates among Caucasian and Asian-American patients with genotype 1 and 2/3 infection whose HCV genotypes were accurately classified by core sequencing testing. **METHODS:** A cohort of 269 consecutive treatment-naïve HCV-infected patients with genotype 1 or 2/3 (157 Caucasians and 112 Asians) treated with PEG-IFN+RBV from January 2001 to November 2007 at four community-based gastroenterology clinics in Northern California were studied. The analysis of data was by intention-to-treat. **RESULTS:** The SVR rates for patients with genotype 1 were 45% for Caucasians and 52% for Asians ( $P=0.37$ ). The SVR rates for patients with genotype 2/3 infection was 77% for Asians and 74% for Caucasians ( $P=0.7$ ). On multivariate logistic regression analyses adjusting for age, alanine aminotransferase (ALT), baseline viral load, HCV genotype, and treatment adherence, we did not find Asian ethnicity to predict SVR. On a separate analysis, we found that Asians who had HCV genotype 1 or 1b by the less accurate INNO-LiPA assay had significantly higher SVR rates than Caucasians with genotype 1 (64% vs. 45%, respectively,  $P=0.03$ ). **CONCLUSIONS:** SVR rates were similar in Asian Americans and Caucasians infected with HCV genotype 1 or 2/3 when HCV genotype classification was accurately determined.

**Insulin resistance predicts rapid virological response in non-diabetic, non-cirrhotic genotype 1 HCV patients treated with peginterferon alpha-2b plus ribavirin.** Grasso A, Malfatti F, De Leo P, et al. *J Hepatol.* 2009 Dec;51(6):984-90. Epub 2009 Jul 23.

[http://www.ncbi.nlm.nih.gov/pubmed/19695729?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19695729?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**BACKGROUND/AIMS:** The rapid decline in hepatitis C virus RNA is crucial for determining the outcome of therapy in patients with genotype 1 chronic hepatitis C. However, the variables influencing the early phase of viral decay are still largely unexplored. We aimed to assess which pre-treatment variable may predict rapid virologic response (RVR) and sustained virologic response

(SVR). **METHODS:** We evaluated 90 consecutive non-diabetic patients with genotype 1 chronic hepatitis C without cirrhosis, treated with peginterferon alpha-2b plus ribavirin. Viral load (COBAS Amplicore, Roche) was measured at 1, 4 and 12 weeks after starting treatment, and then 24 weeks after the end of treatment. **RESULTS:** The overall SVR was 47%. The SVR in patients with RVR was 100%. Age, GGT levels, viral load, steatosis, fibrosis and HOMA-IR were significantly associated with RVR in univariate analysis. After logistic regression, HOMA-IR proved to be the strongest independent predictor of RVR (OR 0.37, 95% CI: 0.16-0.89;  $p=0.027$ ), whereas fibrosis had a weaker independent association with RVR (OR 0.32, 95% CI: 0.1-1.04;  $p=0.057$ ). Among the eight pre-treatment variables, both BMI and steatosis were significantly associated with HOMA-IR, either in univariate or in multivariate analyses. **CONCLUSIONS:** Our data suggest that insulin resistance is strongly associated with RVR, thus reflecting the important role played by metabolic factors in the early phase of viral kinetics. HOMA-IR would appear to be a useful tool in predicting RVR and should be evaluated at baseline in all chronic hepatitis C patients before initiating antiviral treatment.

**Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATAHIC Study.** Grebely J, Petoumenos K, Matthews GV, et al. Drug Alcohol Depend. 2009 Nov 16. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19926405?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19926405?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Despite that the majority of hepatitis C virus (HCV) infection occurs among injection drug users (IDUs), little is known about HCV treatment uptake in this group, particularly during recent infection. We evaluated uptake of treatment for recent HCV infection, including associated factors, within a population predominantly made up of IDUs. The Australian Trial in Acute Hepatitis C was a study of the natural history and treatment of recent HCV infection. All participants with detectable HCV RNA at screening were offered HCV treatment, assessed for eligibility and those initiating treatment were identified. Logistic regression analyses were used to identify predictors of HCV treatment uptake. Between June 2004 and February 2008, 163 were enrolled, with 146 positive for HCV RNA at enrolment. The mean age was 35 years, 77% ( $n=113$ ) participants had ever injected illicit drugs and 23% ( $n=34$ ) reported having ever received methadone or buprenorphine treatment. The uptake of HCV treatment was 76% (111 of 146) among those who were eligible on the basis of positive HCV RNA. Estimated duration of HCV infection (OR=1.03 per week, 95% CI=1.00-1.06,  $P=0.035$ ) and  $\log_{10}$  HCV RNA (OR=1.92 per  $\log_{10}$  increase, 95% CI=1.36-2.73,  $P<0.001$ ) were independently associated with treatment uptake whereas injection drug use was not. **This study demonstrates** that a high uptake of HCV treatment can be achieved among participants with recently acquired HCV infection. Decisions about whether to initiate treatment for recently acquired HCV were mainly driven by clinical factors, rather than factors related to sociodemographics or injecting behaviors.

**Sustained virological response to pegylated interferon and ribavirin is maintained during long-term follow-up of chronic hepatitis C patients\*** Giannini EG, Basso M, Savarino V, Picciotto A. Aliment Pharmacol Ther. 2009 Nov 19. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19925499?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19925499?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** There are few data in the literature regarding the long-term virological follow-up of chronic hepatitis C patients who obtain sustained virological response (SVR) to pegylated interferon (PEG-IFN) and ribavirin therapy. **AIM:** To assess the durability of SVR to PEG-IFN and ribavirin therapy during long-term follow-up of chronic hepatitis C patients. **METHODS:** We

evaluated a cohort of 231 chronic hepatitis C patients who had at least 48 weeks follow-up after SVR to PEG-IFN and ribavirin treatment. Median duration of follow-up after SVR was 164 weeks, and exceeded 5 years in 30% of the cohort. Patients underwent consistent clinical, biochemical, and virological evaluations every 6 months during follow-up. Results: SVR was maintained in 211 patients (91%) while HCV-RNA became positive in 2 patients (<1%) within 1 year after SVR, and in 18 patients (8%) serum HCV-RNA was transiently positive in at least one follow-up evaluation. Clinical outcome was not significantly different between patients with persistently negative and transiently positive serum HCV-RNA. **CONCLUSIONS:** SVR to PEG-IFN and ribavirin is maintained in 99% of patients during long-term follow-up. Late virological relapse occurred within 1 year after SVR, and from a clinical perspective after this period patients can be considered cured of infection.

### **Mortality and drug exposure in a 5-year cohort of patients with chronic liver disease.**

Hug BL, Lipsitz SR, Seger DL, et al. Swiss Med Wkly. 2009 Nov 19. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19924579?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19924579?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** Chronic liver diseases are common in the general population. Drug treatment in this group may be challenging, as many drugs are hepatically metabolised and hepatotoxic. Objectives: We aimed to assess the mortality of patients with chronic liver disease according to specific drug exposures and the three laboratory parameters creatinine, bilirubin and International Normalised Ratio (INR). **METHODS:** We conducted a multicentre, 5-year retrospective cohort study in two tertiary university referral hospitals and a secondary referral hospital, using a research database to evaluate the crude and adjusted mortality. **RESULTS:** Of 1 159 362 individual patients 1.7% (n = 20 158) had chronic liver disease and in this group 36.8% had unspecified chronic non-alcoholic liver disease, 30.1% chronic hepatitis C and 11.9% cirrhosis of the liver. 8.4% of patients presented a diagnosis associated with alcohol. The 4-year survival rates were significantly higher in the group with the most normal laboratory values (94.3%) versus 34.5% in the group with elevated parameters (p <0.001). Overall, drug exposure was not associated with higher mortality; in adjusted multivariate analysis the hazard ratio for anti-cancer drugs was 2.69 (95% CI 1.32-5.46). Of individual drugs, mortality hazard ratios for amiodarone, morphine oral, acetazolamide, sirolimus and lamivudine were 2.46 (95% CI 1.68-3.61), 2.26 (95% CI 1.78-2.86), 2.10 (95% CI 1.19-3.70), 1.81 (95% CI 1.02-3.21) and 1.72 (95% CI 1.17-2.53) respectively. **CONCLUSIONS:** Drug exposure in general was not associated with higher mortality except for a few categories. Mortality in patients with chronic liver disease was high and is associated with simple laboratory values.

### **Pegylated-interferon-associated retinopathy in chronic hepatitis patients.** Lim JW, Shin MC.

Ophthalmologica. 2009 Nov 24;224(4):224-229. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19940529?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19940529?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**PURPOSE:** To investigate the clinical features of pegylated-interferon (PEG-IFN)-associated retinopathy in chronic hepatitis patients. **METHODS:** We examined a consecutive case series of 46 patients who were treated with PEG-IFN for chronic hepatitis C or B between October 2007 and September 2008. All patients underwent regular ophthalmologic examinations every 3 weeks during the 6 months after treatment. **RESULTS:** Ten of the 46 patients (21.73%) developed retinal abnormalities. PEG-IFN-associated retinopathy occurred a mean of 7.25 +/- 10.28 weeks after treatment and manifested itself as cotton wool spots and retinal hemorrhages. All patients, except for 1 with a retinal vein occlusion, recovered without cessation of treatment. **CONCLUSIONS:** PEG-IFN-associated retinopathy in chronic hepatitis patients was reversible, and patients recovered

without visual complications; however, 1 patient did present with an irreversible visual impairment. This type of retinopathy is usually asymptomatic, and clinicians should closely observe patients for 3 months after treatment.

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## **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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**Plasma prohepcidin levels in patients with chronic viral hepatitis: relationship with liver fibrosis.** Olmez OF, Gurel S, Yilmaz Y. Eur J Gastroenterol Hepatol. 2009 Nov 24. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19940783?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19940783?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**OBJECTIVES:** Iron is deemed to play a crucial role in the pathophysiology of liver damage in patients with chronic viral hepatitis. Hcpicidin has recently emerged as the key hormone in the regulation of iron balance and recycling. We assessed plasma prohepcidin levels in patients with chronic viral hepatitis and investigated the association of this molecule with iron parameters, histologic activity index, and liver fibrosis scores. **METHODS:** We enrolled 35 patients with chronic hepatitis C, 27 with chronic hepatitis B, and 21 healthy controls. Plasma levels of prohepcidin were measured by enzyme-linked immunosorbent assay. **RESULTS:** Mean prohepcidin levels were significantly lower in patients with chronic hepatitis B than in those with chronic hepatitis C ( $P < 0.001$ ) and healthy comparison controls ( $P < 0.05$ ). In patients with chronic hepatitis C, prohepcidin was independently associated with liver fibrosis scores ( $\beta = -0.009$ , standard error = 0.003,  $P < 0.05$ ). No association of prohepcidin with iron parameters was found. **CONCLUSION:** Significantly lower prohepcidin levels are frequently found in patients with chronic hepatitis B. Levels of this molecule may represent a biochemical correlate of fibrosis in chronic hepatitis C virus infection.

**Peripheral CXCR3-associated chemokines as biomarkers of fibrosis in chronic hepatitis C virus infection.** Zeremski M, Dimova R, Brown Q, et al. J Infect Dis. 2009 Dec 1;200(11):1774-80.

[http://www.ncbi.nlm.nih.gov/pubmed/19848607?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19848607?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** CXCR3-associated chemokines CXCL9-CXCL11 promote histologic progression in chronic hepatitis C virus (HCV) infection, as indicated by elevated intrahepatic levels of messenger RNA in patients with advanced inflammation and fibrosis. We evaluated the potential of peripheral chemokine levels to discriminate among patients with chronic HCV infection who had different stages of fibrosis. **METHODS:** Peripheral levels of CXCR3-associated chemokines were measured by enzyme-linked immunosorbent assay of plasma samples obtained from 93 patients with chronic HCV infection. Of the subjects, 79 (85%) were white, and 68 (73%) were infected with HCV genotype 1. **RESULTS:** Expression of all 3 chemokines, when analyzed as a group, was significantly associated with intrahepatic inflammation and fibrosis. Plasma levels of CXCL10 were significantly elevated in patients with advanced fibrosis, whereas CXCL9 levels were significantly elevated in patients with advanced inflammation. By proportional odds multivariate modeling, we observed an association between fibrosis and CXCL10 ( $P < .002$ ) as well as between fibrosis and inflammation ( $P < .001$ ). Of the individual parameters, the CXCL10 level was most useful in identifying patients with more-severe (stage 3-4) fibrosis. Discriminatory ability was improved by the combination of CXCL10 and CXCL9. **CONCLUSIONS:** The strong association between CXCR3-associated chemokines and fibrosis suggests that they may have promise as noninvasive markers of hepatic fibrosis in a predominantly white HCV genotype 1-infected population.

**Hepatitis C virus infection reduces hepatocellular polarity in a vascular endothelial growth factor dependent manner.** Mee CJ, Farquhar MJ, Harris HJ, et al. *Gastroenterology*. 2009 Nov 25. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19944696?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19944696?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND AND AIMS:** Hepatitis C virus (HCV) infection leads to progressive liver disease, frequently culminating in fibrosis and hepatocellular carcinoma. The mechanisms underlying liver injury in chronic hepatitis C are poorly understood. This study evaluated the role of vascular endothelial growth factor (VEGF) in hepatocyte polarity and HCV infection. **METHODS:** We utilized polarized hepatoma cell lines and the recently described infectious HCV JFH-1 cell culture system to study the role of VEGF in regulating hepatoma permeability and HCV infection.

**RESULTS:** VEGF negatively regulates hepatocellular tight junction (TJ) integrity and cell polarity by a novel VEGF receptor 2 dependent pathway. VEGF reduced hepatoma TJ integrity, induced a re-organization of occludin and promoted HCV entry. Conversely, inhibition of hepatoma expressed VEGF with the receptor kinase inhibitor Sorafenib or with neutralizing anti-VEGF antibodies promoted polarization and inhibited HCV entry, demonstrating an autocrine pathway. HCV infection of primary hepatocytes or hepatoma cell lines promoted VEGF expression and reduced their polarity. Importantly, treatment of HCV infected cells with VEGF inhibitors restored their ability to polarize, demonstrating a VEGF-dependent pathway. **CONCLUSION:** Hepatic polarity is critical to normal liver physiology. HCV infection promotes VEGF expression that depolarizes hepatoma cells, promoting viral transmission and lymphocyte migration into the parenchyma that may promote hepatocyte injury.

**Polymorphisms of some cytokines and chronic hepatitis B and C virus infection.** Gao QJ, Liu DW, Zhang SY, et al. *World J Gastroenterol*. 2009 Nov 28;15(44):5610-9.

[http://www.ncbi.nlm.nih.gov/pubmed/19938203?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19938203?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**AIM:** To study the relationship between the polymorphisms in some cytokines and the outcome of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. **METHODS:** Samples were obtained from 203 patients infected with HBV and/or HCV while donating plasma in 1987, and 74 controls were obtained from a rural area of North China. Antibodies to HBV or HCV antigens were detected by enzyme-linked immunoassay. The presence of viral particles in the serum was determined by nested reverse-transcriptase polymerase chain reaction (PCR). Hepatocellular injury, as revealed by alanine aminotransferase (ALT) and aspartate aminotransferase level, was detected by a Beckman LX-20 analyzer. DNA was extracted from blood cells. Then, the single nucleotide polymorphisms of IL-2-330, IFN-gamma+874, IL-10-1082/-592 and IL-4-589 were investigated by restriction fragment length polymorphism-PCR or sequence specific primer-PCR. **RESULTS:** Persistent infection with HBV, HCV, and HBV/HCV coinfection was associated with IL-2-330 TT genotype and T allele, IFN-gamma+874 AA genotype, and IL-10-1082 AA genotype. The clinical outcome of HBV and/or HCV infection was associated with IL-2-330 TT genotype and T allele, IFN-gamma+874 AA genotype, and IL-10-1082 AA genotype. IL-2-330 GG genotype frequency showed a negative correlation with clinical progression, IL-10-1082 AA genotype frequency showed a positive correlation and IL-10-1082 AG genotype frequency showed a negative correlation with clinical progression. HCV RNA positive expression was associated with IL-10-1082 AA genotype and the A allele frequency. Abnormal serum ALT level was associated with IL-10-592 AC genotype frequency and IL-4-589 CC genotype, CT genotype, and the C allele. **CONCLUSION:** These results suggest that polymorphisms in some cytokine genes influence persistent HBV and HCV infection, clinical outcome, HCV replication, and liver damage.

**Factors that influence an HIV coinfecting patient's decision to start hepatitis C treatment.**

Osilla KC, Ryan G, Bhatti L, Goetz M, Witt M, Wagner G. AIDS Patient Care STDS. 2009 Nov 22. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19929229?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19929229?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Liver disease is a leading cause of morbidity and mortality among patients coinfecting with HIV and hepatitis C (HCV), yet few HIV coinfecting patients actually receive HCV treatment. Providers must first be willing to prescribe treatment, but the patient ultimately makes the decision to accept or decline a treatment recommendation. We used a process model framework to explore the factors influencing patients' treatment decision-making. We conducted semistructured interviews with 35 HIV coinfecting patients and 11 primary care providers at three HIV clinics in Los Angeles, California. Patients reported that stability of HIV disease, perceived need for HCV treatment, treatment readiness, willingness to deal with side effects, absence of substance abuse, and stability of mental health and overall life circumstances are key factors influencing treatment decision-making. Patients also spoke of the influence of the trusting relationship that many had with their provider, and providers acknowledged an awareness of the influence of how they present the risks and benefits of HCV treatment and the overall tone of their recommendation (encouraging, dissuasive, or neutral). **These results** speak to a social decision-making process between the patient and provider—a partnership that involves sequential interactions whereby both the patient and provider may influence the other's evaluation of the patient's readiness for treatment, with treatment initiation dependent on both agreeing on the need for treatment and the patient's readiness for treatment.

**Is 1 alanine transaminase >200 IU enough to define an alanine transaminase flare in HIV-infected populations? A new definition derived from a large cohort study.**

Bansi L, Turner J, Gilson R, et al. J Acquir Immune Defic Syndr. 2009 Nov 1;52(3):391-6.

[http://www.ncbi.nlm.nih.gov/pubmed/19553826?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=7](http://www.ncbi.nlm.nih.gov/pubmed/19553826?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=7)

**OBJECTIVES:** Recent studies have suggested that highly active antiretroviral therapy may lead to rises in alanine transaminase (ALT) among HIV-infected patients. However, the definition of an ALT flare is arbitrary and the extent to which such increases represent normal fluctuations has not been explored. **METHODS:** Using data from untreated, hepatitis B virus/hepatitis C virus-negative, HIV-infected patients, we derived a definition for an ALT flare by exploring a series of ALT thresholds (from 100 to 200 IU/L). The resulting definition (2 consecutive ALTs > 200 measured >2 weeks apart) was applied to all patients in the UK Collaborative HIV Cohort (CHIC) Study, and Poisson regression was used to identify factors associated with ALT flares. **RESULTS:** Five hundred and twenty six of 12,206 eligible patients (4.3%) had > or =1 ALT flare, resulting in a total of 615 episodes of ALT flares. The overall rate of an ALT flare was 1.19 (95% confidence interval: 1.10 to 1.28) per 100 person-years. Higher risk of ALT flare was associated with lower CD4 counts, detectable viral loads, being under follow-up in earlier calendar years, prior clinical AIDS, receipt of nevirapine either with didanosine/stavudine or without didanosine/stavudine, receipt of ritonavir, detectable anti-hepatitis C virus, and detectable hepatitis B surface antigen.

**CONCLUSIONS:** Associations between known risk factors may be under/over estimated if using single values, that is, 1 ALT > 200, to define ALT flares. We recommend studies to use a more stringent measure and suggest our derived definition of an ALT flare.

**Analysis of the efficacy of treatment with peginterferon alpha-2a and ribavirin in patients coinfecting with hepatitis B virus and hepatitis C virus.** Yu JW, Sun LJ, Zhao YH, Kang P, Gao J, Li SC. *Liver Int.* 2009 Nov;29(10):1485-93. Epub 2009 Jul 7.

[http://www.ncbi.nlm.nih.gov/pubmed/19602134?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19602134?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**OBJECTIVE:** To study the virological features of patients coinfecting with hepatitis B virus (HBV) and hepatitis C virus (HCV) and the efficacy of combination therapy with peginterferon alpha-2a and ribavirin in these patients. **METHODS:** The epidemiological and virological data of 50 patients coinfecting with HBV and HCV were analysed. The virological response rates of patients treated with peginterferon alpha-2a and ribavirin between the HBV and HCV coinfection group and the HCV mono-infection group were compared. **RESULTS:** HCV-dominant virus strains accounted for 92.0% of the 50 coinfecting individuals, and HCV- and HBV-dominant virus strains accounted for the remaining 8.0%. The HBV DNA level of the patients coinfecting with HBV and HCV was  $4.6 \pm 0.9 \log_{10}$  copies/ml, which was significantly lower than that in the HBV mono-infection group ( $5.9 \pm 1.2 \log_{10}$  copies/ml) ( $t=5.964$ ,  $P<0.01$ ). The HBeAg-positive rate (12.0%, 6/50) of the coinfection group was significantly lower than (45.3%, 19/42) that of the HBV mono-infection group ( $\chi^2=12.743$ ,  $P<0.01$ ). The partial early virological response (pEVR) rate and the end-of-treatment virological response (ETVR) rate (50.0%, 15/30; 90.0%, 27/30) of patients with genotype 1 in the coinfection group were significantly higher than those (16.0%, 4/25; 56.0%, 14/25) in the HCV mono-infection group ( $\chi^2=6.971$ ,  $P=0.008$ ;  $\chi^2=8.307$ ,  $P=0.004$ ). The relapse rate (55.6%, 15/27) of patients with genotype 1 in the coinfection group was significantly higher than that (21.4%, 3/14) in the HCV mono-infection group ( $\chi^2=4.360$ ,  $P=0.037$ ). The sustained virological response (SVR) rate (40.0%, 12/30) of patients with genotype 1 in the coinfection group was compared with that of the HCV mono-infection group (44.0%, 11/25) ( $\chi^2=0.090$ ,  $P=0.765$ ). There was no significant difference in the on-treatment virological response, ETVR, SVR and relapse rates between two groups for patients with genotype 2. The incidence of side effects (30%, 15/50) of patients in the coinfection group was significantly higher than that (13%, 6/46) in the HCV mono-infection group ( $\chi^2=4.031$ ,  $P=0.045$ ). The reactivation rate of HBV DNA (33.3%, 9/27) with HCV SVR was significantly higher than that of patients without SVR (8.7%, 2/23) ( $\chi^2=4.393$ ,  $P=0.036$ ). **CONCLUSIONS:** The replication of HBV was suppressed, and HCV was the dominant virus strain. Compared with HCV-mono-infected patients, pEVR, ETVR and relapse rates of patients with genotype 1 in the coinfection group were high, while they shared similar SVR rates. HBV and HCV coinfection had no impact on the rate of virological response for genotype 2.

**Psychiatric management of HIV/HCV- co-infected patients beginning treatment for hepatitis C virus infection: survey of provider practices.** Weiss JJ, Morgello S. *Gen Hosp Psychiatry.* 2009 Nov-Dec;31(6):531-7. Epub 2009 Jun 9.

[http://www.ncbi.nlm.nih.gov/pubmed/19892211?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19892211?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**OBJECTIVE:** To determine expert clinical practice in the management of psychiatric status of HIV/hepatitis C virus (HCV)-coinfecting patients initiating pegylated interferon/ribavirin for the treatment of hepatitis C. **METHOD:** Two hundred thirty-six expert providers were identified and invited by email to complete an online anonymous survey. **RESULTS:** Ninety-two providers (39%) completed the survey, 24 (26%) of whom are psychiatrists. More than one third of providers indicate that they use or offer the option of antidepressant use prophylactically in HIV-positive patients with no past or current depression beginning HCV treatment, and more than three quarters do so in patients with a history of depression but no current symptoms of depression. The most

experienced nonpsychiatrist providers were more likely to use antidepressants prior to the start of treatment in HIV-coinfected patients as compared to in HCV monoinfected patients. There is consensus among providers to leave psychiatric medication unchanged in patients currently treated for unipolar depression. **CONCLUSIONS:** Many expert providers prescribe antidepressants to HIV/HCV-coinfected patients initiating Hepatitis C treatment in the absence of symptoms of depression, despite the lack of data supporting this approach in this population. Research is needed to provide an evidence base to guide the optimal psychiatric management of HIV/HCV-coinfected patients beginning hepatitis C treatment.

**Survey of both hepatitis B virus (HBsAg) and hepatitis C virus (HCV-Ab) coinfection among HIV positive patients.** Mohammadi M, Talei G, Sheikhan A, et al. *Virology*. 2009 Nov 18;6(1):202. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19922624?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19922624?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** HIV, HBV and HCV is major public health concerns. Because of shared routes of transmission, HIV-HCV coinfection and HIV-HBV coinfection are common. HIV-positive individuals are at risk of coinfection with HBV and HCV infections. The prevalence rates of coinfection with HBV and HCV in HIV-patients have been variable worldwide depending on the geographic regions, and the type of exposure. **AIM:** This study aimed to examine HBV and HCV coinfection serologically and determine the shared and significant factors in the coinfection of HIV-positive patients. **METHODS:** This descriptive, cross-sectional study was carried out on 391 HIV-positive patients including 358 males and 33 females in Lorestan province, west Iran, to survey coinfection with HBsAg and anti-HCV. The retrospective demographic data of the subjects was collected and the patients' serums were analyzed by ELISA kits including HBsAg and anti-HCV. The collected data was analyzed with SPSS software (15) and Chi-square. Fisher's exact test with 5% error intervals was used to measure the correlation of variables and infection rates. Results The results of the study indicated that the prevalence of coinfection in HIV-positive patients with hepatitis viruses was 94.4% (370 in 391), out of whom 57 (14.5%) cases were HBsAg positive, 282 (72%) cases were anti-HCV positive, and 31 (7.9%) cases were both HBsAg and anti-HCV positive. **CONCLUSION:** There was a significant correlation between coinfection with HCV and HBV and/or both among HIV-positive patients depending on different variables including sex, age, occupation, marital status, exposure to risk factors. ( $p < 0.001$ ).

**Factors associated with prevalent hepatitis C infection among HIV-infected women with no reported history of injection drug use: the Women's Interagency HIV Study (WIHS).**

Frederick T, Burian P, Terrault N, et al. *AIDS Patient Care STDS*. 2009 Nov;23(11):915-23.

[http://www.ncbi.nlm.nih.gov/pubmed/19877800?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19877800?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Although the primary mode of hepatitis C virus (HCV) transmission is exposure to blood products or injection drug use (IDU), studies have found varying independent risk factors for HCV infection among persons with no history of IDU or exposure to blood products. For HIV-infected women, sexual transmission may be another potential source of HCV infection. HIV-infected and HIV-negative women at risk for HIV enrolled in the Women's Interagency HIV Study (WIHS) during October 1994 to November 1995 and again between October 2001 and November 2002 were studied. Clinical and demographic factors associated with HCV seroprevalence were assessed in multivariate logistic regression models controlling for history of blood transfusion and IDU. Among 3636 women with HCV results, 31.5% were HCV antibody positive (HCV+) including 13.5% with no reported history of IDU or blood transfusions. Multivariate logistic regression analyses stratified

on IDU showed that among women with no history of IDU, sex with an IDU male was independently associated with HCV positivity (odds ratio [OR] = 2.8, 95% confidence [CI] = 2.1, 3.8,  $p < 0.0001$ ) after controlling for blood transfusion, age, HIV infection, unemployment, birth in the United States, history of hepatitis B infection, and current smoking status. Further stratification on HIV status showed that the association was significant only for the HIV+ (OR = 1.9, 95% CI = 1.3, 2.7,  $p = 0.0007$ ) compared to the HIV- women (OR = 1.1, 95% CI = 0.4, 2.7) although these odds ratios were not significantly different ( $p = 0.25$ ). For HIV-positive women with no reported history of IDU, sex with an IDU male was independently associated with HCV suggesting that sexual transmission may be an important mode of HCV transmission for these high-risk women.

**Long-term outcome of hepatitis B and hepatitis C virus co-infection and single HBV infection acquired in youth.** Zampino R, Marrone A, Merola A, et al. *J Med Virol.* 2009 Dec;81(12):2012-20.

[http://www.ncbi.nlm.nih.gov/pubmed/19856471?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19856471?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

Co-infection with HBV and HCV seems to be associated with more severe liver disease in retrospective and cross-sectional studies in adults, but no data are available when co-infection is acquired in youth. The long-term outcome of infection acquired in youth was assessed in patients co-infected with HBV and HCV and in patients with HBV infection only. Twenty-seven patients with HBV and HCV co-infection and 27 patients infected with HBV only were enrolled. Seventy-six per cent of the patients were treated with alpha-interferon for 1 year. After a median follow-up of 23 years, the annual progression rate of fibrosis was 0.07 in patients co-infected with HBV and HCV, and in those infected with HBV it was 0.07 and 0.11 ( $P < 0.004$ ) for HBe and anti-HBe-positive patients, respectively. In co-infected patients, the development of cirrhosis was observed in 2 (7.4%) and of hepatocellular carcinoma (HCC) in 1 (3.7%), while in those with HBV, cirrhosis appeared in one patient (3.7%). Alcohol intake (OR = 9.5 +/- 1.2; 95% CI = 6.6-13.9;  $P < 0.0001$ ) was independently associated with cirrhosis and HCC. alpha-interferon showed no efficacy during treatment, but the treated group showed higher HCV RNA clearance during post-treatment follow-up. Co-infection with HBV and HCV and single HBV infection acquired in youth showed a low rate of progression to liver fibrosis, no liver failure, and low development of HCC during a median follow-up of 23 years (range 17-40).

**Therapeutic response to peg-IFN-alpha-2b and ribavirin in HIV/HCV co-infected African-American and Caucasian patients as a function of HCV viral kinetics and interferon pharmacodynamics.** Rozenberg L, Haagmans BL, Neumann AU, et al. *AIDS.* 2009 Nov 27;23(18):2439-50.

[http://www.ncbi.nlm.nih.gov/pubmed/19898214?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19898214?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**METHOD:** In this study we sought to characterize the relationship between several pharmacokinetic and pharmacodynamic parameters and virologic responses among HIV/hepatitis C virus genotype-1 co-infected patients receiving pegylated interferon-alpha-2b (peg-IFN2b) and ribavirin. We also tried to establish the underlying mechanisms that lead to poor sustained virologic responder rates observed with African-Americans against Caucasians and compared their results with those observed in a cohort of hepatitis C virus mono-infected patients. **RESULTS:** Among our studied population, a viral decline of more than 1.0 log at day 3 combined with viral load of less than 5.0 log IU/ml at day 28 predicted sustained virologic responders with negative predictive value 100% and positive predictive value 100%. African-Americans had significantly ( $P < 0.01$ ) slower hepatitis C virus viral kinetics as compared to Caucasians. However, peg-IFN2b concentrations and

pharmacokinetic parameters, peg-IFN2b(max) and peg-IFN2b half-life, were similar in both groups and did not predict sustained virologic responders. Nevertheless, the pharmacodynamic parameter EC(50), estimated from nonlinear fitting of the viral kinetics together with peg-IFN2b concentration data, showed that HIV/ hepatitis C virus co-infected African-Americans have lower sensitivity to interferon-alpha thus giving rise to slower viral decline. The combined pharmacokinetic/pharmacodynamic parameter IFN(max)/EC(90) was an excellent predictor of sustained virologic responders, thus showing the importance of maintaining peg-IFN2b levels above EC(90) to achieve successful treatment. **CONCLUSION:** Further studies are needed to evaluate whether these pharmacodynamic predictions are a result of differential host response to peg-IFN2b or other viral factors conferring relative resistance to peg-IFN2b.

### **Hepatitis C virus is infrequently evaluated and treated in an urban HIV clinic population.**

Scott JD, Wald A, Kitahata M, et al. AIDS Patient Care STDS. 2009 Nov;23(11):925-9.

[http://www.ncbi.nlm.nih.gov/pubmed/19827950?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed.ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19827950?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed.ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

This retrospective cohort study of HIV/hepatitis C virus (HCV) coinfecting patients evaluated time trends and rates of HCV evaluation for patients seen between January 1, 1997 and October 30, 2004. Survival analysis and Cox proportional hazards modeling were used to describe the time to evaluation and covariates associated with this outcome. Patients were predominantly white and male. Of 248 eligible patients, 108 (44%) were evaluated for HCV treatment. The median time to evaluation was 2.98 years. Of 108 evaluated, 17 (16%) received at least one dose of interferon and/or ribavirin. The median time to treatment after being evaluated was 1.39 years. Of the 17 (35%) treated 6 patients had a sustained virologic response, but only 2.4% of the original number of patients were cured. Approximately one half of patients in an HIV-specialty clinic were evaluated for HCV therapy and 16% received treatment, but the median time to treatment from the time of HCV diagnosis was over 4 years. Further efforts to identify and to overcome barriers to HCV treatment are warranted.

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## **COMPLEMENTARY AND ALTERNATIVE MEDICINE**

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### **Lamiridosins, Hepatitis C Virus Entry Inhibitors from *Lamium album*.**

Zhang H, Rothwangl K, Mesecar AD, Sabahi A, Rong L, Fong HH. J Nat Prod. 2009 Nov 11.

[Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19904996?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed.ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=8](http://www.ncbi.nlm.nih.gov/pubmed/19904996?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed.ResultsPanel.Pubmed_RVDocSum&ordinalpos=8)

Phytochemical study of the aqueous extract of the flowering tops of *Lamium album* led to identification of the antiviral iridoid isomers lamiridosins A and B (1, 2). These compounds were found to significantly inhibit hepatitis C virus entry (IC<sub>50</sub> 2.31 μM) in vitro. Studies of 14 iridoid analogues showed that, while the parent iridoid glucosides demonstrated no anti-HCV entry activity, the aglycones of shanzhiside methyl ester (4), loganin (5), loganic acid (6), geniposide (10), verbenalin (12), eurostoside (15), and picoside II (17) exhibited significant anti-HCV entry and anti-infectivity activities.

### **Zinc supplementation improves the outcome of chronic hepatitis C and liver cirrhosis.**

Matsuoka S, Matsumura H, Nakamura H, et al. J Clin Biochem Nutr. 2009 Nov;45(3):292-303. Epub 2009 Oct 28.

[http://www.ncbi.nlm.nih.gov/pubmed/19902019?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19902019?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

We treated patients with C-viral chronic hepatitis (CH) and liver cirrhosis (LC) with polaprezinc and determined prospectively the effect on long-term outcome. 62 patients were enrolled. Of these, 32 were administered 1.0 g polaprezinc and the remainder were not administered polaprezinc. We measured the serum zinc concentrations using conventional atomic absorption spectrometry and conducted a prospective study to determine the long-term outcome of the polaprezinc therapy. Changes of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in the polaprezinc administration group were significantly lower than those of the untreated group. The decrease in platelet count was clearly less than that of the untreated group. The factors that inhibited increases in serum zinc concentrations following administration of polaprezinc included low serum zinc concentration states. Furthermore, the reductions of AST and ALT levels in the low zinc group were significantly greater than those of the high zinc group. When the patients who were administered polaprezinc were divided into two groups whose zinc concentrations increased (zinc responders) or remained stable or decreased (zinc non-responders), the zinc responders had a clearly lower cumulative incidence of HCC than the zinc non-responders. We conclude zinc supplementation improved the long-term outcome in C-viral CH and LC patients.

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#### EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Frequency of hepatitis C and d super infection in patients with hepatitis B related complex liver disorders.** Baig S, Siddiqui AA, Ahmed WU, Qureshi H, Arif A. J Coll Physicians Surg Pak. 2009 Nov;19(11):699-703.

[http://www.ncbi.nlm.nih.gov/pubmed/19889265?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19889265?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**OBJECTIVE:** To determine the frequency of super infection of hepatitis C and D in patients with hepatitis B related complex liver disorders and the distribution of HBV genotypes in these patients. Study Design: Descriptive study. Place and Duration of Study: The Gastroenterology Unit of PMRC in JPMC, Karachi, from July 2006 to June 2007. **METHODOLOGY:** All patients registered for HBV associated infections were selected. Blood was drawn from 180 patients who fulfilled the inclusion criteria. Those with an incomplete test profile were excluded. All clinical conditions were investigated through liver function tests, coagulation profile, and findings at abdominal ultrasonography, upper gastrointestinal endoscopy and liver biopsy. Liver cirrhosis and hepatocellular carcinoma (HCC) were diagnosed either on the basis of histology, or on a combination of radiological, endoscopic and laboratory data. Hepatitis B virus DNA was extracted from serum, and subjected to a nested PCR using the type specific primers for HBV genotype. Descriptive statistics were used for frequency and mean determination. **RESULTS:** The 129 patients finally selected for statistical analysis included 108 (84%) males and 21 (16%) females. The age ranged from 6- 68 years (mean=31.5 +/-12.39 years). There were 70 (54.2%) patients of non-cirrhotic, chronic hepatitis (CLD), 38 (29.4%) carriers, 12 (9.3%) cirrhotics and 9 (6.9%) HCC patients. Among the 129 patients, 45 (34.9%) were positive for double infection with HDV. These included 35 CLD cases, 7 cirrhotic and 3 carriers, 4 (3.1%) patients were positive for double infection with HCV including one with CLD, 2 with cirrhosis and one with HCC. Triple infection with HBV/HDV/HCV was present in 4 (3.1%) patients who had CLD. Approximately 59% (n=76) patients were not coinfecting, though 9 had developed HCC. The genotype distribution of HBV was observed as D in 98 (76%) patients, A in 24 (18.6%), and AD mix in 7 (5.4%). Genotypes B, C, E or F were not found. Accordingly, genotype D strains were the predominant strains among all

categories. **CONCLUSION:** The frequency of super infection of hepatitis C and D was found to be highest in HBV cirrhosis patients compared to patients having chronic liver disease (non-cirrhotics) and carriers. Genotype D of hepatitis B virus was found dominant in all hepatitis B related complex liver disorders.

**[Hepatitis C virus genotyping: Comparison of the Abbott RealTime HCV genotype II assay and NS5B sequencing.]** [Article in French] Vaghefi P, Marchadier E, Dussaix E, Roque-Afonso AM. *Pathol Biol (Paris)*. 2009 Nov 24. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/pubmed/19942365?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19942365?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**PURPOSE OF THE STUDY:** Hepatitis C virus genotyping is needed for treatment decision and monitoring. The results of a genotyping assay based on real-time PCR and TaqMan chemistry were compared with the results of NS5B region sequencing. **MATERIALS AND METHODS:** One hundred and two sera (genotypes 1-6) were tested. Amplification and detection of viral RNA were performed with the Abbott RealTime HCV Genotype II assay targeting 5'non-coded region (5'NC) for the identification of genotypes 1 to 6 and NS5B, for 1a and 1b subtypes detection. Sequencing of 5'NC fragment was used to resolve discrepant results. **RESULTS:** No indeterminate results were obtained. Concordance with NS5B sequencing was 93% (95 on 102), 96% at the genotype level (98 on 102) and 93% for genotype 1 subtyping (40 on 43). Discordant genotyping results were a 2f subtype identified as 5, a 6a typed as 1, a 3a identified as a 1-3 co-infection and a 4r identified as a 1-4 co-infection. Discordant subtyping results were 2 1b subtypes only typed as 1 and a 1e identified as 1a. **CONCLUSION:** Abbott RealTime HCV Genotype II assay is a rapid, automated and simple to interpret method for HCV genotyping. It allows the detection of possible mixed infections which might have a negative impact on therapeutic response. However, the discrepant results found in this small series underline the need for assay optimization.

**Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis.** Fierbinteanu-Braticevici C, Andronescu D, Usvat R, et al. *World J Gastroenterol*. 2009 Nov 28;15(44):5525-32.

[http://www.ncbi.nlm.nih.gov/pubmed/19938190?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19938190?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**AIM:** To investigate the diagnostic accuracy of acoustic radiation force impulse (ARFI) imaging as a noninvasive method for the assessment of liver fibrosis in chronic hepatitis C (CHC) patients.

**METHODS:** We performed a prospective blind comparison of ARFI elastography, APRI index and FibroMax in a consecutive series of patients who underwent liver biopsy for CHC in University Hospital Bucharest. Histopathological staging of liver fibrosis according to the METAVIR scoring system served as the reference. A total of 74 patients underwent ARFI elastography, APRI index, FibroMax and successful liver biopsy. **RESULTS:** The noninvasive tests had a good correlation with the liver biopsy results. The most powerful test in predicting fibrosis was ARFI elastography. The diagnostic accuracy of ARFI elastography, expressed as area under receiver operating characteristic curve (AUROC) had a validity of 90.2% (95% CI AUROC = 0.831-0.972,  $P < 0.001$ ) for the diagnosis of significant fibrosis ( $F \geq 2$ ). ARFI sonoelastography predicted even better F3 or F4 fibrosis (AUROC = 0.993, 95% CI = 0.979-1). **CONCLUSION:** ARFI elastography had very good accuracy for the assessment of liver fibrosis and was superior to other noninvasive methods (APRI Index, FibroMax) for staging liver fibrosis.

**Antiviral treatment of recurrent hepatitis C after liver transplantation: predictors of response and long-term outcome.** Selzner N, Renner EL, Selzner M, et al. *Transplantation*. 2009 Nov 27;88(10):1214-21.

[http://www.ncbi.nlm.nih.gov/pubmed/19935376?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19935376?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

**BACKGROUND:** Efficacy and long-term outcome of antiviral therapy for recurrent hepatitis C after liver transplantation is poorly defined. **AIM:** This study aimed at assessing the efficacy of antiviral therapy regarding sustained hepatitis C virus (HCV) clearance, liver histology, and patient survival. **METHODS:** We retrospectively reviewed all 446 patients who received a liver allograft at our institution for HCV-related cirrhosis between January 1992 and December 2006. Two hundred thirty-two patients (52%) were eligible for antiviral therapy based on predefined criteria (Metavir stage  $\geq 1$  and/or grade  $\geq 2$ ; protocol biopsies). One hundred seventy-two patients (39%) had no contraindication for treatment, received more than or equal to 1 dose of interferon-alpha-based combination therapy, and form the basis of this analysis. Therapy was aimed for 48 weeks; median posttreatment follow-up was 68 months. **RESULTS:** The overall sustained virological response (SVR) rate was 50% (genotype 1/4: 40%; genotype 2/3: 76%). SVR was higher on cyclosporine A (CsA) (56%) than on tacrolimus (44%,  $P=0.05$ ), largely because of a lower relapse rate (6% vs. 19%,  $P=0.01$ ). In multivariate analysis, genotype 2/3, CsA use, donor age, and pretreatment necroinflammatory activity were independently associated with SVR. SVR significantly improved histology and long-term survival (actuarial 5-year survival 96% vs. 69% in nonresponders,  $P<0.0001$ ). **CONCLUSION:** Antiviral therapy of recurrent hepatitis C after liver transplantation is able to clear HCV in half the patients, more likely on CsA than on tacrolimus, and markedly improves outcome.

**Needle sharing in regular sexual relationships: An examination of serodiscordance, drug using practices, and the gendered character of injecting.** Bryant J, Brener L, Hull P, Treloar C. *Drug Alcohol Depend*. 2009 Nov 24. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19942380?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19942380?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND:** This paper examines correlates of needle and other equipment sharing among injecting drug users (IDU) in regular heterosexual relationships. **METHODS:** A cross-sectional survey collected data from people obtaining sterile needles and syringes from pharmacies in New South Wales, Australia. 181 IDU in regular heterosexual relationships provided information about their own drug and injecting practices and those of their partners. **RESULTS:** Compared to female partners, male partners reported more frequent injecting, more commonly injected their partners, scored and prepared the drugs, and obtained the needles. Couples were less likely to share needles with each other if they reported a low-to-moderate connection with drug using networks compared to a moderate-to-high connection (AOR 0.4, 95% CI 0.19-0.95) or if the respondent partner reported sharing injecting equipment (needles and/or ancillary equipment) with friends in the last 6 months (AOR 3.2, 95% CI 1.34-7.86). Couples were more likely to share ancillary equipment with each other if they spent most or all of their injecting time together (AOR 4.1, 95% CI 1.40-11.31) or if the respondent reported sharing injecting equipment with friends (AOR 5.3, 95% CI 1.73-16.37). Couples with discordant hepatitis C status were no more or less likely than those with concordant status to share needles or ancillary injecting equipment. **CONCLUSIONS:** Injecting practices in regular heterosexual relationships do not appear to be organised around hepatitis C status but are influenced by gender, the couples' connection with other IDU, and extent to which they share the equipment with those outside of their relationship.

**Adverse outcomes in Alaska Natives who recovered from or have chronic hepatitis C infection.** McMahon BJ, Bruden D, Bruce MG, et al.

[http://www.ncbi.nlm.nih.gov/pubmed/19909749?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum&ordinalpos=1](http://www.ncbi.nlm.nih.gov/pubmed/19909749?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=1)

**BACKGROUND & AIMS:** The factors associated with adverse outcome from hepatitis C virus (HCV) infection are incompletely understood. To determine the incidence and risk factors associated with the development of end-stage liver disease (ESLD) and liver-related death (LRD), we conducted a retrospective-prospective population-based study in a cohort of Alaska Native Persons chronically infected with HCV from 1994 to 2005. **METHODS:** We followed 960 persons prospectively for an average of 7.2 years and retrospectively for 12.1 years using data from medical records and serum samples. We compared data from subjects that were chronically infected with those who recovered from HCV infection, stratified by alcohol use. Survival models were used to examine factors associated with ESLD and LRD in chronically infected patients. **RESULTS:** During prospective follow-up, 80 (8.8%) and 47 (5.2%) patients developed ESLD and LRD, respectively. In examining incidence per 100 person years, no difference was found among heavy alcohol users in the incidence of LRD (2.28 vs 3.50;  $P=.34$ ) or ESLD (3.21 vs. 5.69;  $P=0.13$ ) in persons with chronic HCV compared to those recovered from HCV infection. In subjects that consumed more than 50 gm/day of alcohol, the incidences of LRD were 0.77 and 0.09 ( $P=0.01$ ) and of ESLD were 1.58 vs 0.36 ( $P=0.002$ ), respectively, in subjects with chronic infection vs those that recovered. Multivariate analysis revealed that older age, heavy alcohol use, and HCV genotype 3 were associated with ESLD. **CONCLUSIONS:** A history of heavy alcohol use is associated with the highest incidence of LRD and ESLD, regardless of whether patients are chronically infected or recover from HCV infection.

**The disposition of hepatitis C antibody-positive patients in an urban hospital.** Putka B, Mullen K, Birdi S, Merheb M. J Viral Hepat. 2009 Nov;16(11):814-21.

[http://www.ncbi.nlm.nih.gov/pubmed?term=%22Putka%20B%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Putka%20B%22%5BAuthor%5D&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVAbstract)

Previous studies have indicated that only 26-61% of hepatitis C virus (HCV) antibody-positive patients are referred to specialists who treat HCV. However, these studies were conducted in homogeneous populations and before pegylated interferon and ribavirin became the standard of care for chronic HCV infection. The aims of this study were: (i) to determine the percentage of HCV antibody-positive patients who were referred to specialists for further management in an urban, racially diverse population, (ii) to determine the percentage of referred patients who attend specialty clinics, and (iii) to identify factors that predict referral and follow-up. All patients with a positive HCV antibody test in 2005 were identified by an inquiry of Epic, our electronic medical record system. All medical records were reviewed for demographics, location where the test was ordered (inpatient vs outpatient), specialty ordering the test, referral, clinic attendance, detectability of HCV RNA and liver function tests. Univariate and multivariate logistic regression were used to evaluate each variable's effect on referral and clinic attendance. Overall, 251 of 375 (67%) antibody positive patients were referred to HCV specialists. Of the 251 referrals, 166 (66%) attended at least one specialty clinic appointment. Patients were more likely to be referred if their HCV antibody was ordered in the outpatient setting (77% outpatient vs 38% inpatient,  $P < 0.001$ ) ordered by a family practitioner (79% FP vs 64% for internal medicine doctor vs 58% for all other specialties,  $P = 0.01$ ) had detectable RNA (88% detectable vs 65% not detectable vs 23% RNA status not available,  $P < 0.001$ ) or elevation of alanine aminotransferase (75% elevated vs 56% not elevated,  $P < 0.001$ ). Location, HCV RNA status and ALT elevation remained significant in a multivariate logistic

regression model. These data confirm that up to one-third of HCV antibody-positive patients are not referred to HCV specialists, despite the availability of improved treatment regimens. Additional patients are lost to follow-up after being referred. The reasons for suboptimal referral and specialty clinic attendance rates are probably multifactorial. Institution of reflexive RNA testing for positive antibody tests and additional education of those physicians who encounter HCV-positive individuals may improve both rates.

### **Public health impact of antiviral therapy for hepatitis C in the United States.**

Volk ML, Tocco R, Saini S, Lok AS. *Hepatology*. 2009 Dec;50(6):1750-5.

[http://www.ncbi.nlm.nih.gov/pubmed/19824079?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed\\_RVDocSum&ordinalpos=2](http://www.ncbi.nlm.nih.gov/pubmed/19824079?itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum&ordinalpos=2)

Despite dramatic improvements in antiviral therapy for hepatitis C, there is reason to believe that the uptake of antiviral therapy remains limited. The aims of this study were to determine the number of patients being treated with antiviral therapy in the U.S., to estimate the public health impact of these treatment patterns, and to identify barriers to treatment for patients with hepatitis C. Data on the number of new patient pegylated interferon prescriptions each year, from 2002-2007, was obtained from Wolters Kluwer Inc., which maintains an electronic audit of pharmacies nationwide. A Markov model was created of the population with chronic hepatitis C in the U.S. from 2002 to 2030, and was used to estimate the number of liver-related deaths caused by hepatitis C that will be prevented by current treatment patterns. The National Health and Nutrition Evaluation Survey (NHANES) Hepatitis C Follow-Up Questionnaire was used to investigate reasons for lack of treatment and to identify strategies for improving access. Approximately 663,000 patients received antiviral therapy between 2002 and 2007, and treatment rates appear to be declining. If this trend continues, only 14.5% of liver-related deaths caused by hepatitis C from 2002-2030 will be prevented by antiviral therapy. Results from the NHANES questionnaire suggest that the primary barrier to treatment is lack of diagnosis, with 69/133 (adjusted proportion 49%) of respondents previously unaware that they had hepatitis C. Conclusion: Efforts to improve rates of diagnosis and treatment will be required if the future public health burden of hepatitis C is to be ameliorated.