

Caring Ambassadors Hepatitis C Program Newsletter  
www.HepCChallenge.org  
September 2009



CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	1-4
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	4-7
HIV/HCV COINFECTION	7-10
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS	10-13

---

**CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

---

**Validation of three non-invasive markers in assessing the severity of liver fibrosis in chronic hepatitis C.** Shaikh S, Memon MS, Ghani H, et al. J Coll Physicians Surg Pak. 2009 Aug;19(8):478-82

[http://www.ncbi.nlm.nih.gov/pubmed/19651008?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19651008?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**OBJECTIVE:** To compare various biochemical markers i.e. APRI (AST to platelet ratio index), aspartate aminotransferase (AST) alanine aminotransferase (ALT) ratio, FIB-4 (AST, platelet, AST and age) with biopsy for assessing the severity of hepatic fibrosis in patients with hepatitis C. Study Design: Descriptive study. **PLACE AND DURATION OF STUDY:** Medical Department, Liaquat University of Medical and Health Sciences, Jamshoro, from July 2005 to March 2007.

**METHODOLOGY:** Consecutive hepatitis C virus RNA positive and previously untreated patients were studied. Liver biopsy with histological evaluation and AST/ALT ratio, AST to platelet ratio index and FIB-4 were assessed in all patients. Receiver operative curves were developed. Results: There were 158 patients (109 males, 49 females). On histological grounds non-advanced fibrosis (F0-1) was present in 74 (46.5%) of cases, whereas 84 (53.5%) patients had advanced (F2-4) fibrosis. The area under the receiver operating characteristic curves of APRI < 0.05-1 and FIB-4 < 1.45 were 0.7 and 0.74 respectively, which means that APRI < 1 and FIB-4 < 1.45 will exclude advanced fibrosis in 70% and 74% of patients respectively. An APRI of > 1 and FIB-4 will predict advanced fibrosis in 87% and 98% of patients respectively. AST/ALT ratio was inferior to both of these biomarkers. **CONCLUSION:** Both APRI and FIB-4 not only exclude minimal fibrosis but can predict advanced fibrosis in the majority of the patients. The simultaneous use of several indirect markers of liver fibrosis does not improve their diagnostic accuracy.

**Ethnicity and body mass index are associated with hepatitis C presentation and progression.** Kallwitz ER, Layden-Almer J, Dhamija M, et al. Clin Gastroenterol Hepatol. 2009 Aug 14. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kallwitz%20ER%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Kallwitz%20ER%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND & AIMS:** Ethnicity and the metabolic syndrome are believed to affect progression of hepatitis C virus (HCV) infection, but the interaction between these factors is unknown. We evaluated the association between elements of the metabolic syndrome and ethnicity in the histologic progression of HCV in a large, diverse cohort. **METHODS:** We retrospectively evaluated clinical data and liver biopsy samples from 812 patients that had no cause of liver disease other than HCV infection. Liver biopsies were scored for steatosis, necroinflammatory activity and fibrosis. For each patient with a known risk factor for viral acquisition, fibrosis index (fibrosis

stage/duration of infection) was calculated as an indicator of disease progression. **RESULTS:** Hispanics had significantly higher fibrosis index (0.13+/-0.09) than non-Hispanic Whites (0.11+/-0.07) and African Americans (0.10+/-0.06; p=0.001). Fibrosis index correlated with body mass index (BMI), older age at infection, ethnicity, and degree of steatosis. Cirrhosis was present in 50% of Hispanics, 38% of non-Hispanic Whites, and 24% of African Americans (p<0.001). The presence of cirrhosis was additionally associated with older age, longer duration of infection, BMI, alcohol consumption and diabetes. In multivariate analysis, only BMI and ethnicity were associated with both fibrosis index and presentation with cirrhosis. Patients with higher BMIs, diabetes mellitus and steatosis had higher degrees of necroinflammation. **CONCLUSION:** Ethnicity and BMI were each associated with the progression of fibrosis and the presence of cirrhosis. Hispanics had the highest fibrosis index and prevalence of cirrhosis, whereas African Americans had the lowest. Ethnic differences in fibrosis index and cirrhosis persisted after controlling for elements of metabolic syndrome.

**Focal distribution of hepatitis C virus RNA in infected livers.** Stiffler JD, Nguyen M, Sohn JA, Liu C, Kaplan D, Seeger C. 36: PLoS One. 2009 Aug 18;4(8):e6661.

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Stiffler%20JD%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Stiffler%20JD%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** Hepatitis C virus (HCV) is a plus-strand RNA virus that replicates by amplification of genomic RNA from minus strands leading to accumulation of almost one thousand copies per cell under in vitro cell culture conditions. In contrast, HCV RNA copy numbers in livers of infected patients appear to be much lower, estimated at a few copies per cell.

**METHODOLOGY/PRINCIPAL FINDINGS:** To gain insights into mechanisms that control HCV replication in vivo, we analyzed HCV RNA levels as well as expression of interferon beta (IFNbeta) and several interferon stimulated genes (ISGs) from whole liver sections and micro-dissected subpopulations of hepatocytes in biopsy samples from 21 HCV-infected patients. The results showed that intrahepatic HCV RNA levels range from less than one copy per hepatocyte to a maximum of about eight. A correlation existed between viral RNA levels and IFNbeta expression, but not between viral RNA and ISG levels. Also, IFNbeta expression did not correlate with ISG levels. Replication of HCV RNA occurred in focal areas in the liver in the presence of a general induction of ISGs. **CONCLUSION/SIGNIFICANCE:** The low average levels of HCV RNA in biopsy samples can be explained by focal distribution of infected hepatocytes. HCV replication directly induces IFNbeta, which then activates ISGs. The apparent lack of a correlation between levels of IFNbeta and ISG expression indicates that control of the innate immune response during HCV infections depends on multiple factors.

**Laparoscopic splenectomy with peginterferon and ribavirin therapy for patients with hepatitis C virus cirrhosis and hypersplenism.** Akahoshi T, Tomikawa M, Korenaga D, et al. Surg Endosc. 2009 Aug 19. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19690915?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19690915?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** This study aimed to evaluate whether laparoscopic splenectomy (Lap-Sp) contributes to the completion and curability of combined peginterferon and ribavirin (peg-IFN + RIB) therapy for cirrhotic patients with pancytopenia due to hypersplenism. **METHODS:** From December 2004 to September 2007, 21 patients underwent Lap-Sp before treatment with peg-IFN + RIB. All the patients were Child-Pugh class A or B with a mean platelet count of 5.7 x 10(4)/mm(3) and a mean leukocyte count of 2,830/mm(3). The hepatitis C virus (HCV) genotype was 1b for 18 patients and 2b for 3 patients. Of the 21 patients, 17 had a viral load exceeding 100

KIU/ml, and 4 had a load of less than 100 KIU/ml. **RESULTS:** All the patients underwent Lap-Sp without severe complications. The average hospital stay was 12.7 days (range, 6-23 days). Platelet counts increased from a mean of  $5.7 \pm 2.2 \times 10^4/\text{mm}^3$  preoperatively to  $19.6 \pm 7.6 \times 10^4/\text{mm}^3$  postoperatively and remained above  $7.0 \times 10^4/\text{mm}^3$  during the subsequent peg-IFN + RIB therapy. The full course of therapy was completed for nine patients, with five obtaining a sustained virologic response and one obtaining a biologic response. The five patients who obtained a sustained virologic response had either HCV type 2b or 1b with a low viral load (<100 KIU). At this writing, treatment is ongoing for the remaining 12 patients. **CONCLUSIONS:** Laparoscopic splenectomy allows patients with HCV cirrhosis and hypersplenism to receive full-dose peg-IFN + RIB therapy. Patients with HCV, genotype 2 or 1b and a low viral load, and hypersplenism may be good candidates for Lap-Sp.

**Factors influencing long-term changes of mental health after interferon-alpha treatment of chronic hepatitis C.** Schmidt F, Janssen G, Martin G, et al. *Aliment Pharmacol Ther.* 2009 Aug 18. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19691667?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19691667?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**AIM:** To evaluate long-term effects of antiviral treatment with interferon-alpha (IFN-alpha) on mental health in patients with psychiatric risk factors. **METHOD:** We prospectively investigated long term mental health changes in 81 HCV-infected patients. Psychiatric outcome was measured with the Montgomery Asberg Depression Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), the Global Social Functioning Scale (GAF) and the Global Clinical Impression Scale (CGI) six months after the end of antiviral treatment with IFN-alpha and ribavirin. **RESULTS:** 49% of the patients showed a worsening and 27.2% an improvement of depression scores six months after antiviral therapy. The most important predictor for a long-term improvement of depression scores was a pre-treatment MADRS-score  $\geq 5$  (OR 14.21, CI (95%): 2.51 - 81.30). Patients with pre-existing psychiatric disorders (OR = 0.117, CI (95%): 0.024 - 0.558), methadone substitution (OR = 0.20, CI (95%): 0.045 - 0.887) or genotype 2/3 (OR = 0.341, CI (95%): 0.138 - 0.845) were significantly less likely to show a long term worsening of depressive symptoms. **CONCLUSION:** Pre-existing psychiatric risk factors increase the chance for a long term improvement and reduce the risk for a long term worsening of mental health after antiviral treatment of chronic hepatitis C with IFN-alpha.

**Efficacy and tolerability of rituximab with or without PEGylated interferon alfa-2b plus ribavirin in severe hepatitis C virus-related vasculitis: A long-term followup study of thirty-two patients.** Terrier B, Saadoun D, Sène D, et al. *Arthritis Rheum.* 2009 Aug;60(8):2531-40.

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Terrier%20B%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Terrier%20B%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**OBJECTIVE:** To report on the long-term followup of a cohort of patients with hepatitis C virus (HCV)-related vasculitis treated with rituximab with or without PEGylated interferon alfa-2b (PEG-IFN alfa-2b) plus ribavirin. **METHODS:** The study group comprised 32 HCV RNA-positive patients with HCV-related vasculitis: 20 patients were treated with rituximab and PEG-IFN alfa-2b (9 of whom had not previously received antiviral treatment and 11 of whom had experienced disease resistance to or relapse with antiviral treatment), and 12 antiviral-intolerant patients were treated with rituximab alone. **RESULTS:** Treatment with rituximab and PEG-IFN alfa-2b plus ribavirin induced a complete clinical response and a partial clinical response in 80% and 15% of patients, respectively, a complete immunologic response and a partial immunologic response in 67% and 33% of patients, respectively, and a sustained virologic response in 55% of patients. Treatment with

rituximab alone induced a complete clinical response and a partial clinical response in 58% and 9% of patients, respectively, and a complete immunologic response and a partial immunologic response in 46% and 36% of patients, respectively. B cell depletion was achieved in 96% of patients, and B cell recovery began after a median delay of 12 months. After a mean +/- SD followup period of 23 +/- 12 months, 22% of patients experienced a clinical relapse, and 34% of patients experienced an immunologic relapse. All relapses were associated with the absence of virologic control, and 78% of relapses were associated with B cell recovery. Six patients were re-treated with rituximab. All 6 of these patients had a complete clinical response, 50% had a complete immunologic response, and 50% had a partial immunologic response. Rituximab was well tolerated overall. **CONCLUSION:** Rituximab is an effective treatment of severe and/or refractory HCV-related vasculitis. Relapses were consistently associated with the absence of virologic control. The clinical and immunologic efficacy of rituximab after repeated infusion appeared to be the same as that observed after induction therapy.

### **Leukocyte interferon-alpha and ribavirin for treatment of chronic hepatitis C patients**

**intolerant to pegylated-interferon.** Adinolfi LE, Durante-Mangoni E, Salzillo M, et al. Intern Emerg Med. 2009 Aug 1. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Adinolfi%20LE%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Adinolfi%20LE%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Treatments for chronic hepatitis C (CHC) patients intolerant to pegylated interferons (peg-IFNs) are lacking. Thus, such patients remain at high risk of developing an advanced and decompensated liver disease. Leukocyte IFN-alpha (Le-IFN-alpha) seems to possess a safer profile than other natural and recombinant alpha-interferons, but no information is available for peg-IFN intolerant patients. Accordingly, we evaluated the safety and efficacy of Le-IFN-alpha in patients intolerant to peg-IFNs. Twenty-five consecutive CHC patients intolerant to peg-IFNs were prospectively enrolled. HCV genotype 1 was present in 80% and cirrhosis in 68% of cases. Thirteen patients (52%) had thrombocytopenia. Le-IFN-alpha (3 MU three times a week) was administered for 48 weeks plus ribavirin 800 or 1,000 mg/day for HCV genotype 2/3 and 1, respectively. The follow-up was at 24 weeks. Compliance with treatment was satisfactory if the patient received 80% of the therapeutic regimen. An intention-to-treat analysis was done. Eighty-eight percent of CHC patients completed the prescribed treatment course with Le-IFN-alpha. In these patients the side effects, when observed, were mild to moderate, and did not require Le-IFN-alpha dose adjustment. Le-IFN-alpha showed significantly less hematological toxicity than peg-IFN (4 vs 48%;  $P < 0.02$ ). The overall sustained virologic response was 32%, i.e., 24% for cirrhotics and 50% for CHC, and 25% for genotype 1 and 60% for genotypes 2/3. The data indicate that Le-IFN-alpha plus ribavirin is a useful and effective treatment for CHC patients who are intolerant to peg-IFNs.

---

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

---

### **Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance**

Dongliang Ge<sup>1</sup>, Jacques Fellay<sup>1</sup>, Alexander J. et al. *Nature* advance online publication 16 August 2009

Chronic infection with hepatitis C virus (HCV) affects 170 million people worldwide and is the leading cause of cirrhosis in North America<sup>1</sup>. Although the recommended treatment for chronic infection involves a 48-week course of peginterferon--2b (PegIFN--2b) or --2a (PegIFN--2a) combined with ribavirin (RBV), it is well known that many patients will not be cured by treatment, and that patients of European ancestry have a significantly higher probability of being cured than

patients of African ancestry. In addition to limited efficacy, treatment is often poorly tolerated because of side effects that prevent some patients from completing therapy. For these reasons, identification of the determinants of response to treatment is a high priority. Here we report that a genetic polymorphism near the IL28B gene, encoding interferon-3 (IFN-3), is associated with an approximately twofold change in response to treatment, both among patients of European ancestry ( $P = 1.06 \times 10^{-25}$ ) and African-Americans ( $P = 2.06 \times 10^{-3}$ ). Because the genotype leading to better response is in substantially greater frequency in European than African populations, this genetic polymorphism also explains approximately half of the difference in response rates between African-Americans and patients of European ancestry.

#### **Endotoxin receptor CD14 gene variants and histological features in chronic HCV infection.**

Askar E, Ramadori G, Mihm S. World J Gastroenterol. 2009 Aug 21;15(31):3884-90.

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Askar%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Askar%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**AIM:** To analyze the correlation between CD14 rs2569190/C-159T single nucleotide polymorphism (SNP) and disease progression in chronic hepatitis C. **METHODS:** Liver biopsy specimens from a total of 137 and 349 patients with chronic hepatitis C were separately evaluated with respect to necroinflammatory activity (grading) and architectural changes (staging). In one group, further histological lesions characteristic for hepatitis C, hepatitis C virus subtypes, and biochemical parameters of liver disease were also investigated. Samples of genomic DNA were genotyped for the respective SNP by 5'-nuclease assays using fluorescent dye-labeled allele-specific probes.

**RESULTS:** Genotype distribution did not deviate from the Hardy-Weinberg equilibrium. In the first group, patients homozygous for the variant allele T were found to be younger than C allele carriers ( $39.6 \pm 12.5$  vs  $45.7 \pm 11.5$ ,  $P = 0.008$ ). Among the histological lesions studied, portal lymphoid aggregates were more frequently observed among TT homozygotes than among C carriers ( $21/37$  vs  $32/100$ ,  $P = 0.008$ ). The presence of portal lymphoid aggregates was closely correlated with hepatic inflammation ( $P = 0.003$ ) and with bile duct damage ( $P < 0.001$ ). The degree of fibrosis, in contrast, was not found to be related to the CD14 gene C-159T polymorphism.

**CONCLUSION:** The data suggest a possible relationship between CD14 C-159T polymorphism and the formation of portal lymphoid aggregates, but not liver fibrosis progression in chronic hepatitis C.

#### **Modulations of cell cycle checkpoints in HCV associated disease.** Sarfraz S, Hamid S, Ali S, Jafri W, Siddiqui A. BMC Infect Dis. 2009 Aug 10;9(1):125

**BACKGROUND:** Impaired proliferation of hepatocytes has been reported in chronic Hepatitis C virus infection. Considering the fundamental role played by cell cycle proteins in controlling cell proliferation, altered regulation of these proteins could significantly contribute to HCV disease progression and subsequent hepatocellular carcinoma. This study aimed to identify the alterations in cell cycle genes expression with respect to early and advanced disease of chronic HCV infection.

**METHODS:** Using freshly frozen liver biopsies, mRNA levels of 84 cell cycle genes in pooled RNA samples from patients with early or advanced fibrosis of chronic HCV infection were studied. To associate mRNA levels with respective protein levels, four genes (p27, p15, KNTC1 and MAD2L1) with significant changes in mRNA levels ( $> 2$ -fold,  $p$ -value  $< 0.05$ ) were selected, and their protein expressions were examined in the liver biopsies of 38 chronic hepatitis C patients.

**RESULTS:** In the early fibrosis group, increased mRNA levels of cell proliferation genes as well as cell cycle inhibitor genes were observed. In the advanced fibrosis group, DNA damage response genes were up-regulated while those associated with chromosomal stability were down-regulated. Increased expression of CDK inhibitor protein p27 was consistent with its mRNA level detected in

early group while the same was found to be negatively associated with liver fibrosis. CDK inhibitor protein p15 was highly expressed in both early and advanced group, but showed no correlation with fibrosis. Among the mitotic checkpoint regulators, expression of KNTC1 was significantly reduced in advanced group while MAD2L1 showed a non-significant decrease. **CONCLUSION:** Collectively these results are suggestive of a disrupted cell cycle regulation in HCV-infected liver. The information presented here highlights the potential of identified proteins as predictive factors to identify patients with high risk of cell transformation and HCC development.

**Hepatic inflammation mediated by hepatitis C virus core protein is ameliorated by blocking complement activation.** Chang ML, Yeh CT, Lin DY, Ho YP, Hsu CM, Bissell DM. BMC Med Genomics. 2009 Aug 8;2(1):51. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Chang%20ML%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Chang%20ML%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** The pathogenesis of inflammation and fibrosis in chronic hepatitis C virus (HCV) infection remains unclear. Transgenic mice with constitutive HCV core over-expression display steatosis only. While the reasons for this are unclear, it may be important that core protein production in these models begins during gestation, in contrast to human hepatitis C virus infection, which occurs post-natally and typically in adults. To more realistically model the effect of core protein production in the adult liver, we developed a mouse with conditional expression of HCV core and examined the effect of core protein production in the adult liver. **METHOD:** Liver biopsy samples from transgenic mice with tetracycline(tet)-regulated conditional core protein expression were evaluated immunohistologically. Microarray analysis of HCV core transgenic mice with steatohepatitis pointed to a role of the complement pathway. This was further explored by blocking complement activation by in vivo administration of CD55 (decay accelerating factor for complement). **RESULTS:** Transgenic mice exhibited low, intermediate, or high HCV core protein expression when fed a permissive diet of standard chow. Aside from hepatic steatosis, hepatic inflammation and fibrosis were seen in mice with intermediate levels of core protein. Microarray analyses of inflamed liver demonstrated activation of both the complement and coagulation pathways. Administration of CD55 reduced hepatic inflammation. **CONCLUSIONS:** Transgenic mice that conditionally express intermediate HCV core protein develop inflammation, steatosis, and fibrosis. These effects mediated by HCV core are reduced by administration of CD55, a regulator of the complement pathway. The model may be valuable in investigating the pathogenesis of liver inflammation in chronic hepatitis C.

**Genetic variation in CLDN1 and susceptibility to hepatitis C virus infection.** Bekker V, Chanock SJ, Yeager M, et al. J Viral Hepat. 2009 Aug 7. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Bekker%20V%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Bekker%20V%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Claudin-1 is a recently discovered co-receptor for hepatitis C virus (HCV) that is required for late-stage binding of the virus. Because variants in the gene that encodes claudin-1 (CLDN1) could play a role in HCV infection, we conducted a 'whole gene association study' among injection drug users (IDUs) to examine whether CLDN1 genetic variants were associated with the risk of HCV infection or with viral clearance. In a cross sectional study, we examined genotype results for 50 single nucleotide polymorphisms (SNPs) across the CLDN1 gene region, comparing genotypes among participants with chronic HCV (n = 658) to those in IDUs who had cleared HCV (n = 199) or remained HCV-uninfected (n = 68). Analyses were controlled for racial ancestry (African-American or European-American) by stratification and logistic regression modeling. We found that participants who remained uninfected more often carried CLDN1 promoter region SNPs -15312C

[odds ratio (OR), 1.72; 95% confidence interval (CI) 1.00-2.94; P = 0.048], -7153A (OR, 2.13; 95% CI, 1.25-3.62; P = 0.006) and -5414C (OR, 1.78; 95% CI, 1.06-3.00; P = 0.03). HCV-uninfected participants less often carried CLDN1 IVS1-2983C (OR, 0.55; 95% CI, 0.31-0.97; P = 0.04), which lies in intron 1. CLDN1 -15312C, -7153A and -5414C formed a haplotype in both the African-American and European-American participants and a haplotype analysis supported the association of CLDN1 -7153A in the HCV-uninfected participants. The analyses of HCV clearance revealed no associations with any SNP. These results indicate that genetic variants in regulatory regions of CLDN1 may alter susceptibility to HCV infection.

---

## HIV/HCV COINFECTION

---

**Treat early or wait and monitor? A qualitative analysis of provider hepatitis C virus treatment decision-making in the context of HIV coinfection.** Wagner G, Ryan G, Osilla KC, Bhatti L, Goetz M, Witt M. AIDS Patient Care STDS. 2009 Aug 10. [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/pubmed/19663714?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19663714?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Liver disease is a leading cause of death among patients with HIV coinfecting with hepatitis C (HCV); yet, studies show that less than 10% receive HCV treatment, in part because of limited treatment response, high treatment toxicity, and psychosocial barriers to treatment readiness. Using a process model framework, we sought to explore the factors and processes by which providers make HCV treatment decisions for HIV-coinfecting patients. We conducted 22 semistructured interviews with primary care providers and support staff at three HIV clinics in Los Angeles, California, in which rates of HCV treatment uptake varied from 10% to 38%. Providers agreed that stable HIV disease, favorable genotype, and significant signs of liver disease progression are all signs of need for treatment. However, two divergent treatment approaches emerged for genotype 1 and 4 patients with minimal disease, and in definitions of patient readiness. Providers with lower treatment rates preferred to delay treatment in hopes of better future treatment options, and were more conservative in requiring complete mental health screens and treatment and abstinence from substance use. Conversely, providers with higher treatment rates viewed all patients as needing treatment as soon as possible, and defined readiness more leniently, with some willing to treat even in the context of untreated depression and drug use, so long as ability to adhere well was demonstrated. Regardless of whether an aggressive or cautious approach to treatment is used, development of effective programs for promoting patient treatment readiness is critical to ensuring greater treatment uptake.

**Management of hepatitis C virus infection in HIV/HCV co-infected patients: clinical review.** Singal AK, Anand BS. World J Gastroenterol. 2009 Aug 14;15(30):3713-24. [http://www.ncbi.nlm.nih.gov/pubmed/19673011?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19673011?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Nearly one fourth of individuals with human immunodeficiency virus (HIV) infection have hepatitis C virus (HCV) infection in the US and Western Europe. With the availability of highly active antiretroviral therapy and the consequent reduction in opportunistic infections, resulting in the prolongation of the life span of HIV-infected patients, HCV co-infection has emerged as a significant factor influencing the survival of HIV patients. Patients with HIV/HCV co-infection have a faster rate of fibrosis progression resulting in more frequent occurrences of cirrhosis, end-stage liver disease, and hepatocellular carcinoma. However, the mechanism of interaction between the two viruses is not completely understood. The treatment for HCV in co-infected patients is

similar to that of HCV mono-infection; i.e., a combination of pegylated interferon and ribavirin. The presence of any barriers to anti-HCV therapy should be identified and eliminated in order to recruit all eligible patients. The response to treatment in co-infected patients is inferior compared to the response in patients with HCV mono-infection. The sustained virologic response rate is only 38% for genotype-1 and 75% for genotype-2 and -3 infections. Liver transplantation is no longer considered a contraindication for end-stage liver disease in co-infected patients. However, the 5 year survival rate is lower in co-infected patients compared to patients with HCV mono-infection (33% vs 72%,  $P = 0.07$ ). A better understanding of liver disease in co-infected patients is needed to derive new strategies for improving outcome and survival.

**Determination of hepatitis C virus-infected, monocyte lineage reservoirs in individuals with or without HIV coinfection.** Coquillard G, Patterson BK. *J Infect Dis.* 2009 Sep 15;200(6):947-54. Because previous reports found an association between hepatitis C virus (HCV) coinfection and progression of human immunodeficiency virus (HIV) disease, we investigated whether HIV and HCV may reciprocally influence viral replication in monocyte lineage cells in vivo. Using a novel technique called simultaneous ultrasensitive subpopulation staining/hybridization in situ (SUSHI), we rapidly and unequivocally identified HCV reservoirs in peripheral blood from HCV-infected individuals with and without HIV coinfection. We found that HCV infects both CD14(+), CD16(+)(+) monocytic cells and CD14(+)(+), CD16(+)(+) monocytic cells but not CD14(+)(+), CD16- cells in individuals infected with HCV with or without HIV coinfection. To address these HCV tropism differences, we found that the HCV receptor CD81 is highly expressed on CD14(+), CD16(+)(+) and CD14(+)(+), CD16(+)(+) cells but not on monocytes (CD14(+)(+), CD16-). These findings have important implications for the diagnosis and treatment of HCV infection, mother-to-child transmission of HCV, and possible virus-virus interactions in HCV-HIV coinfecting individuals.

**Occult hepatitis B virus infection in a cohort of HIV-positive patients: Correlation with hepatitis C virus coinfection, virological and immunological features.** Morsica G, Ancarani F, Bagaglio S, et al. *Infection.* 2009 Aug 7. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Morsica%20G%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Morsica%20G%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)  
**BACKGROUND:** An evaluation of the prevalence of occult hepatitis B virus (HBV) infection in HIV-positive individuals is important as HBV infection may have an impact on the outcome of the liver disease in these patients. **MATERIALS AND METHODS:** Of the 1,593 HIV-positive subjects enrolled in the Italian Cohort Naïve Antiretroviral (ICONA) program, 175 (10.9%) were selected for inclusion in the study on the basis of hepatitis B surface antigen (HBsAg) negativity and antibody to hepatitis B core antigen (anti-HBc) positivity; 101/175 (58%) were also anti-hepatitis C virus (HCV) positive. HBV-DNA was detected in plasma using a highly sensitive PCR assay (detection limit: 2.6 copies/ml). Two different genomic regions were assayed. Quantification was performed by real-time PCR. The HBV genotype was determined in 20 cases with occult HBV infection. Data on the antiretroviral therapy (ART) regimen was obtained in 169 individuals: 53 (31.4%) patients were ART-naïve, 46 (27.2%) were under ART without lamivudine or tenofovir, and the remaining 70 (41.4%) were under ART including lamivudine or tenofovir. **RESULTS:** 27/175 (15%) patients had detectable HBV-DNA in their plasma: 21/101 (21%) were anti-HCV positive and 6/74 (8%) were anti-HCV negative. Genotype D was invariably found in the 20 cases analyzed. Occult HBV infection was significantly higher in HCV-coinfecting subjects: adjusted OR 5.02, 95% CI 1.31-19.26,  $p = 0.02$ . The value was not associated with immune status, HIV load, or ART regimen. **CONCLUSIONS:** In relation to the high prevalence of occult HBV infection, particularly

in HIV/HCV-coinfected individuals, it is necessary to clarify the clinical impact of this cryptic infection by monitoring HBV-DNA in plasma using the correct approach. Similarly to HBsAg-positive individuals of the Mediterranean area, HBV genotype D is invariably detected in this cohort of HIV-infected patients with occult HBV infection.

**Longitudinal evaluation of viral interactions in treated HIV-hepatitis B co-infected patients with additional hepatitis C and D virus.** Boyd A, Lacombe K, Mialhes P, et al. *J Viral Hepat.* 2009 Aug 4. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Boyd%20A%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Boyd%20A%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Virological interactions of hepatitis B (HBV), hepatitis C (HCV) and hepatitis D (HDV) viruses in HIV-infected patients have been poorly characterized especially under treatment influences. Undetection rates of hepatitis viruses were longitudinally analyzed in a 3-year cohort of 308 HIV-HBV co-infected patients and compared using Generalized Estimating Equation models adjusted for age, HIV-RNA, CD4 cell-count and antiviral treatment. Chronic hepatitis co-infection in HIV-infected patients (age years, SD) was: 265 HBV (40.7, 8.2); 19 HBV-HCV (39.7, 4.1); 12 HBV-HDV (35.2, 9.9); 12 HBV-HCV-HDV (39.2, 5.2). At inclusion, treatment with lamivudine/tenofovir was not significantly different between co-infection groups. HBV suppression was significantly associated with HDV (aOR = 3.85, 95%CI 1.13-13.10, P = 0.03) and HCV tri-infection (aOR = 2.65, 95%CI 1.03-6.81, P = 0.04), but marginally associated with HIV-HBV-HCV-HDV (aOR = 2.32, 95%CI 0.94-5.74, P = 0.07). In quad-infection, lower HDV-undetectability (vs HIV-HBV-HDV, P = 0.2) and higher HCV-undetectability (vs HIV-HBV-HCV, P = 0.1) were demonstrated. The degree of HBV suppression varied between visits and co-infection groups [range of aOR during follow-up (vs HIV-HBV co-infection): HIV-HBV-HCV = 2.23-5.67, HIV-HBV-HDV = 1.53-15.17]. In treated co-infected patients, HDV expressed continuous suppression over HCV- and HBV-replications. Peaks and rebounds from undetectable hepatitis B, C and/or D viremia warrant closer follow-up in this patient population. HDV-replication was uncontrolled even with antiviral treatment.

**Diagnosis of advanced fibrosis in HIV and hepatitis C virus-coinfected patients via a new noninvasive index: the HGM-3 index.** Resino S, Micheloud D, Miralles P, et al. *HIV Med.* 2009 Aug 3. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Resino%20S%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Resino%20S%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** Noninvasive tests are increasingly being used for the assessment of liver fibrosis. We aimed to develop a serum index for the identification of advanced fibrosis ( $F \geq 3$ ) in HIV/hepatitis C virus (HCV)-coinfected patients. **METHODS:** We carried out a cross-sectional study on a group of 195 patients comprised of an estimation group (EG; n=127) and a validation group (VG; n=68) who all underwent liver biopsy and had not received previous interferon therapy. Liver fibrosis was estimated using the METAVIR score. We developed a new serum index (HGM-3) dependent on levels of platelets, alkaline phosphatase, hepatic growth factor, tissue inhibitor of metalloproteinase-1 and hyaluronic acid. **RESULTS:** In the EG, the area under the receiver operating characteristic curve (AUC-ROC) of HGM-3 for identification of  $F \geq 3$  was 0.939 [95% confidence interval (CI) 0.899, 0.979] which was significantly higher than the AUC-ROC of the HGM-2, FIB-4, aspartate aminotransferase to platelet ratio (APRI) and Forns' indexes. With HGM-3  $< 0.135$  for  $F < 3$ , 57 patients were correctly identified and two patients were misclassified. We found the presence of  $F < 3$  with 96.6% certainty. The negative likelihood ratio (LR) was  $< 0.1$  and the diagnostic odds ratio (DOR) was  $> 40$ . With HGM-3  $> 0.570$  in the EG for  $F \geq 3$ , 31 patients

were correctly identified, and five patients were misclassified. We found the presence of F $\geq$ 3 with 86.1% certainty. The positive LR was  $>12$  and the DOR was  $>40$ . For the VG, the diagnostic accuracy values were similar to the values for the EG. **CONCLUSIONS:** HGM-3 appears to be an accurate noninvasive method for the diagnosis of bridging fibrosis and cirrhosis in HIV/HCV-coinfected patients.

---

## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

---

**Quality of life considerations for patients with chronic hepatitis C.** Foster GR. J Viral Hepat. 2009 Sep;16(9):605-11. Epub 2009 Aug 5.

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Foster%20GR%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Foster%20GR%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Chronic infection with the hepatitis C virus (HCV) has a profound effect on health-related quality of life (HRQoL) - with fatigue, depression and neurocognitive deficits among the most common complaints. Neuropsychiatric symptoms have prompted research to determine whether the HCV acts within the central nervous system. Replicating virus has been found in central nervous tissues, and changes in neurotransmitter levels in the frontal white matter of patients with chronic hepatitis C are correlated with impaired attention and concentration. Other symptoms of chronic hepatitis C that decrease HRQoL include associated sexual dysfunction and depression. Treatment of chronic HCV infection may temporarily worsen HRQoL, and common adverse effects of currently available agents include fatigue, muscle aches, depression and cognitive deficits. The relationship between sustained viral response and improvement in HRQoL is nonetheless well accepted. Although treatment-related adverse effects may dissuade people from starting therapy and reduce compliance with associated reductions in sustained viral response, for the majority of patients viral clearance produces improvements in both HRQoL and long-term prognosis. Novel agents, with improved adverse effect profiles, may afford more patients the opportunity to achieve a sustained viral response.

**Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco.** Tsui JI, Vittinghoff E, Hahn JA, Evans JL, Davidson PJ, Page K. Drug Alcohol Depend. 2009 Jul 30. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Tsui%20JI%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Tsui%20JI%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

**BACKGROUND:** The rationale for screening populations at risk for hepatitis C virus infection (HCV) includes the possibility of altering risk behaviors that impact disease progression and transmission. This study prospectively examined young injection drug users (IDU) to determine if behaviors changed after they were made aware of HCV seroconversion. **METHODS:** We estimated the effects of HCV seroconversion coupled with post-test counseling on risk behaviors (alcohol use, non-injection and injection drug use, lending and sharing injecting equipment, and having sex without a condom) and depression symptoms using conditional logistic regression, fitting odds-ratios for immediately after disclosure and 6 and 12 months later, and adjusting for secular effects. **RESULTS:** 112 participants met inclusion criteria, i.e. they were documented HCV seronegative at study onset and subsequently seroconverted during the follow-up period, with infection confirmed by HCV RNA testing. HCV seroconversion was independently associated with a decreased likelihood of consuming alcohol (OR=0.52; 95% CI: 0.27-1.00,  $p=0.05$ ) and using non-injection drugs (OR=0.40; 95% CI: 0.20-0.81,  $p=0.01$ ) immediately after disclosure, however, results were not sustained over time. There were significant ( $p<0.05$ ) declines in the use of alcohol,

injection and non-injection drugs, and sharing equipment associated with time that were independent from the effect of seroconversion. **CONCLUSIONS:** Making young IDU aware of their HCV seroconversion may have a modest effect on alcohol and non-injection drug use that is not sustained over time.

**The evolution of the major hepatitis C genotypes correlates with clinical response to interferon therapy.** Pang PS, Planet PJ, Glenn JS. PLoS One. 2009 Aug 11;4(8):e6579.

[http://www.ncbi.nlm.nih.gov/pubmed/19668364?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19668364?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** Patients chronically infected with hepatitis C virus (HCV) require significantly different durations of therapy and achieve substantially different sustained virologic response rates to interferon-based therapies, depending on the HCV genotype with which they are infected. There currently exists no systematic framework that explains these genotype-specific response rates. Since humans are the only known natural hosts for HCV—a virus that is at least hundreds of years old—one possibility is that over the time frame of this relationship, HCV accumulated adaptive mutations that confer increasing resistance to the human immune system. Given that interferon therapy functions by triggering an immune response, we hypothesized that clinical response rates are a reflection of viral evolutionary adaptations to the immune system. **METHODS AND FINDINGS:** We have performed the first phylogenetic analysis to include all available full-length HCV genomic sequences ( $n = 345$ ). This resulted in a new cladogram of HCV. This tree establishes for the first time the relative evolutionary ages of the major HCV genotypes. The outcome data from prospective clinical trials that studied interferon and ribavirin therapy was then mapped onto this new tree. This mapping revealed a correlation between genotype-specific responses to therapy and respective genotype age. This correlation allows us to predict that genotypes 5 and 6, for which there currently are no published prospective trials, will likely have intermediate response rates, similar to genotype 3. Ancestral protein sequence reconstruction was also performed, which identified the HCV proteins E2 and NS5A as potential determinants of genotype-specific clinical outcome. Biochemical studies have independently identified these same two proteins as having genotype-specific abilities to inhibit the innate immune factor double-stranded RNA-dependent protein kinase (PKR).

**CONCLUSION:** An evolutionary analysis of all available HCV genomes supports the hypothesis that immune selection was a significant driving force in the divergence of the major HCV genotypes and that viral factors that acquired the ability to inhibit the immune response may play a role in determining genotype-specific response rates to interferon therapy.

**Assessment and proposal of a new combination of screening criteria for hepatitis C in France.** King LA, Le Strat Y, Meffre C, Delarocque-Astagneau E, Desenclos JC. Eur J Public Health. 2009 Aug 10. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19667051?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19667051?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND:** The current French hepatitis C virus infection screening programme is not yet reaching all populations at risk. In order to better identify individuals that would benefit from a screening test, we investigated an expanded combination of personal characteristics as potential screening criteria for this infection. **METHODS:** We constructed two multiple-regression models predicting hepatitis C antibody seropositivity using the population sample from the 2004 French national hepatitis C antibody seroprevalence survey (SPS) ( $n = 14\,416$ ): one representing current screening guidelines and another constructed from personal characteristics collected for the SPS. Performance of the two predictive models was statistically compared and we internally validated the better performing model. **RESULTS:** The expanded screening criteria model better discriminated

seropositive and seronegative individuals [area under the ROC curve (AUC) 0.869 (95% CI 0.861-0.873)] than the current screening guidelines model [AUC 0.821 (95% CI 0.810-0.824)]. This performance difference was statistically significant ( $P < 0.00001$ ). The expanded criteria model contains the variables age, sex, pre-1992 blood transfusion, intra-venous drug use, receipt of medical welfare for precarious individuals, previous surgeries, illicit nasal drug use, previous hepatitis C screening, tattoo, raised alanine aminotransferase level and birth in a hepatitis C high/moderate-prevalence country. **CONCLUSION:** Results indicate that an expanded combination of screening criteria better predicted hepatitis C antibody status and thus individuals needing screening than the current French-screening guidelines. The proposed combination of screening criteria could more effectively target hepatitis C risk-populations in France and could serve as the basis for a decision-making screening tool for the general population.

**Ultrasound surveillance for early detection of hepatocellular carcinoma among patients with chronic hepatitis C.** Sato T, Tateishi R, Yoshida H, et al. *Hepatol Int.* 2009 Aug 6. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/pubmed/19669240?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19669240?ordinalpos=13&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

**BACKGROUND AND AIMS:** Ultrasonography is the most frequently used modality in surveillance for HCC among patients with chronic hepatitis C. However, the optimal surveillance interval is still controversial and the usefulness of supplementary tumor marker determination has not been confirmed. **METHODS:** A total of 243 cases of naive HCC were detected among 1,431 patients with chronic hepatitis C under outpatient-based surveillance. The mode of HCC detection, including ultrasound surveillance interval, was retrospectively examined and the relation between the interval and detected tumor size was analyzed. Tumor volume doubling time was estimated from exponential increase in serum tumor marker levels when applicable. **RESULTS:** HCC was first detected by ultrasonography in 221 patients. Ultrasound surveillance interval, ranging between 2 and 8 months, was not correlated with the size of tumor at detection. Patients with cirrhosis were likely to be surveyed at shorter intervals. The size of tumor exceeded 30 mm only in three (1.4%) cases. They were all positive for a biomarker and the estimated tumor doubling time was short. In 14 cases, HCC was first detected by CT indicated by abnormal rise in tumor marker levels despite negative ultrasound findings. In the remaining eight cases, ultrasonography had been replaced by CT as surveillance modality because of excessive obesity or coarseness of liver parenchyma. **CONCLUSIONS:** Ultrasound surveillance at 6-month intervals was appropriate in general for the detection of HCC at a size smaller than 30 mm. However, in patient with established cirrhosis, more frequent screening would be needed to detect tumors of the same size.

**A methodology for successfully producing global translations of patient reported outcome measures for use in multiple Countries.** Two R, Verjee-Lorenz A, Clayson D, et al. *Value Health.* 2009 Aug 20. [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Two%20R%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Two%20R%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

The production of accurate and culturally relevant translations of patient reported outcome (PRO) measures is essential for the success of international clinical trials. Although there are many reports in publication regarding the translation of PRO measures, the techniques used to produce single translations for use in multiple countries (global translations) are not well documented. This article addresses this apparent lack of documentation and presents the methodology used to create global translations of the Chronic Liver Disease Questionnaire-Hepatitis C Virus (CLDQ-HCV). The challenges of creating a translation for use in multiple countries are discussed, and the criteria for a

global translation project explained. Based on a thorough translation and linguistic validation methodology including a concept elaboration, multiple forward translations, two back translations, reviews by in-country clinicians and the instrument developer, pilot testing in each target country and multiple sets of proofreading, the key concept of the global translation methodology is consistent international harmonization, achieved through the involvement of linguists from each target country at every stage of the process. This methodology enabled the successful resolution of the translation issues encountered, and resulted in consistent translations of the CLDQ-HCV that were linguistically and culturally appropriate for all target countries.

**Prevalence of hepatitis C infection in New York City, 2004.** Bornschlegel K, Berger M, Garg RK, et al. *J Urban Health*. 2009 Aug 12. [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Bornschlegel%20K%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed\\_ReportSelector.Pubmed\\_RVAbstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Bornschlegel%20K%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract)

Hepatitis C virus (HCV) is the leading cause of chronic liver disease in the United States. Accurate hepatitis C prevalence estimates are important to guide local public health programs but are usually unavailable to local health jurisdictions. National surveys may not reflect local variation, a particular challenge for urban settings with disproportionately large numbers of residents in high-risk population groups. In 2004, the New York City Department of Health and Mental Hygiene conducted the NYC Health and Nutrition Examination Survey, a population-based household survey of non-institutionalized NYC residents ages 20 and older. Study participants were interviewed and blood specimens were tested for antibody to HCV (anti-HCV); positive participants were re-contacted to ascertain awareness of infection and to provide service referrals. Of 1,786 participants with valid anti-HCV results, 35 were positive for anti-HCV, for a weighted prevalence of 2.2% (95% confidence interval [CI] 1.5% to 3.3%). Anti-HCV prevalence was high among participants with a lifetime history of injection drug use (64.5%, 95% CI 39.2% to 83.7%) or a lifetime history of incarceration as an adult (8.4%, 95% CI 4.3% to 15.7%). There was a strong correlation with age; among participants born between 1945 and 1954, the anti-HCV prevalence was 5.8% (95% CI 3.3% to 10.0%). Of anti-HCV positive participants contacted (51%), 28% (n = 5) first learned of their HCV status from this survey. Continued efforts to prevent new infections in known risk behavior groups are essential, along with expansion of HCV screening and activities to prevent disease progression in people with chronic HCV.