

# Caring Ambassadors Program

## Hepatitis C Newsletter

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### CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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**Safety and pharmacokinetics of IDX184, a liver-targeted nucleotide polymerase inhibitor of the hepatitis c virus, in healthy subjects.** Zhou XJ, Pietropaolo K, Chen J, Khan S, Sullivan-Bólyai J, Mayers D. Antimicrob Agents Chemother. 2010 Nov 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21060109>

IDX184 is a nucleotide prodrug designed to enhance formation in the liver of the active triphosphate of 2'-methylguanosine (2'-MeG), a potent and specific polymerase inhibitor of the hepatitis C virus (HCV). In the present study, single ascending oral doses of 5, 10, 25, 50, 75 and 100mg IDX184 were administered sequentially to cohorts of 8 healthy subjects randomized 6:2, active:placebo. Plasma and urine pharmacokinetic sampling was performed over 120h after dosing. Upon absorption, IDX184 rapidly disappeared from plasma with a mean half-life ( $t_{1/2}$ ) of approximately 1 h while plasma concentrations of 2'-MeG gradually increased. Consistent with a liver-targeting approach, plasma exposure of IDX184 and 2'-MeG was low and was also dose-related: the mean maximum concentrations ranged from 1.1 to 17ng/ml for IDX184 and 1.7 to 19ng/ml for 2'-MeG, and the respective mean total area-under-the-curve ranged from 1.2 to 22.7 and 17.3 to 334ng•h/ml. Mean 2'-MeG plasma concentrations 24h after dosing were 0.6-3ng/ml for the 25-100mg doses. Mean 2'-MeG  $t_{1/2}$  ranged from 18 to 43h for doses of 25mg and above. Mean cumulative urine excretion was 0.2% and 12-20% of administered doses for the unchanged IDX184 and 2'-MeG, respectively. IDX184 was safe and well tolerated; no serious adverse events, dose-dependent adverse events (AEs) or dose-limiting toxicities were observed. The incidence of AEs and laboratory abnormalities was low and similar among subjects receiving IDX184 or placebo. All AEs were mild to moderate and resolved at the end of study. The favorable safety and pharmacokinetic profiles support further clinical evaluation of IDX184 in HCV-infected patients.

**Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C.** Conjeevaram HS, Wahed AS, Afdhal N, et al. Gastroenterology. 2010 Nov 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21070775>

**BACKGROUND & AIMS:** Chronic hepatitis C is associated with an increased prevalence of insulin resistance, which might result from liver disease, metabolic factors, or the hepatitis C virus (HCV) itself. The effect of antiviral treatment on insulin sensitivity is not well known. We evaluated changes in insulin resistance and weight in patients with hepatitis C during and after peginterferon and ribavirin therapy. **METHODS:** Virahep-C was a prospective, multi-center study of a 48-week course of combination antiviral therapy in patients infected with HCV genotype 1. Insulin resistance

was estimated by the homeostasis model assessment index (HOMA2-IR) based on fasting glucose and insulin levels. **RESULTS:** Among 341 patients, 40% had insulin resistance (HOMA2-IR > 2.0). The presence of insulin resistance was associated with increasing age, body mass index, (BMI) and fibrosis stage. Among patients with insulin resistance at the start of the trial, median decreases in HOMA2-IR values during treatment were 0.74 at 24 weeks and 0.89 at 48 weeks, whereas BMI decreased by 1.2 and 2.2 kg/m<sup>2</sup> at the same timepoints ( P <0.001 for all). At follow-up, HOMA2-IR and BMI levels returned toward baseline values in patients that did not respond or relapsed, but HOMA2-IR values remained significantly lower in patients with sustained virological response (SVR) ( P <0.001), despite increases in BMI. **CONCLUSIONS:** In patients with HCV genotype 1 infections, therapy with peginterferon and ribavirin is associated with decreases in body weight and insulin resistance. Among patients with insulin resistance before treatment, resolution of HCV infection results in sustained improvements in the homeostasis model assessment index, so HCV could have a direct role in the pathogenesis of insulin resistance. All studies published in Gastroenterology are embargoed until 3PM ET of the day they are published as corrected proofs on-line. Studies cannot be publicized as accepted manuscripts or uncorrected proofs.

**Long-term outcome after antiviral therapy of patients with hepatitis C virus infection and decompensated cirrhosis.** Iacobellis A, Perri F, Valvano MR, Caruso N, Niro GA, Andriulli A.

Clin Gastroenterol Hepatol. 2010 Nov 16. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21092761>

**BACKGROUND & AIMS:** We evaluated the long-term outcomes following antiviral therapy of patients with decompensated cirrhosis and hepatitis C virus (HCV) infection. **METHODS:** Seventy-five patients with HCV infection and decompensated cirrhosis received therapy with peginterferon alfa-2b and ribavirin. We compared adverse-event profiles and mortality rates between patients with or without sustained virological responses (SVRs). The mean follow-up time off therapy was 51±18 months (range 3-78 months). **RESULTS:** Seven patients with HCV genotypes 1 or 4 (16%) and 17 patients with genotypes 2 or 3 (55%) achieved SVRs. The mean survival times were 53 months among patients that did not achieve SVRs (95% confidence interval [CI], 48-59 months) and 73 months among those that did achieve SVRs (95% CI, 67-80 months) (P=0.004). During the study, 25 patients died (2 with and 23 without SVRs). In the follow up period, 8/24 patients with SVRs (33.3%) and 49 of 51 without SVRs (96.1%) experienced further events of decompensation (P<0.0001). The hospital re-admission rates for patients with and without SVRs were 7.4 and 56 per 1000 person-months, respectively (ratio of 7.5 without/with SVR; 95% CI, 4.0-16.0; P<0.0001). At the end of the follow-up period, the incidence of hepatocellular carcinoma was not associated with clearance of HCV. **CONCLUSIONS:** Among patients with cirrhosis that is secondary to HCV infection and who have progressed to a stage of liver decompensation, an SVR following anti-viral therapy is a positive prognostic factor.

**Hepatitis C treatment among racial and ethnic groups in the IDEAL trial.** Muir AJ, Hu KQ,

Gordon SC, et al. J Viral Hepat. 2010 Nov 25. doi: 10.1111/j.1365-2893.2010.01402.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21108699>

**SUMMARY:** Previous studies of chronic hepatitis C virus (HCV) treatment have demonstrated variations in response among racial and ethnic groups including poorer efficacy rates among African American and Hispanic patients. The individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial enrolled 3070 patients from 118 United States centres to compare treatment with peginterferon (PEG-IFN) alfa-2a and ribavirin (RBV) and two doses of PEG-IFN alfa-2b and RBV. This analysis examines treatment response among the major racial and ethnic groups in the trial. Overall, sustained virologic response (SVR) rates were 44% for white, 22% for African American, 38% for Hispanic and 59% for Asian American patients. For patients with

undetectable HCV RNA at treatment week 4, the positive predictive value of SVR was 86% for white, 92% for African American, 83% for Hispanic and 89% for Asian American patients. The positive predictive values of SVR in those with undetectable HCV RNA at treatment week 12 ranged from 72% to 81%. Multivariate regression analysis using baseline characteristics demonstrated that treatment regimen was not a predictor of SVR. Despite wide-ranging SVR rates among the different racial and ethnic groups, white and Hispanic patients had similar SVR rates. In all groups, treatment response was largely determined by antiviral activity in the first 12 weeks of treatment. Therefore, decisions regarding HCV treatment should consider the predictive value of the early on-treatment response, not just baseline characteristics, such as race and ethnicity.

**Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6.** Lam KD, Trinh HN, Do ST, et al. *Hepatology*. 2010 Nov;52(5):1573-80.

<http://www.ncbi.nlm.nih.gov/pubmed/21038410>

Hepatitis C virus (HCV) genotype is an important criteria in determining duration of therapy and predictor of sustained virologic response (SVR) to pegylated interferon (PEG IFN) and ribavirin (RBV) therapy. Optimal duration of therapy for patients with HCV genotype 6 is not known. We conducted a multicenter, open-label randomized controlled trial of patients with HCV genotype 6 at five gastroenterology clinics in the western U.S. Patients were stratified by viral load and histologic stage and assigned to receive PEG IFN- $\alpha$ 2a 180  $\mu$ g subcutaneously weekly and weight-based oral RBV 800 to 1,200 mg daily for 24 or 48 weeks. Primary outcome measurement was SVR rate by intention-to-treat analysis. From February 2005 to October 2007 a total of 60 patients (age  $51 \pm 10$  years, 47% male, log HCVRNA  $6.3 \pm 1.1$  IU/mL) were enrolled: 27 patients to 24 weeks and 33 patients to 48 weeks of therapy. In the 24-week and 48-week groups, 96% and 97% achieved early virologic response ( $P = 0.90$ ); 89% versus 94% achieved end of therapy virologic response ( $P = 0.48$ ). SVR was achieved in 70% versus 79% of patients assigned to 24 weeks versus 48 weeks ( $P = 0.45$ ). Rapid virologic response (RVR) was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 82% and 83% of those with RVR achieved SVR versus 33% and 29% for the 24-week and 48-week groups, respectively ( $P = 0.07$  and  $P = 0.02$ ). **CONCLUSION:** There was no significant difference in SVR rates in patients with HCV genotype 6 treated with PEG IFN- $\alpha$ 2a and RBV for 24 versus 48 weeks.

**Frequent multiple hepatitis C virus infections among injection drug users in a prison setting.** Pham ST, Bull RA, Bennett JM, et al. *Hepatology*. 2010 Nov;52(5):1564-72.

<http://www.ncbi.nlm.nih.gov/pubmed/21038409>

Recent data indicate that multiple hepatitis C virus (HCV) infections (mixed infection, superinfection, and reinfection) are common among injection drug users (IDUs). **In this study**, we identified and characterized multiple HCV infection episodes among HCV-seronegative IDU prison inmates ( $n = 488$ ) enrolled in the Hepatitis C Incidence and Transmission Study cohort. Incident HCV infection with detectable HCV RNA was identified in 87 subjects, 48 of whom completed additional follow-up to screen for reinfection or superinfection. All HCV RNA-detectable samples were tested for multiple infection through a series of specifically designed nested reverse-transcription polymerase chain reaction (nRT-PCR) with sequencing and HCV RNA level measurement. Sequencing revealed that 22 of 87 (25.3%) subjects were infected by two or more viruses. Nine (10.3%) subjects were designated as prevalent cases of incident mixed infection, because two distinct HCV strains were detected at the first viremic time point. Fifteen further cases of multiple HCV infection (superinfection or reinfection) were identified, two of which also showed baseline incident mixed infections. The incidence of new HCV infection (superinfection and reinfection) during follow-up was 40/100 person-years (95% confidence interval, 33-44/100 person-years). Spontaneous clearance of viruses from one subtype and persistence of the other subtype after

mixed infection was observed in eight subjects. In these subjects, the virus with higher HCV RNA levels superseded the other. **CONCLUSION:** This study comprehensively analyzed frequent multiple HCV infections in a high-risk cohort and provides further insight into infection dynamics and immunity after exposure to variant viral strains. The data presented suggest that HCV RNA levels play an important role in viral competition.

**Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project.** Lindenburg CE, Lambers FA, Urbanus AT, et al. Eur J Gastroenterol Hepatol. 2010 Oct 29. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21042221>

**BACKGROUND:** Although hepatitis C virus (HCV) treatment has shown to be effective, uptake of treatment among active drug users is still low. The Drug Users Treatment for Chronic Hepatitis-C project aims to offer active drug users in Amsterdam HCV testing and treatment using a multidisciplinary approach. **METHODS:** The study population comprises drug users participating in the Amsterdam Cohort Studies and drug users referred to the Drug Users Treatment for Chronic Hepatitis-C unit. Drug users were offered HCV testing and, if chronically infected, medical and psychiatric screening and HCV treatment. Various specialists collaborated to provide optimal care. We assessed test-uptake and treatment-uptake and outcomes. **RESULTS:** Four hundred and ninety-seven Amsterdam Cohort Studies drug users were offered HCV testing: 449 out of 497 (90%) accepted. HCV antibodies were found in 267 out of 449 (60%); 183 out of 267 (69%) were HCV-viremic and 49 out of 183 (27%) were HIV-co-infected. Of the 134 HCV-monoinfected patients, 102 (76%) initiated additional medical screening and 44 started treatment by 1 July 2009. Sixty-two drug users referred from methadone clinics were also HCV-monoinfected, of whom 14 started treatment by 1 July 2009. In total 58 persons were treated: 16 (27%) with genotype 1 or 4, 42 (72%) with genotype 2 or 3. Eighty-four percent used methadone, 97% used drugs (heroin, cocaine or amphetamine) at least once in the 6 months before treatment, 19% were active injectors. Sixty-two percent used alcohol, 41% had psychiatric disease other than substance abuse. Of the 57 individuals with sufficient follow-up, 37 (65%) achieved sustained virological response. **CONCLUSION:** In a multidisciplinary setting, HIV-negative drug users with chronic HCV infection can be treated successfully despite active drug or alcohol use and psychiatric diseases. Therefore, access to HCV therapy using an integrated approach should be increased for this population.

**Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response.** Buti M, Lurie Y, Zakharova NG, et al. Hepatology. 2010 Oct;52(4):1201-7.

<http://www.ncbi.nlm.nih.gov/pubmed/20683847>

The benefit of extending treatment duration with peginterferon (PEG-IFN) and ribavirin (RBV) from 48 weeks to 72 weeks for patients with chronic hepatitis C genotype 1 infection has not been well established. In this prospective, international, open-label, randomized, multicenter study, 1,428 treatment-naïve patients from 133 centers were treated with PEG-IFN alfa-2b (1.5 µg/kg/week) plus RBV (800-1,400 mg/day). Patients with detectable hepatitis C virus (HCV) RNA and a  $\geq 2$ -log(10) drop in HCV RNA levels at week 12 (slow responders) were randomized 1:1 to receive 48 weeks (n = 86) or 72 weeks (n = 73) of treatment. Sustained virologic response (SVR) rates were 43% in slow responders treated for 48 weeks and 48% in slow responders treated for 72 weeks (P = 0.644). Relapse rates were similar in slow responders treated for 48 or 72 weeks (47% versus 33%, P = 0.169). The safety profile was similar in both treatment arms; serious adverse events leading to discontinuation of treatment were observed in 3.5% of slow responders treated for 48 weeks and 8.2% of those treated for 72 weeks. Among slow responders with a  $< 2$ -log drop in HCV RNA at week 8, SVR was 39% in the 72-week arm and 19% in the 48-week arm. **CONCLUSION:** These

data suggest that 48 weeks of therapy with PEG-IFN alfa-2b plus RBV (800-1,400 mg/day) should remain a standard-of-care treatment for treatment-naïve G1 slow responders.

**Systemic vasculitis in patients with hepatitis C virus infection with and without detectable mixed cryoglobulinemia.** Terrier B, Sène D, Dechartres A, et al. *J Rheumatol.* 2010 Oct 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20952479>

**OBJECTIVE:** To describe hepatitis C virus (HCV)-related systemic vasculitis in patients without detectable mixed cryoglobulinemia (MC) and to compare them to typical cases of HCV-MC vasculitis. **METHODS:** Twelve HCV RNA+ patients with histologically proven vasculitis in the absence of detectable MC (cases) were retrospectively compared with 48 HCV RNA+ patients with MC vasculitis (controls). Each case was matched with 4 controls for age and sex.

**RESULTS:** The main epidemiological and virologic features were similar between cases and controls. No clinical difference was found, except for lower rates of arthralgias (33% vs 71%;  $p = 0.02$ ) and purpura (50% vs 83%;  $p = 0.03$ ) in cases. Cases showed higher mean serum C3 ( $1.17 \pm 0.21$  vs  $0.93 \pm 0.23$  g/l;  $p = 0.01$ ) and median C4 levels (0.25 vs 0.04 g/l;  $p < 0.001$ ), lower median serum IgM levels (0.6 vs 1.9 g/l;  $p < 0.001$ ), and lower rates of rheumatoid factor positivity (8% vs 82%;  $p < 0.001$ ) than controls. The main histologic features were similar between cases and controls. Immunofluorescence analysis of skin biopsy from 1 case revealed perivascular deposits of C3 and IgA. After treatment, overall clinical response of vasculitis (75% vs 83%) and sustained virological response (40% vs 64%;  $p = 0.3$ ) were similar between cases and controls, except for higher complete clinical response (42% vs 73%;  $p = 0.05$ ) in controls. **CONCLUSION:** HCV-related systemic vasculitis may occur in the absence of detectable MC. Our findings suggest that such vasculitis probably results from immune complex-mediated mechanisms, and that the therapeutic management of such vasculitis should be similar to that of HCV-MC vasculitis.

**Sporadic reappearance of minute amounts of HCV RNA after successful therapy stimulates cellular immune responses.** Veerapu NS, Raghuraman S, Liang TJ, Heller T, Rehermann B.

*Gastroenterology.* 2010 Oct 29. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21040725>

**BACKGROUND & AIMS:** Several studies have reported persistence of hepatitis C virus (HCV) RNA in the circulation after treatment-induced or spontaneous recovery. We investigated whether the HCV RNA represents persistence of HCV infection or re-infection. **METHODS:** We studied 117 patients that recovered from HCV infection (98 following therapy and 19 spontaneously). A reverse transcriptase (RT)-PCR assay was used to detect the 5'UTR of HCV RNA. T-cell responses were studied by ELISpot analysis of interferon- $\gamma$ . **RESULTS:** Plasma samples from 15% of patients who recovered following treatment and none who recovered spontaneously tested positive for HCV RNA. Lymphocytes from 3 patients that responded to therapy and 1 that recovered spontaneously tested positive. The frequency of HCV RNA detection in plasma correlated inversely with the time after the end of treatment. Post-treatment HCV 5'-UTR sequences matched pre-treatment sequences in 85% of cases. T-cell responses were significantly greater at timepoints with detectable trace amounts of HCV RNA than at timepoints without detectable HCV RNA ( $P=0.035$ ) and were primarily against nonstructural HCV antigens. The immune hierarchy was preserved over 5 years in patients; post-treatment HCV RNA sequences matched pretreatment sequences, indicating HCV RNA persistence. An altered immune hierarchy with dominant immune responses, shifting from nonstructural to structural antigens, was observed in a single patient. The genotype of the detected post-treatment HCV RNA differed from that of the pretreatment genotype in this patient, indicating re-infection with HCV. **CONCLUSIONS:** Trace amounts of HCV RNA of pretreatment sequence persisted and re-appeared sporadically in the circulation within 8 years after recovery from hepatitis

C but not thereafter, indicating that patients are cured of HCV infection. Reappearance of HCV RNA induced HCV-specific T-c.

**Cervicovaginal shedding of hepatitis C viral RNA is associated with the presence of menstrual or other blood in cervicovaginal fluids.** Wang CC, Cook L, Tapia KA, et al. *J Clin Virol.* 2010 Oct 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20951635>

**BACKGROUND:** The role of sexual activity in hepatitis C virus (HCV) transmission remains controversial. Studies to date have not explored the relationship between HCV shedding in cervicovaginal fluids and the presence of menstrual or other blood. **OBJECTIVES:** Since cross-sectional studies may underestimate the prevalence of viral shedding, we performed a 56-day longitudinal study of cervical HCV shedding. **STUDY DESIGN:** Women self-collected cervicovaginal swabs for 56 consecutive days, while keeping a diary of menses and genital symptoms. Swabs were tested for HCV RNA and cellular DNA by quantitative PCR, and hemoglobin by spectrophotometry. **RESULTS:** Sixteen women contributed a total of 701 cervicovaginal swabs (mean collection period 48 days, range 18-56). Detection of HCV RNA was associated with detection of hemoglobin. Premenopausal women were more likely than postmenopausal women to have HCV RNA detected in cervicovaginal fluids. For premenopausal women, detection of HCV RNA was more likely during menstruation (OR=56.4) or when hemoglobin was detected in cervicovaginal fluids, even if menstruation was not occurring (OR=35.4). No woman post-hysterectomy had HCV RNA detected in cervicovaginal fluids on any day, regardless of whether hemoglobin was detected. **CONCLUSIONS:** Our findings are consistent with a low likelihood of sexual transmission of HCV. The results suggest that shedding of HCV RNA in the female genital tract is associated with the presence of blood, and requires the presence of a cervix. Clinicians should consider advising premenopausal women who are concerned about transmitting infection that infectivity may increase during menstruation.

**Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): A randomised, double-blind, placebo-controlled, dose-escalation trial.** Gane EJ, Roberts SK, Stedman CA, et al. *Lancet.* 2010 Oct 30;376(9751):1467-75. Epub 2010 Oct 14.

<http://www.ncbi.nlm.nih.gov/pubmed/20951424>

**BACKGROUND:** Present interferon-based standard of care treatment for chronic hepatitis C virus (HCV) infection is limited by both efficacy and tolerability. We assessed the safety, tolerability, and antiviral activity of an all-oral combination treatment with two experimental anti-HCV drugs—RG7128, a nucleoside polymerase inhibitor; and danoprevir, an NS3/4A protease inhibitor—in patients with chronic HCV infection. **METHODS:** Patients from six centres in New Zealand and Australia who were chronically infected with HCV genotype 1 received up to 13 days oral combination treatment with RG7128 (500 mg or 1000 mg twice daily) and danoprevir (100 mg or 200 mg every 8 h or 600 mg or 900 mg twice daily) or placebo. Eligible patients were sequentially enrolled into one of seven treatment cohorts and were randomly assigned by interactive voice or web response system to either active treatment or placebo. Patients were separately randomly assigned within each cohort with a block size that reflected the number of patients in the cohort and the ratio of treatment to placebo. The random allocation schedule was computer generated. Dose escalation was started in HCV treatment-naïve patients; standard of care treatment-experienced patients, including previous null responders, were enrolled in higher-dose danoprevir cohorts. Investigators, personnel at the study centre, and patients were masked to treatment allocation. However, the pharmacist who prepared the doses, personnel involved in pharmacokinetic sample analyses, statisticians who prepared data summaries, and the clinical pharmacologists who reviewed the data before deciding to initiate dosing in the next cohort were not masked to treatment

allocation. The primary outcome was change in HCV RNA concentration from baseline to day 14 in patients who received 13 days of combination treatment. All patients who completed treatment with the study drugs were included in the analyses. This study is registered with ClinicalTrials.gov, NCT00801255. **FINDINGS:** 88 patients were randomly assigned to a study drug treatment regimen (n=74 over seven treatment groups; 73 received at least one dose of study drug) or to placebo (n=14, all of whom received at least one dose). The median change in HCV RNA concentration from baseline to day 14 ranged from -3•7 to -5•2 log(10) IU/mL in the cohorts that received 13 days of combination treatment. At the highest combination doses tested (1000 mg RG7128 and 900 mg danoprevir twice daily), the median change in HCV RNA concentration from baseline to day 14 was -5•1 log(10) IU/mL (IQR -5•6 to -4•7) in treatment-naïve patients and -4•9 log(10) IU/mL in previous standard of care null responders (-5•2 to -4•5) compared with an increase of 0•1 log(10) IU/mL in the placebo group. The combination of RG7128 and danoprevir was well tolerated with no treatment-related serious or severe adverse events, no grade 3 or 4 changes in laboratory parameters, and no safety-related treatment discontinuations. **INTERPRETATION:** This oral combination of a nucleoside analogue polymerase inhibitor and protease inhibitor holds promise as an interferon-free treatment for chronic HCV.

**The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents chronic hepatitis C.** Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. . Gastroenterology. 2010 Oct 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21036173>

**BACKGROUND & AIMS:** Although randomized trials of adults infected with hepatitis C virus (HCV) have shown that ribavirin increases efficacy of pegylated interferon (PEG), such trials have not been performed in children. We conducted a randomized, controlled trial of PEG and ribavirin, compared with PEG and placebo, in children 5-17 years old with chronic hepatitis C.

**METHODS:** HCV RNA-positive children from 11 university medical centers were randomly groups assigned to receive either the combination of peginterferon alfa-2a (PEG 2a; 180 µg/1.73 m<sup>2</sup> body surface area, subcutaneously each week; n=59) and ribavirin (15 mg per kilogram orally in 2 doses daily) or PEG2a and placebo for 48 weeks (n=55). The primary endpoint was sustained virologic response (SVR, lack of detectable HCV RNA at least 24 weeks after stopping therapy).

**RESULTS:** An SVR was achieved in 53% of children treated with PEG 2a and ribavirin, compared with 21% of children who received PEG 2a and placebo (P<0.001). Early virologic response (> 2 log(10) IU reduction in HCV RNA at 12 weeks) had a negative predictive value of only 0.89 in children with genotype 1, indicating that these children might benefit from 24 weeks of therapy before stopping treatment. Side effects, especially neutropenia, led to dose modification in 40% of children. Eighty-two percent of the PEG/ribavirin and 86% of the PEG/placebo group were in compliance with the year-2 follow-up visit; the durability of virologic response was 100% in both groups. **CONCLUSIONS:** The combination of PEG and ribavirin is superior to PEG and placebo as therapy for chronic hepatitis C in children and adolescents. All studies published in Gastroenterology are embargoed until 3PM ET of the day they are published as corrected proofs on-line. Studies cannot be publicized as accepted manuscripts or uncorrected proofs.

**Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or 2b to patients with chronic hepatitis C.** Marcellin P, Fornis X, Goeser T, et al. Gastro-enterology. 2010 Oct 26. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21034744>

**BACKGROUND & AIMS:** Recent studies demonstrated that 12 weeks of telaprevir, administered every 8 hours (q8h), combined with peginterferon alfa-2a plus ribavirin (peginterferon alfa-2a/ribavirin), significantly increased the rate of hepatitis C virus (HCV) eradication (sustained virologic response [SVR]) in patients infected with HCV genotype-1 compared with approved

therapy. We investigated the efficacy, safety, tolerability, and pharmacokinetics of telaprevir given q8h or every 12 hours (q12h), in combination with peginterferon alfa 2a or 2b. **METHODS:** Treatment-naïve patients (n=161) infected with HCV genotype-1 were randomly assigned to groups that were given open-label telaprevir (750 mg q8h or 1125 mg q12h), in combination with standard doses of peginterferon alfa-2a (180 µg/week) and ribavirin (1000-1200 mg/day) or peginterferon alfa-2b (1.5 µg/kg/week) and ribavirin (800-1200 mg/day). Patients received triple therapy for 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa and ribavirin, based on virologic response. **RESULTS:** Baseline characteristics were similar for all groups. SVR rates were 81.0%-85.0% among groups; most patients received 24 weeks of therapy (68.0%). There were no significant differences in SVR rates (intent-to-treat analysis) among groups ( $P \geq 0.787$ ), between the pooled q8h and q12h groups ( $P = 0.997$ ), or between the pooled peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin groups ( $P = 0.906$ ). The safety profile was similar among all groups. **CONCLUSIONS:** A high proportion (>80%) of patients achieved a SVR regardless of the telaprevir dosing frequency (q8h or q12h) or type of peginterferon alfa used (alfa-2a or alfa-2b). All studies published in Gastroenterology are embargoed until 3PM ET of the day they are published as corrected proofs on-line. Studies cannot be publicized as accepted manuscripts or uncorrected proofs.

### **Prophylactic treatment with escitalopram of pegylated interferon alfa-2a-induced depression in hepatitis c: a 12-week, randomized, double-blind, placebo-controlled trial.**

Diez-Quevedo C, Masnou H, Planas R, et al. J Clin Psychiatry. 2010 Oct 5. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21034680>

**BACKGROUND:** Depression is one of the main reasons for treatment withdrawal and failure in chronic hepatitis C patients treated with interferon. Antidepressants are useful for its treatment, but whether they can also be used for prevention has yet to be established. **METHOD:** To evaluate the efficacy and safety of escitalopram for preventing interferon alfa-2a-induced depression, we conducted an investigator-initiated multicenter, randomized, double-blind, placebo-controlled trial in 133 chronic hepatitis C patients without baseline mental disorders who were randomly assigned to receive escitalopram or placebo during the first 12 weeks of treatment. Primary efficacy outcomes were the development of DSM-IV major depression and scores on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hospital Anxiety and Depression Scale (HADS). Primary safety end points were biochemical and virological responses. Patients were recruited between March 2005 and July 2006. **RESULTS:** Rates of major depression were low (5.4%) and did not differ between placebo (3.2%) and escitalopram (7.6%). MADRS and HADS scores significantly increased during treatment ( $P < .001$  and  $P = .028$ , respectively), but there were no differences between treatment groups. Sustained virological response was achieved by 69.2% of patients, 70.4% in the placebo group and 67.9% in the escitalopram group. **CONCLUSIONS:** Findings do not support the use of an antidepressant to prevent interferon-induced depression during the first 12 weeks of treatment in chronic hepatitis C patients at low psychiatric risk. Future studies should be directed to subpopulations of patients at high psychiatric risk.

### **A multidisciplinary therapeutic approach for reducing the risk of psychiatric side effects in patients with chronic hepatitis C treated with pegylated interferon $\alpha$ and ribavirin.**

Neri S, Bertino G, Petralia A, et al. J Clin Gastroenterol. 2010 Oct;44(9):e210-7. <http://www.ncbi.nlm.nih.gov/pubmed/20838237>

**GOALS:** To evaluate the effectiveness of psychiatric counseling in reducing the rate of development of psychiatric side effects of antiviral therapy with interferon- $\alpha$  and ribavirin among study participants compared with standard clinical monitoring alone. **BACKGROUND:** Interferon- $\alpha$  is used to treat chronic hepatitis C. Interferons may induce adverse events that usually, but not always, reverse within a few days after the end of therapy. **STUDY:** Two hundred eleven patients with

chronic hepatitis C, genotype 1b were treated with peginterferon and ribavirin for 48 weeks in a prospective trial. Two groups were randomly created. Group A was interviewed by a team of gastroenterologists, psychiatrists, and psychologists and treated with psychotherapy once a month. Group B was monitored once a month according to a conventional protocol that did not include psychotherapy. SVR (sustained viral response), severe psychiatric symptom onset, and mood progression were assessed (P calculated using Fisher exact test, Friedman test, Dunn posttest, and Mann-Whitney U-test). **RESULTS:** At baseline, there was no difference in depressive symptoms or liver histologic score between the 2 groups. The onset rate of severe psychiatric manifestations was 4.7% (Group A) and 16.1% (Group B) between the 24th and 36th weeks ( $P < 0.01$ ). Fifteen participants in Group A and 39 in Group B required antidepressants and benzodiazepines ( $P < 0.05$ ). **CONCLUSIONS:** Patients can develop depressive symptoms during interferon therapy. Multidisciplinary medical treatment with psychiatric counseling provided during the treatment of chronic hepatitis C may contribute to the decrease or prevent the higher rates of depression associated with interferon treatment.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**Survival of hepatitis C virus in syringes: implication for transmission among injection drug users.** Paintsil E, He H, Peters C, Lindenbach BD, Heimer R. *J Infect Dis.* 2010 Oct 1;202(7):984-90.

<http://www.ncbi.nlm.nih.gov/pubmed/20726768>

**BACKGROUND:** We hypothesized that the high prevalence of hepatitis C virus (HCV) among injection drug users might be due to prolonged virus survival in contaminated syringes.

**METHODS:** We developed a microculture assay to examine the viability of HCV. Syringes were loaded with blood spiked with HCV reporter virus (Jc1/GLuc2A) to simulate 2 scenarios of residual volumes: low void volume (2 microL) for 1-mL insulin syringes and high void volume (32 microL) for 1-mL tuberculin syringes. Syringes were stored at 4 degrees C, 22 degrees C, and 37 degrees C for up to 63 days before testing for HCV infectivity by using luciferase activity. **RESULTS:** The virus decay rate was biphasic ( $t_{1/2\alpha} = 0.4$  h and  $t_{1/2\beta} = 28$  hh). Insulin syringes failed to yield viable HCV beyond day 1 at all storage temperatures except 4 degrees, in which 5% of syringes yielded viable virus on day 7. Tuberculin syringes yielded viable virus from 96%, 71%, and 52% of syringes after storage at 4 degrees, 22 degrees, and 37 degrees for 7 days, respectively, and yielded viable virus up to day 63. **CONCLUSIONS:** The high prevalence of HCV among injection drug users may be partly due to the resilience of the virus and the syringe type. Our findings may be used to guide prevention strategies.

**Hepatitis C virus-specific CD8+ T cell frequencies are associated with the responses of pegylated interferon- $\alpha$  and ribavirin combination therapy in patients with chronic hepatitis C virus infection.** Tatsumi T, Takehara T, Miyagi T, et al. *Hepatology Res.* 2010 Oct 7. doi: 10.1111/j.1872-034X.2010.00734.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21040277>

**AIM:** Hepatitis C virus (HCV)-specific cytotoxic T lymphocytes (CTLs) play critical roles in elimination of the HCV-infected hepatocytes. However, the mechanism of HCV elimination by pegylated interferon- $\alpha$  (peg-IFN $\alpha$ ) plus ribavirin is not fully understood. We examined HCV-specific CTL responses during this combination therapy. **METHODS:** CD8+ T cells were isolated from 16 HCV infected patients treated by this combination therapy and were subjected to IFN- $\gamma$  enzyme-linked immunospot (ELISPOT) assay. **RESULTS:** The numbers of IFN- $\gamma$  spots against HCV Core or NS3 protein-derived peptides in HCV patients before treatment were similar to those in healthy donors, and those in HCV patients significantly increased 4 weeks after the initiation of combination therapy. All HCV Core or NS3 proteins-derived peptides specific CD8+ T cells

responses in pre-treated patients were not associated with ALT levels and HCV viral loads of HCV patients before treatment. And those in pre-treated patients were similar between sustained virologic responder (SVR) patients and non-SVR patients. Significant increase of HCV Core or NS3 proteins-derived peptides specific CD8+ T cells responses between before and 4 weeks after this combination therapy were observed in SVR patients, but not in non-SVR patients. Conclusions: These results demonstrated that significant increase of HCV-specific CD8+ T cells at 4 weeks after the initiation of IFN treatment might be associated with the elimination of HCV. **Our findings suggest** that the reactivity against HCV Core and NS3 proteins-derived peptides might be useful in predicting the clinical outcome of the combination therapy of peg-IFN $\alpha$  and ribavirin.

**Early viral and peripheral blood mononuclear cell responses to pegylated interferon and ribavirin treatment: the first 24 h.** Devitt E, Lawless MW, Sadlier D, A Browne J, Walsh C, Crowe J. *Eur J Gastroenterol Hepatol.* 2010 Oct;22(10):1211-20.

<http://www.ncbi.nlm.nih.gov/pubmed/20631625>

**OBJECTIVES:** This study explored gene expression differences in predicting response to pegylated interferon (IFN-PEG) and ribavirin (RBV) in hepatitis C infection. Current treatment for hepatitis C virus (HCV) with IFN-PEG alpha-2a/b and RBV is an expensive regimen with frequent significant side-effects where less than 60% of patients ultimately achieve a sustained virological response. Responders and nonresponders may not be identified for up to 6 months post-treatment. This dichotomy may be because of differences in the molecular genetic response.

**METHODS:** Peripheral blood mononuclear cell samples were obtained from a cohort of 31 infected individuals within the first 24 h of treatment and the extracted RNA was hybridized to genome expression microarrays. Hepatitis C viral kinetics was also examined in these patients. The ability of differentially regulated genes to predict response to therapy was assessed with treatment outcome. **RESULTS:** Distinct patterns of gene expression distinguished responders from nonresponders to HCV treatment. The ultimate response to treatment with IFN-PEG and RBV was observed within the first 24 h of treatment by a greater drop in viral load (mean HCV RNA decline of  $1.92 \pm 1.26 \log_{10}$  IU/ml) in responders compared with nonresponders ( $P < 0.007$ ). Induced genes achieved maximal response within 12 h of therapy which coincided with a rapid decline in HCV RNA between 12 and 24 h. This study revealed that peripheral blood mononuclear cell metallothionein 2A, CCRL2, tumour necrosis factor-alpha-induced protein 6 (TNFAIP6) and IFN-induced protein with tetratricopeptide repeats 2 expression predicted viral treatment response to therapy verified by quantitative real time polymerase chain reaction. **CONCLUSION:** This study has identified a noninvasive gene microarray pattern and a set of verified genes to be predictive of hepatitis C patient response to IFN-PEG and RBV treatment within the first 24 h. The potential of this noninvasive diagnostic approach and identified genes as biomarkers of response to treatment warrants further investigation.

**Increased natural killer cell cytotoxicity and NKp30 expression protects against hepatitis C virus infection in high-risk individuals and inhibits replication in vitro.** Golden-Mason L, Cox AL, Randall JA, Cheng L, Rosen HR. *Hepatology.* 2010 Nov;52(5):1581-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20812318>

CD56(pos) natural killer (NK)/natural T (NT) cells are important innate effectors providing the first line of defense against viral infection. Enhanced NK activity has been shown to protect from human immunodeficiency virus-1 infection. However, the role played by these innate effectors in protection against or development of hepatitis C virus (HCV) infection is unknown. We characterized CD56(pos) populations in 11 injection drug users (IDUs) who remained uninfected despite being repeatedly exposed to HCV. NK profiles in exposed but uninfected (EU) individuals were compared with preinfection samples (median 90 days prior to HCV seroconversion) collected from 14 IDUs who were exposed and subsequently became infected (EI) and unexposed normal control subjects

(n = 8). Flow cytometric analysis of CD56(pos) populations demonstrated that EUs had a higher proportion of CD56(low) mature (P = 0.0011) NK cells compared with EI subjects. Bead-isolated NKs (> 90% purity) from EUs had significantly higher interleukin-2 (IL-2)-induced cytolytic activity against the NK-sensitive cell line K562 at an effector-to-target ratio of 10:1 (P < 0.0001). NKp30, a natural cytotoxicity receptor involved in NK activation, is highest on NK/NT cells in EUs relative to infected subjects. Using the JFH-1 infection system, we demonstrated that NKp30(high) cells in the absence of exogenous stimulation significantly reduce infection of hepatocytes. **CONCLUSION:** CD56(pos) populations in EUs are enriched for effector NKs displaying enhanced IL-2-induced cytolytic activity and higher levels of the natural cytotoxicity receptor NKp30-activating receptor. In addition, NKp30(high) cells are more effective in preventing infection of Huh-7.5 cells than their NKp30(low/neg) counterparts. **These data support the hypothesis** that NK cells contribute to anti-HCV defense in vivo in the earliest stages of infection, providing innate protection from HCV acquisition.

**DEB025 (Alisporivir) inhibits hepatitis C virus replication by preventing a cyclophilin a induced cis-trans isomerisation in domain II of NS5A.** Coelmont L, Hanouille X, Chatterji U, et al. PLoS One. 2010 Oct 27;5(10):e13687.

<http://www.ncbi.nlm.nih.gov/pubmed/21060866>

DEB025/Debio 025 (Alisporivir) is a cyclophilin (Cyp)-binding molecule with potent anti-hepatitis C virus (HCV) activity both in vitro and in vivo. It is currently being evaluated in phase II clinical trials. DEB025 binds to CypA, a peptidyl-prolyl cis-trans isomerase which is a crucial cofactor for HCV replication. Here we report that it was very difficult to select resistant replicons (genotype 1b) to DEB025, requiring an average of 20 weeks (four independent experiments), compared to the typically <2 weeks with protease or polymerase inhibitors. This indicates a high genetic barrier to resistance for DEB025. Mutation D320E in NS5A was the only mutation consistently selected in the replicon genome. This mutation alone conferred a low-level (3.9-fold) resistance. Replacing the NS5A gene (but not the NS5B gene) from the wild type (WT) genome with the corresponding sequence from the DEB025(res) replicon resulted in transfer of resistance. Cross-resistance with cyclosporine A (CsA) was observed, whereas NS3 protease and NS5B polymerase inhibitors retained WT-activity against DEB025(res) replicons. Unlike WT, DEB025(res) replicon replicated efficiently in CypA knock down cells. However, DEB025 disrupted the interaction between CypA and NS5A regardless of whether the NS5A protein was derived from WT or DEB025(res) replicon. NMR titration experiments with peptides derived from the WT or the DEB025(res) domain II of NS5A corroborated this observation in a quantitative manner. Interestingly, comparative NMR studies on two 20-mer NS5A peptides that contain D320 or E320 revealed a shift in population between the major and minor conformers. These data suggest that D320E conferred low-level resistance to DEB025 probably by reducing the need for CypA-dependent isomerisation of NS5A. Prolonged DEB025 treatment and multiple genotypic changes may be necessary to generate significant resistance to DEB025, underlying the high barrier to resistance.

**CX3CL1-CX3CR1 interaction prevents carbon tetrachloride-induced liver inflammation and fibrosis in mice.** Aoyama T, Inokuchi S, Brenner DA, Seki E. Hepatology. 2010 Oct;52(4):1390-400.

<http://www.ncbi.nlm.nih.gov/pubmed/20683935>

Chronic liver disease is associated with hepatocyte injury, inflammation, and fibrosis. Chemokines and chemokine receptors are key factors for the migration of inflammatory cells such as macrophages and noninflammatory cells such as hepatic stellate cells (HSCs). The expression of CX3CR1 and its ligand, CX3CL1, is up-regulated in chronic liver diseases such as chronic hepatitis C. However, the precise role of CX3CR1 in the liver is still unclear. Here we investigated the role of the CX3CL1-CX3CR1 interaction in a carbon tetrachloride (CCl<sub>4</sub>)-induced liver inflammation and

fibrosis model. CX3CR1 was dominantly expressed in Kupffer cells in the liver. In contrast, the main source of CX3CL1 was HSCs. Mice deficient in CX3CR1 showed significant increases in inflammatory cell recruitment and cytokine production [including tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ); monocyte chemoattractant protein 1; macrophage inflammatory protein 1 $\beta$ ; and regulated upon activation, normal T cell expressed, and secreted (RANTES)] after CCl(4) treatment versus wild-type (WT) mice. This suggested that CX3CR1 signaling prevented liver inflammation. Kupffer cells in CX3CR1-deficient mice after CCl(4) treatment showed increased expression of TNF- $\alpha$  and transforming growth factor  $\beta$  and reduced expression of the anti-inflammatory markers interleukin-10 (IL-10) and arginase-1. Coculture experiments showed that HSCs experienced significantly greater activation by Kupffer cells from CCl(4)-treated CX3CR1-deficient mice versus WT mice. Indeed, augmented fibrosis was observed in CX3CR1-deficient mice versus WT mice after CCl(4) treatment. Finally, CX3CL1 treatment induced the expression of IL-10 and arginase-1 in WT cultured Kupffer cells through CX3CR1, which in turn suppressed HSC activation.

CONCLUSION: The CX3CL1-CX3CR1 interaction inhibits inflammatory properties in Kupffer cells/macrophages and results in decreased liver inflammation and fibrosis.

**Conformational anti-cytochrome P4502E1 (CYP2E1) auto-antibodies contribute to necro-inflammatory injury in chronic hepatitis C.** Sutti S, Vidali M, Mombello C, Sartori M, Albano E. *J Viral Hepat.* 2010 Oct;17(10):685-90. doi: 10.1111/j.1365-2893.2010.01359.x.  
<http://www.ncbi.nlm.nih.gov/pubmed/20738774>

Circulating auto-antibodies against cytochrome P4502E1 (CYP2E1) have been observed in a significant fraction of patients with chronic hepatitis C (CHC). This study investigated the clinical significance of these auto-antibodies in relation to their antigen specificity. The presence of anti-CYP2E1 IgG was investigated in 137 consecutive patients with biopsy-proven CHC. Anti-CYP2E1 IgG above control threshold levels was detected in 52 (38%) subjects. By combined immunoprecipitation and western blotting, we observed that among anti-CYP2E1 IgG-positive sera, 23 (44%) were unreactive towards denaturated CYP2E1, indicating a prevalent recognition of conformational CYP2E1 antigens. Conformational anti-CYP2E1 auto-antibodies were unrelated to circulating gamma-globulins, alcohol intake or infection by specific HCV genotypes. The presence of anti-CYP2E1 auto-antibodies was associated with an 11-fold (OR 10.9 95%CI 1.4-86.6 P = 0.008) increased prevalence of necro-inflammatory grading  $\geq 4$  (Ishack's criteria) and 4-fold (OR 4.0; 95%CI 1.3-11.7: P = 0.014) increased prevalence of fibrosis staging  $\geq 2$ , respectively. Multivariate analysis confirmed conformational anti-CYP2E1 IgG (P = 0.005) and age (P = 0.033) as independent predictors of necro-inflammatory grading  $\geq 4$ . The development of anti-CYP2E1 auto-antibodies targeting conformational CYP2E1 epitopes is associated with more severe liver damage in CHC.

**A new natural  $\alpha$ -helical peptide from the venom of the scorpion *Heterometrus petersii* kills HCV.** Yan R, Zhao Z, He Y, et al. *Peptides.* 2010 Oct 13. [Epub ahead of print]  
<http://www.ncbi.nlm.nih.gov/pubmed/20950663>

Hepatitis C virus (HCV) is a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. There is no vaccine available for HCV, and almost half of patients cannot be cured using standard combination therapy. Thus, new anti-HCV strategies and drugs are urgently needed. Here, the gene encoding a new  $\alpha$ -helical peptide, Hp1090, was screened from the venomous gland cDNA library of the scorpion *Heterometrus petersii*. Structural analysis showed that Hp1090 is an amphipathic  $\alpha$ -helical peptide. In vitro HCV RNA inhibitory assays indicated that Hp1090 peptide inhibited HCV infection with an IC(50) of 7.62 $\mu$ g/ml (5.0 $\mu$ M), whereas Hp1035 peptide, showing high homology to Hp1090, exhibited no anti-HCV activity. Hp1090 acted as a viricide against HCV particles in vitro and prevented the initiation of HCV infection. Furthermore, this peptide interacted with HCV particles directly and rapidly permeabilized phospholipid membranes. Collectively, it

seems that Hp1090 is virocidal for HCV in vitro, directly interacting with the viral membrane and decreasing the virus infectivity. These results suggest that Hp1090 could be considered an anti-HCV lead compound with virocidal mechanism that offers a potential therapeutic approach to HCV infection. Our work opens a new avenue for antiviral drug discovery in natural scorpion venom.

**Dynamic coinfection with multiple viral subtypes in acute hepatitis C.** Smith JA, Aberle JH, Fleming VM, et al.

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

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

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## HIV/HCV COINFECTION

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**Modeling the probability of sustained virological response to Therapy with pegylated interferon plus ribavirin in patients coinfecting with hepatitis C virus and HIV.** Medrano J, Neukam K, Rallón N, et al. Clin Infect Dis. 2010 Nov 15;51(10):1209-16.

<http://www.ncbi.nlm.nih.gov/pubmed/20964522>

**BACKGROUND:** A single-nucleotide polymorphism (SNP) near the IL28B gene (rs12979860) strongly predicts sustained virological response to pegylated interferon plus ribavirin (pegIFN-RBV) treatment for chronic hepatitis C virus (HCV) infection. Given that therapy is poorly tolerated and rates of response are lower in patients coinfecting with HCV and human immunodeficiency virus (HIV), the recognition of predictors of response is a high priority in this population. **METHODS:** A baseline noninvasive index was derived on the basis of the probability of achieving sustained virological response in a group of 159 HIV-HCV-coinfecting patients treated at one clinic in Spain. The index was then validated using data from a separate cohort of 86 coinfecting individuals. Only individuals who had completed a course of pegIFN-RBV therapy and had validated outcomes were considered. **RESULTS:** The final score included 4 variables: 2 host-related variables (IL28B SNP rs12979860 and liver stiffness) and 2 HCV-related variables (genotype and viral load). The area under the receiver operating characteristic curve was 0.89 in the derivation group and 0.85 in the validation group. **CONCLUSIONS:** The probability of achieving sustained virological response with pegIFN-RBV therapy in HIV-HCV-coinfecting patients can be reliably estimated prior to initiation of therapy using an index that includes 4 noninvasive parameters.

**Polymorphism in tumor necrosis factor-related apoptosis-inducing ligand receptor 1 is associated with poor viral response to interferon-based hepatitis C virus therapy in HIV/hepatitis C virus-coinfecting individuals.** Rizza SA, Cummins NW, Rider DN, Saeed S, Klein MB, Badley AD. AIDS. 2010 Nov 13;24(17):2639-44.

<http://www.ncbi.nlm.nih.gov/pubmed/20802294>

**OBJECTIVE(S):** HIV/hepatitis C virus (HCV) coinfection causes accelerated liver disease compared to HCV monoinfection, and only 30-60% of HIV/HCV-coinfected individuals respond to HCV therapy with pegylated interferon and ribavirin. There are currently no biomarkers that predict treatment response in these coinfecting patients. **DESIGN:** We investigated whether there is an association between HCV treatment response and SNPs of apoptosis-related genes during HIV/HCV coinfection. **METHOD:** Genomic DNA from 53 HIV/HCV-coinfected individuals was analyzed for 82 SNPs of 10 apoptosis-related genes.

**RESULTS:** We found that the presence of the rs4242392 SNP in tumor necrosis factor receptor superfamily, member 10a (TNFRSF10A), which encodes for tumor necrosis factor-related apoptosis-inducing ligand receptor 1, predicts poor outcome to HCV therapy, in HIV/HCV-coinfected patients [odds ratio 5.91 (95% confidence interval 1.63-21.38, P = 0.007)].

**CONCLUSION:** The rs4242392 SNP of the tumor necrosis factor-related apoptosis-inducing ligand receptor 1 gene predicted poor interferon-based HCV treatment response in HIV/HCV-coinfected patients.

**Transient elastography: a non-invasive tool for assessing liver fibrosis in HIV/HCV patients.** Li Vecchi V, Soresi M, Colomba C, et al. World J Gastroenterol. 2010 Nov 7;16(41): 5225-32.

<http://www.ncbi.nlm.nih.gov/pubmed/21049556>

**AIM:** To assess the prevalence of advanced liver fibrosis (ALF) in human immunodeficiency virus (HIV), hepatitis C virus (HCV) and HIV/HCV patients using transient elastography, and to identify factors associated with ALF. **METHODS:** Between September 2008 and October 2009, 71 HIV mono-infected, 57 HIV/HCV co-infected and 53 HCV mono-infected patients on regular follow-up at our Center were enrolled in this study. Alcohol intake, the main parameters of liver function, presence of HCV-RNA, HIV-RNA, duration of highly active anti-retroviral therapy (HAART) and CD4 cell count were recorded. ALF was defined as liver stiffness (LS)  $\geq 9.5$  kPa. To estimate liver fibrosis (LF) a further 2 reliable biochemical scores, aspartate aminotransferase platelet ratio index (APRI) and FIB-4, were also used. **RESULTS:** LS values of co-infected patients were higher than in either HIV or HCV mono-infected patients ( $\chi^2$ (MH) = 4, P < 0.04). In fact, LS  $\geq 9.5$  was significantly higher in co-infected than in HIV and HCV mono-infected patients ( $\chi^2$  = 5, P < 0.03). Also APRI and the FIB-4 index showed more LF in co-infected than in HIV mono-infected patients (P < 0.0001), but not in HCV mono-infected patients. In HIV/HCV co-infected patients, the extent of LS was significantly associated with alcohol intake (P < 0.04) and lower CD4+ cell count (P < 0.02). In HCV patients, LS was correlated with alcohol intake (P < 0.001) and cholesterol levels (P < 0.03). Body mass index, diabetes, HCV- and HIV-viremia were not significantly correlated with LS. In addition, 20% of co-infected patients had virologically unsuccessful HAART; in 50% compliance was low, CD4+ levels were < 400 cells/mm<sup>3</sup> and LS was > 9.5 kPa. There was no significant correlation between extent of LF and HAART exposure or duration of HAART exposure, in particular with specific dideoxynucleoside analogues.

**CONCLUSION:** ALF was more frequent in co-infected than mono-infected patients. This result correlated with lower CD4 levels. Protective immunological effects of HAART on LF progression outweigh its hepatotoxic effects.

**The French national prospective cohort of patients co-infected with HIV and HCV (ANRS CO13 HEPAVIH): Early findings, 2006-2010.** Loko MA, Salmon D, Carrieri P, et al. BMC Infect Dis. 2010 Oct 22;10(1):303. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20969743>

**BACKGROUND:** In France, it is estimated that 24% of HIV-infected patients are also infected with HCV. Longitudinal studies addressing clinical and public health questions related to HIV-HCV co-infection (HIV-HCV clinical progression and its determinants including genetic dimension,

patients' experience with these two diseases and their treatments) are limited. The ANRS CO 13 HEPAVIH cohort was set up to explore these critical questions. Objectives: To describe the cohort aims and organization, monitoring and data collection procedures, baseline characteristics, as well as follow-up findings to date. **METHODS:** Inclusion criteria in the cohort were: age > 18 years, HIV-1 infection, chronic hepatitis C virus (HCV) infection or sustained response to HCV treatment. A standardized medical questionnaire collecting socio-demographic, clinical, biological, therapeutic, histological, ultrasound and endoscopic data is administered at enrolment, then every six months for cirrhotic patients or yearly for non-cirrhotic patients. Also, a self-administered questionnaire documenting socio-behavioral data and adherence to HIV and/or HCV treatments is administered at enrolment and yearly thereafter.

**RESULTS:** A total of 1,175 patients were included from January 2006 to December 2008. Their median age at enrolment was 45 years and 70.2% were male. The median CD4 cells count was 442 (IQR: 304-633) per microliter and HIV RNA plasma viral load was undetectable in 68.8%. Most participants (71.6 %) were on HAART. Among the 1,048 HIV-HCV chronically co-infected patients, HCV genotype 1 was predominant (56%) and cirrhosis was present in 25%. As of January, 2010, after a median follow-up of 16.7 months (IQR: 11.3-25.3), 13 new cases of decompensated cirrhosis, nine hepatocellular carcinomas and 20 HCV-related deaths were reported, resulting in a cumulative HCV-related severe event rate of 1.9/100 person-years (95% CI: 1.3-2.5). The rate of HCV-related severe events was higher in cirrhotic patients and those with a low CD4 cells count, but did not differ according to sex, age, alcohol consumption, CDC clinical stage or HCV status.

**CONCLUSION:** The ANRS CO 13 HEPAVIH is a nation-wide cohort using a large network of HIV treatment, infectious diseases and internal medicine clinics in France, and thus is highly representative of the French population living with these two viruses and in care.

**Immunological status does not influence hepatitis C virus or liver fibrosis in HIV-Hepatitis C virus-coinfected patients.** Collazos J, Cartón JA, Asensi V. *AIDS Res Hum Retroviruses*. 2010 Oct 26. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20977357>

The possible effects on liver fibrosis and HCV viral load of the immunological status of HIV-HCV-coinfected patients are unclear. A cohort of HIV-HCV-coinfected patients was divided according to the current CD4 counts into poor ( $\leq 200/\mu\text{l}$ ,  $n = 117$ ) or good ( $\geq 500/\mu\text{l}$ ,  $n = 441$ ) immunological status. The groups were compared for diverse HCV- and fibrosis-related parameters. Fibrosis was evaluated by transient elastometry and other noninvasive indexes. Many variables were significantly associated with the immunological status in univariate analyses, including fibrosis parameters. However, in multivariate analyses current immunological status or nadir CD4 were not associated with HCV viral load ( $p = 0.8$  and  $p = 0.3$ , respectively), liver fibrosis at the time of evaluation ( $p = 0.9$  for both), or fibrosis progression over time ( $p = 0.98$  and  $p = 0.8$ , respectively). The factors independently associated with significant fibrosis, advanced fibrosis, and cirrhosis, as compared with minimal or no fibrosis, were alcohol abuse [OR 3.57 (95% CI 1.43-8.85),  $p = 0.006$ ; OR 10.10 (3.75-27.03),  $p < 0.0001$ ; and OR 31.25 (10.6-90.90),  $p < 0.0001$ , respectively], HBsAg positivity [OR 9.09 (1.47-55.56),  $p = 0.02$ ; OR 55.56 (9.80-333.33),  $p < 0.0001$ ; and OR 43.48 (4.76-476.19),  $p = 0.0008$ , respectively], and platelet counts [OR 0.994 (0.989-0.998),  $p = 0.006$ ; OR 0.990 (0.985-0.995),  $p = 0.0003$ ; and OR 0.985 (0.979-0.991),  $p < 0.0001$ , respectively]. Immunological status did not associate with any fibrosis stage (significant fibrosis,  $p = 0.7$ ; advanced fibrosis,  $p = 0.4$ ; and cirrhosis  $p = 0.9$ ). The current or past immunological status of HIV-HCV-coinfected patients does not seem to have any significant influence on HCV viral load or on the development of liver fibrosis when adjusting for important covariates.

**Women experience higher rates of adverse events during hepatitis C virus therapy in HIV infection: a meta-analysis.** Bhattacharya D, Umbleja T, Carrat F, et al. *J Acquir Immune Defic Syndr.* 2010 Oct 1;55(2):170-5.

<http://www.ncbi.nlm.nih.gov/pubmed/20622678>

**BACKGROUND:** In HIV/ hepatitis C virus (HCV) coinfection, adverse events (AEs) during HCV therapy account for 12%-39% of treatment discontinuations. It is unknown whether sex influences complications. **METHODS:** Meta-analysis to study the effect of sex and other predictors of AEs in 3 randomized trials, ACTG 5071, APRICOT, and ANRSHCO2-RIBAVIC of Interferon (IFN) and Pegylated IFN (PEG), both with and without Ribavirin, in HIV/HCV coinfection. Primary endpoints were AEs requiring treatment discontinuation (AETD) or first dose modification (AEDM). Multi-covariate stratified logistic regression was used to study predictors and assess interactions with sex. **RESULTS:** Twenty-one percent of 1376 subjects were women; 61% had undetectable HIV RNA; 14% were antiretroviral (ARV) therapy naive at entry; median CD4 was 485 cells per cubicmillimeter. Seventeen percent had an AETD and 50% AEDM; women had more AETD than men (24% vs. 16%  $P = 0.003$ ) and AEDM (61% vs. 48%  $P < 0.0001$ ). AETD and AEDM occurred earlier in women; but the types of AETD and AEDM were similar between sexes. Seventy-four percent of AETDs and 49% of AEDMs involved constitutional AEs; 18% of AETD depression; and 26% of AEDM neutropenia. We identified interactions with sex and body mass index (BMI) ( $P = 0.04$ , continuous) and nonnucleoside reverse transcriptase inhibitor ( $P = 0.03$ ); more AETDs were seen in men with lower BMI ( $P = 0.01$ ) and in women on nonnucleoside reverse transcriptase inhibitors ( $P = 0.009$ ). More AEDMs were seen with PEG [odds ratio (OR) = 2.07]; older age (OR = 1.48 per 10 years); decreasing BMI (OR = 1.04 per kg/m); HCV genotype 1, 4 (OR = 1.31); Ishak 5, 6 (OR = 1.42); decreasing Hgb (OR = 1.23 per g/dL); and decreasing absolute neutrophil count (1.04 per 500 cells/mm). Interactions between sex and ARV-naive status ( $P = 0.001$ ) and zidovudine ( $P = 0.001$ ) were identified: There were more AEDMs in ARV-naive women ( $P = 0.06$ ) and ARV-experienced men ( $P = 0.001$ ) and higher AEDMs in women with zidovudine ( $P = 0.0002$ ). **CONCLUSIONS:** Although there was no difference in type of AE, AETD and AEDM were more frequent and occurred earlier in women. In women, ARV regimen may be an important predictor of AETDs during HCV therapy and should be explored as a predictor of AEs in HIV/HCV coinfection trials.

**Evaluation of the possible influence of hepatitis C virus and liver fibrosis on HIV type 1 immunological and virological outcomes.** Collazos J, Cartón J, Asensi V. *HIV Med.* 2010 Oct 14. doi: 10.1111/j.1468-1293.2010.00886.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20946441>

**OBJECTIVES:** The aim of the study was to evaluate the possible effect of hepatitis C virus (HCV) coinfection on the viroimmunological outcomes of HIV-1 infection. **METHODS:** A cross-sectional study of 805 patients with active HCV infection receiving or not receiving antiretroviral therapy (ART) was carried out. **RESULTS:** A number of parameters were significantly associated with undetectable HIV-1 viral load in univariate analyses, such as age, toxic habits, CD4 cell count, liver test results, HCV viral load and ART. However, only current ART ( $P < 0.0001$ ), CD4 cell count ( $P < 0.0001$ ), age ( $P = 0.004$ ) and current injecting drug use ( $P = 0.02$ ) were independently associated with undetectable viral load in multivariate analysis. None of the many HCV- and liver fibrosis-related parameters analysed showed a significant association with HIV-1 viral load or CD4 cell count in multivariate analyses, with the exception of the annual fibrosis progression index which almost reached statistical significance in the subgroup of ART-untreated patients ( $P = 0.06$ ) and was inversely predictive of CD4 cell count in the whole group ( $P = 0.007$ ). However, its relative weight was modest, as it only explained 0.8% of the total variability in CD4 cell count. **CONCLUSIONS:** HCV-related parameters did not significantly affect virological and immunological outcomes of HIV-1 infection in ART-treated and untreated patients. In contrast, liver fibrosis, as measured using

the annual fibrosis progression index, was inversely associated with CD4 cell count, although its weight was relatively small. Therefore, HCV- and liver fibrosis-related factors do not seem appreciably to influence these outcomes from a practical viewpoint in ART-naïve patients, nor impair CD4 and HIV-1 viral load responses to ART.

**Influence of a single nucleotide polymorphism at the main ribavirin transporter gene on the rapid virological response to pegylated interferon-ribavirin therapy in patients with chronic hepatitis C virus infection.** Morello J, Cuenca L, Soriano V, et al. *J Infect Dis.* 2010 Oct 15;202(8):1185-91.

<http://www.ncbi.nlm.nih.gov/pubmed/20812847>

The equilibrative nucleoside transporter 1 (ENT1) is the main protein involved in ribavirin cellular uptake. Polymorphisms at the ENT1 gene may influence ribavirin activity as part of hepatitis C virus (HCV) therapy. A retrospective study was conducted in 109 human immunodeficiency virus (HIV)-infected patients who were infected with HCV genotypes 1 or 4 who had received pegylated interferon (pegIFN)-ribavirin. Single nucleotide polymorphisms (SNPs) at the ENT1 gene were examined using TaqMan 5'-nuclease assays. In the study population, allelic frequencies at rs760370 were as follows: A3 (43 [39%] of 109 patients), AG (50 [46%] of 109 patients), and GG (16 [15%] of 109 patients). Achievement of rapid virological response was more frequent in GG carriers than in AA/AG carriers (50% vs 17%, respectively;  $P = .007$ ). In multivariate analysis, the GG genotype (odds ratio [OR], 15.9; 95% confidence interval [CI], 2.8-92.2;  $P < .002$ ), a baseline serum HCV-RNA level  $< 600,000$  IU/mL (OR, 45.7; 95% CI, 8.7-240.5;  $P < .001$ ) and a serum ribavirin trough concentration  $> 2.5$   $\mu\text{g/mL}$  (OR, 4.8; 95% CI, 1.3-17.1;  $P < .016$ ) were associated with rapid virological response. When 2 or more of these factors were present, positive and negative predictive values of rapid virological response were 65% and 91%, respectively. In summary, a SNP rs760370A $\rightarrow$ G at the ENT1 gene influences the chance of rapid virological response to pegIFN-ribavirin therapy in HIV-infected patients with chronic HCV infection due to HCV genotypes 1 or 4, most likely modulating intracellular ribavirin exposure within hepatocytes.

**Prevalence and factors associated with significant liver fibrosis assessed by transient elastometry in HIV/hepatitis C virus-coinfected patients.** Pineda JA, González J, Ortega E, et al. *J Viral Hepat.* 2010 Oct;17(10):714-9. doi: 10.1111/j.1365-2893.2009.01229.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20002560>

Transient elastometry (TE) could provide a more accurate evaluation of the frequency and risk factors of liver fibrosis in hepatitis C virus (HCV) infection than that based on biopsy. The aim of this study was to assess the prevalence of and factors associated with significant liver fibrosis in a large population of HIV/HCV-coinfected patients. HIV/HCV-coinfected patients, who had participated in a cross-sectional, multicenter, retrospective study of liver fibrosis using noninvasive markers and in whom a determination of liver stiffness (LS) by TE was available, were included in this analysis. Factors potentially associated with significant fibrosis ( $LS \geq 9$  kPa) were analyzed. One thousand three hundred and ten patients fulfilled the inclusion criteria, 526 (40%) of them showed  $LS \geq 9$  kPa and 316 (24%) cirrhosis ( $LS \geq 14$  kPa). The factors independently associated with significant fibrosis [adjusted odds ratio (95% confidence interval,  $P$  value) were the following: older age [1.04 (1.01-1.07), 0.002], daily alcohol intake  $> 50$  g/day [1.58 (1.10-2.27), 0.013] and the length of HCV infection [1.03 (1.00-1.06), 0.023]. A CD4 cell count lower than  $< 200$  per  $\text{mm}^3$  [1.67 (0.99-2.81), 0.053] and HCV genotype 4 [0.66 (0.42-1.02), 0.066] were marginally associated with  $LS \geq 9$  kPa. **In conclusion**, the prevalence of cirrhosis in HIV/HCV-coinfected patients seems to be higher than previously reported in studies based on liver biopsy. Older age, alcohol consumption and lower CD4 cell counts are related with significant fibrosis. The latter association supports an earlier starting of antiretroviral therapy in this setting.

**Prediction of response to pegylated interferon plus ribavirin by IL28B gene variation in patients coinfecting with HIV and hepatitis C virus.** Pineda JA, Caruz A, Rivero A, et al. Clin Infect Dis. 2010 Oct 1;51(7):788-95.

<http://www.ncbi.nlm.nih.gov/pubmed/20804372>

**BACKGROUND:** Variation in the IL28B gene is associated with sustained virologic response (SVR) to pegylated interferon plus ribavirin in hepatitis C virus (HCV)-monoinfected patients with genotype 1. Data on other genotypes and on patients coinfecting with human immune-deficiency virus (HIV) and HCV are more limited. We aimed to assess the predictive ability of variations in the single-nucleotide polymorphism rs12979860 for SVR in HIV/HCV-coinfecting patients, regardless of HCV genotype. **METHODS:** The rs12979860 genotype was determined by polymerase chain reaction in 154 patients who had received therapy against HCV with pegylated interferon plus ribavirin. **RESULTS:** rs12979860 genotype was TT in 20 patients (13%), TC in 66 patients (43%), and CC in 68 patients (44%). Rates of SVR in patients with genotype CC and in those with genotype TC or TT, according to HCV genotype, were, respectively, 50% and 17% ( $P < .001$ ) in patients with genotype 1, 80% and 25% ( $P = .027$ ) in patients with genotype 4, and 93% and 77% ( $P = .115$ ) in patients with genotype 3. The median (interquartile range) low-density lipoprotein cholesterol level in patients with rs12979860 CC was 89 mg/dL (73-120 mg/dL) versus 75 mg/dL (55-91 mg/dL) ( $P = .001$ ) in those with TC or TT. Independent predictors of SVR were HCV genotype 2-3 (odds ratio [OR], 13.98; 95% confidence interval [CI], 4.87-40.1;  $P < .001$ ), rs12979860 CC (OR, 5.05; 95% CI, 2.04-12.5;  $P < .001$ ), baseline plasma HCV RNA load of  $< \text{or} = 600,000$  IU/mL (OR, 1.99; 95% CI, 1.18- 3.34;  $P = .009$ ), and female sex (OR, 4.28; 95% CI, 1.08-16.96;  $P = .039$ ). **CONCLUSIONS:** IL28B gene variations independently predict SVR in HIV/HCV-coinfecting patients with HCV genotype 1 and non-genotype 1 HCV infection. The association between rs12979860 and plasma low-density lipoprotein cholesterol suggests that the system low-density lipoprotein ligand/receptor might be involved in the effect of this genotype.

**Sustained Long-Term Antiviral Maintenance Therapy in HCV/HIV-Coinfecting Patients (SLAM-C).** Sherman KE, Andersen JW, Butt AA, et al. J Acquir Immune Defic Syndr. 2010 Oct 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20921898>

**BACKGROUND:** Hepatitis C virus (HCV)/HIV coinfection treatment is suboptimal with low SVR rates to standard therapies. A multicenter randomized clinical trial designed to assess the efficacy/safety of pegylated interferon maintenance therapy was performed by the National Institutes of Health-funded Aids Clinical Trials Group network. **METHODS:** HCV treatment-naive and nonresponding interferon-experienced subjects with confirmed HCV and HIV, CD4  $> 200$  cells per cubic millimeter, and at least stage 1 fibrosis were enrolled and treated for 12 weeks with pegylated interferon alfa 2a 180 mcg per week (PEG) + weight-based ribavirin to determine response status. Nonresponder subjects (failure to clear HCV RNA or achieve 2-log drop) underwent liver biopsy and were randomized to receive full dose PEG or observation only for 72 weeks. Paired biopsies were evaluated by a central pathologist. **RESULTS:** Three hundred thirty subjects were enrolled; median age was 48 years; 43% white, 37% black, non-Hispanic; 83% male; CD4+ 498 cells per cubic millimeter; 32% were interferon experienced; 74% had entry HIV RNA  $< 50$  copies per milliliter. early virologic responder was observed in 55.9% and 42.5% achieved cEVR. A planned interim analysis occurred when 84 subjects were randomized. With data on 40 paired biopsies available, a safety monitoring board stopped the trial due to lack of fibrosis progression (median = 0 Metavir units/year) in the observation arm. **CONCLUSIONS:** Lack of fibrotic progression in the control arm was unexpected and may represent a short-term PEG/ribavirin therapy effect, high levels of HIV viral suppression, and use of antiretroviral regimens that may be less toxic than prior generations of therapy.

**An artificial neural network improves the non-invasive diagnosis of significant fibrosis in HIV/HCV coinfecting patients.** Resino S, Seoane JA, Bellón JM, et al. *J Infect.* 2010 Nov 10.

[Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21073895>

**OBJECTIVE:** To develop an artificial neural network to predict significant fibrosis ( $F \geq 2$ ) (ANN-SF) in HIV/Hepatitis C (HCV) coinfecting patients using clinical data derived from peripheral blood. **METHODS:** Patients were randomly divided into an estimation group (217 cases) used to generate the ANN and a test group (145 cases) used to confirm its power to predict  $F \geq 2$ . Liver fibrosis was estimated according to the METAVIR score. **RESULTS:** The values of the area under the receiver operating characteristic curve (AUC-ROC) of the ANN-SF were 0.868 in the estimation set and 0.846 in the test set. In the estimation set, with a cut-off value of  $<0.35$  to predict the absence of  $F \geq 2$ , the sensitivity (Se), specificity (Sp), and positive (PPV) and negative predictive values (NPV) were 94.1%, 41.8%, 66.3% and 85.4% respectively. Furthermore, with a cut-off value of  $>0.75$  to predict the presence of  $F \geq 2$ , the ANN-SF provided Se, Sp, PPV and NPV of 53.8%, 94.9%, 92.8% and 62.8% respectively. In the test set, with a cut-off value of  $<0.35$  to predict the absence of  $F \geq 2$ , the Se, Sp, PPV and NPV were 91.8%, 51.7%, 72.9% and 81.6% respectively. Furthermore, with a cut-off value of  $>0.75$  to predict the presence of  $F \geq 2$ , the ANN-SF provided Se, Sp, PPV and NPV of 43.5%, 96.7%, 94.9% and 54.7% respectively. **CONCLUSION:** The ANN-SF accurately predicted significant fibrosis and outperformed other simple non-invasive indices for HIV/HCV coinfecting patients. Our data suggest that ANN may be a helpful tool for guiding therapeutic decisions in clinical practice concerning HIV/HCV coinfection.

**Treatment of acute hepatitis C in human immunodeficiency virus-infected patients: The HEPAIG study.** Piroth L, Larsen C, Binquet C, et al. *Hepatology.* 2010 Dec;52(6):1915-21. doi:

10.1002/hep.23959. Epub 2010 Nov 9.

<http://www.ncbi.nlm.nih.gov/pubmed/21064156>

Acute hepatitis C continues to be a concern in men who have sex with men (MSM), and its optimal management has yet to be established. **In this study,** the clinical, biological, and therapeutic data of 53 human immunodeficiency virus (HIV)-infected MSM included in a multicenter prospective study on acute hepatitis C in 2006–2007 were retrospectively collected and analyzed. The mean hepatitis C virus (HCV) viral load at diagnosis was  $5.8 \pm 1.1 \log_{10}$  IU/mL (genotype 4,  $n = 28$ ; genotype 1,  $n = 14$ , genotype 3,  $n = 7$ ). The cumulative rates of spontaneous HCV clearance were 11.0% and 16.5% 3 and 6 months after diagnosis, respectively. Forty patients were treated, 38 of whom received pegylated interferon and ribavirin. The mean duration of HCV therapy was  $39 \pm 17$  weeks ( $24 \pm 4$  weeks in 14 cases). On treatment, 18/36 (50.0%; 95% confidence interval 34.3–65.7) patients had undetectable HCV RNA at week 4 (RVR), and 32/39 (82.1%; 95% confidence interval 70.0–94.1) achieved sustained virological response (SVR). SVR did not correlate with pretreatment parameters, including HCV genotype, but correlated with RVR (predictive positive value of 94.4%) and with effective duration of HCV therapy (64.3% for  $24 \pm 4$  weeks versus 92.0% for longer treatment;  $P = 0.03$ ). **CONCLUSION:** The low rate of spontaneous clearance and the high SVR rates argue for early HCV therapy following diagnosis of acute hepatitis C in HIV-infected MSM. Pegylated interferon and ribavirin seem to be the best option. The duration of treatment should be modulated according to RVR, with a 24-week course for patients presenting RVR and a 48-week course for those who do not, irrespectively of HCV genotype.

**S-adenosyl-methionine and betaine improve early virological response in chronic hepatitis C patients with previous nonresponse.** Filipowicz M, Bernsmeier C, Terracciano L, Duong FH, Heim MH. *PLoS One*. 2010 Nov 8;5(11):e15492.

<http://www.ncbi.nlm.nih.gov/pubmed/21079746>

**BACKGROUND/AIMS:** Treatment of chronic hepatitis C (CHC) with pegylated interferon  $\alpha$  (pegIFN $\alpha$ ) and ribavirin results in a sustained response in approximately half of patients. Viral interference with IFN $\alpha$  signal transduction through the Jak-STAT pathway might be an important factor underlying treatment failure. S-adenosyl-L-methionine (SAME) and betaine potentiate IFN $\alpha$  signaling in cultured cells that express hepatitis C virus (HCV) proteins, and enhance the inhibitory effect of IFN $\alpha$  on HCV replicons. We have performed a clinical study with the aim to evaluate efficacy and safety of the addition of SAME and betaine to treatment of CHC with pegIFN $\alpha$ /ribavirin. **METHODS:** In this open-label pilot study, 29 patients with CHC who failed previous therapy with (peg)IFN $\alpha$ /ribavirin were treated with SAME, betaine, pegIFN $\alpha$ 2b and ribavirin. Treatment duration was 6 or 12 months, depending on genotype, and the protocol comprised a stopping rule at week 12 if early virological response (EVR) was not achieved. Virological and biochemical response and safety were assessed throughout the treatment.

**RESULTS:** 29 patients were enrolled and treated according to the study protocol. 79% of the patients were infected with genotype 1, 72% had advanced fibrosis, 76% had previously received pegIFN $\alpha$ /ribavirin, and only 14% achieved EVR to the previous treatment. When treated with the study medications, 17 patients (59%) showed an EVR, only 3 (10%) however achieved a sustained virological response (SVR). SAME and betaine were found to be safe when used with pegIFN $\alpha$ /ribavirin. **CONCLUSION:** The addition of SAME and betaine to pegIFN $\alpha$ /ribavirin improves early virological response in CHC.

**Silymarin use and liver disease progression in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis trial.** Freedman ND, Curto TM, Morishima C, et al. *Aliment Pharmacol Ther*. 2010 Nov 2. doi: 10.1111/j.1365-2036.2010.04503.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21083592>

**BACKGROUND:** Silymarin is the most commonly used herbal product for chronic liver disease; yet, whether silymarin protects against liver disease progression remains unclear. Aim To assess the effects of silymarin use on subsequent liver disease progression in 1049 patients of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial who had advanced fibrosis or cirrhosis and had failed prior peginterferon plus ribavirin treatment. **METHODS:** Patients recorded their use of silymarin at baseline and were followed up for liver disease progression (two point increase in Ishak fibrosis score across baseline, year 1.5, and year 3.5 biopsies) and over 8.65 years for clinical outcomes. **RESULTS:** At baseline, 34% of patients had used silymarin, half of whom were current users. Use of silymarin was associated ( $P < 0.05$ ) with male gender; oesophageal varices; higher ALT and albumin; and lower AST/ALT ratio, among other features. Baseline users had less hepatic collagen content on study biopsies and had less histological progression (HR: 0.57, 95% CI: 0.33-1.00; P-trend for longer duration of use=0.026). No effect was seen for clinical outcomes. **CONCLUSIONS:** Silymarin use among patients with advanced hepatitis C-related liver disease is associated with reduced progression from fibrosis to cirrhosis, but has no impact on clinical outcomes (Clinicaltrials.gov #NCT00006164).

**Humanistic and economic impacts of hepatitis C infection in the United States.** Dibonaventura MD, Wagner JS, Yuan Y, L'italien G, Langley P, Ray Kim W. *J Med Econ.* 2010 Nov 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21091098>

**OBJECTIVE:** Prior research examining the effect of hepatitis C virus (HCV) on health-related quality of life (HRQoL) and healthcare costs is flawed because non-patient controls were not adequately comparable to HCV patients. The current study uses a propensity score matching methodology to address the following research question: is the presence of diagnosed hepatitis C (HCV) associated with poorer health-related quality of life (HRQoL) and greater healthcare resource use? **METHODS:** Using data from the 2009 US National Health and Wellness Survey, patients who reported a HCV diagnosis ( $n = 695$ ) were compared to propensity-matched controls ( $n = 695$ ) on measures of HRQoL and healthcare resource use. All analyses applied sampling weights to project to the US population. **RESULTS:** HCV patients reported significantly lower levels of HRQoL relative to the matched-control group, including the physical component score (39.6 vs. 42.7,  $p < 0.0001$ ) and health utilities (0.63 vs. 0.66,  $p < 0.0001$ ). The number of emergency room visits (0.59 vs. 0.44,  $p < 0.05$ ) and physician visits (7.7 vs. 5.9,  $p < 0.05$ ) in the past 6 months were significantly higher for the HCV group relative to matched controls. **CONCLUSION:** The results of this study suggest that HCV represents a substantial burden on patients by having a significant and clinically-relevant impact on key dimensions of HRQoL as well as on utilization of healthcare resources, the latter of which would result in increased direct medical costs. Limitations: Due to limitations of the internet survey approach (e.g., inability to confirm HCV diagnosis), future research is needed to confirm these findings.

**Formal patient education improves patient knowledge of hepatitis c in vulnerable populations.** Surjadi M, Torruellas C, Ayala C, Yee HF Jr, Khalili M. *Dig Dis Sci.* 2010 Oct 24. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20972850>

**BACKGROUND:** Hepatitis C (HCV) knowledge is limited in injection drug users (IDU). Vulnerable populations including IDUs are disproportionately affected by HCV. Effective HCV education can potentially reduce disparity in HCV prevalence and its outcome in this population. **AIM:** This study aimed to assess the impact of formal HCV education and factors associated with improved HCV knowledge in the vulnerable population. **METHODS:** Over 18 months, 201 HCV-infected patients underwent a 2-h standardized education and completed demographic and pre- and post-education questionnaires. **RESULTS:** Patient characteristics were: 69% male, mean age  $49 \pm 10$ , 49% White (26% AA, 10% Latino), 75% unemployed, 83% high school education and above, 64% were IDU, and 7% were HIV co-infected. On multivariate analysis, baseline knowledge scores were higher in patients with at least a high school education (coef 7.1,  $p = 0.045$ ). Baseline knowledge scores were lower in African Americans (coef -12.3,  $p = 0.004$ ) and older patients (coef -0.7,  $p = 0.03$ ). Following HCV education, the overall test scores improved significantly by 14% ( $p = 0.0001$ ) specifically in the areas of HCV transmission ( $p = 0.003$ ), general knowledge ( $p = 0.02$ ), and health care maintenance ( $p = 0.004$ ). There was a high compliance with liver specialty clinic attendance following education. **CONCLUSIONS:** Formal HCV education is effective in improving HCV knowledge. Although White race, younger age, and higher education were predictors of having more HCV knowledge prior to education, all patients independent of racial background had a significant improvement in their knowledge after education. Therefore, promoting effective HCV education among vulnerable populations may be an important factor in reducing the disparities in HCV disease.

**Visceral adiposity index is associated with histological findings and high viral load in patients with chronic hepatitis C due to genotype 1.** Petta S, Amato M, Cabibi D, et al. *Hepatology*. 2010 Nov;52(5):1543-52.

<http://www.ncbi.nlm.nih.gov/pubmed/20799355>

Metabolic factors have been associated with liver damage in patients with genotype 1 chronic hepatitis C (G1 CHC). We tested visceral adiposity index (VAI), a new marker of adipose dysfunction in G1 CHC, patients to assess its association with host and viral factors and its link to both histological findings and sustained virological response (SVR). Two hundred thirty-six consecutive G1 CHC patients were evaluated by way of liver biopsy and anthropometric and metabolic measurements, including insulin resistance (IR), homeostasis model assessment (HOMA), and VAI using waist circumference, body mass index, triglycerides, and high-density lipoprotein cholesterol. All biopsies were scored by one pathologist for staging and grading and graded for steatosis, which was considered moderate to severe if  $\geq 30\%$ . Multiple linear regression analysis revealed that VAI score was independently associated with higher HOMA score ( $P = 0.009$ ),  $\log_{10}$  hepatitis C virus RNA levels ( $P = 0.01$ ), necroinflammatory activity ( $P = 0.04$ ), and steatosis ( $P = 0.04$ ). Multiple logistic regression analysis revealed that IR (OR 3.879, 95% CI 1.727-8.713,  $P = 0.001$ ), higher VAI score (OR 1.472, 95% CI 1.051-2.062,  $P = 0.02$ ), and fibrosis (OR 2.255, 95% CI 1.349-3.768,  $P = 0.002$ ) were linked to steatosis  $\geq 30\%$ . Logistic regression analysis revealed that older age (OR 1.030, 95% CI 1.002-1.059,  $P = 0.03$ ), higher VAI score (OR 1.618, 95% CI 1.001-2.617,  $P = 0.04$ ), and fibrosis (OR 2.608, 95% CI 1.565-4.345,  $P < 0.001$ ) were independently associated with moderate to severe necroinflammatory activity. No independent associations were found between VAI score and both fibrosis and SVR. **CONCLUSION:** In G1 CHC patients, higher VAI score is independently associated with both steatosis and necroinflammatory activity and has a direct correlation with viral load.

**Hepatic microRNA expression is associated with the response to interferon treatment of chronic hepatitis C.** Murakami Y, Tanaka M, Toyoda H, et al. *BMC Med Genomics*. 2010 Oct 22;3:48.

<http://www.ncbi.nlm.nih.gov/pubmed/20969775>

**BACKGROUND:** HCV infection frequently induces chronic liver diseases. The current standard treatment for chronic hepatitis (CH) C combines pegylated interferon (IFN) and ribavirin, and is less than ideal due to undesirable effects. MicroRNAs (miRNAs) are endogenous small non-coding RNAs that control gene expression by degrading or suppressing the translation of target mRNAs. In this study we administered the standard combination treatment to CHC patients. We then examined their miRNA expression profiles in order to identify the miRNAs that were associated with each patient's drug response. **METHODS:** 99 CHC patients with no anti-viral therapy history were enrolled. The expression level of 470 mature miRNAs found their biopsy specimen, obtained prior to the combination therapy, were quantified using microarray analysis. The miRNA expression pattern was classified based on the final virological response to the combination therapy. Monte Carlo Cross Validation (MCCV) was used to validate the outcome of the prediction based on the miRNA expression profile.

**RESULTS:** We found that the expression level of 9 miRNAs were significantly different in the sustained virological response (SVR) and non-responder (NR) groups. MCCV revealed an accuracy, sensitivity, and specificity of 70.5%, 76.5% and 63.3% in SVR and non-SVR and 70.0%, 67.5%, and 73.7% in relapse (R) and NR, respectively. **CONCLUSIONS:** The hepatic miRNA expression pattern that exists in CHC patients before combination therapy is associated with their therapeutic outcome. This information can be utilized as a novel biomarker to predict drug response and can also be applied to developing novel anti-viral therapy for CHC patients.

**Importance of Patient, Provider, and Facility Predictors of Hepatitis C Virus Treatment in Veterans: A National Study.** Kramer JR, Kanwal F, Richardson P, et al. *Am J Gastroenterol.* 2010 Nov 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21063393>

**OBJECTIVES:** Several patient characteristics are known to impact hepatitis C virus (HCV) antiviral treatment rates. However, it is unclear whether, and to what extent, health-care providers or facility characteristics impact HCV treatment rates. **METHODS:** Using national data obtained from the Department of Veterans Affairs (VA) HCV Clinical Case Registry, we conducted a retrospective cohort study of patients with active HCV viremia, who were diagnosed between 2003 and 2004. We evaluated patient-, provider-, and facility-level predictors of receipt of HCV treatment with hierarchical logistic regression. **RESULTS:** The overall HCV treatment rate in 29,695 patients was 14.2%. The strongest independent predictor for receipt of treatment was consultation with an HCV specialist (odds ratio=9.34; 8.03-10.87). Patients were less likely to receive HCV treatment if they were Black, older, male, current users of alcohol or drugs, had HCV genotype 1 or 4, had higher creatinine levels, or had severe anxiety/post-traumatic stress disorder or depression. Patients with high hemoglobin levels, cirrhosis, and persistently high liver enzyme levels were more likely to receive treatment. Patient, provider, and facility factors explained 15, 4, and 4%, respectively, of the variation in treatment rates. **CONCLUSIONS:** Treatment rates for HCV are low in the VA. In addition to several important patient-level characteristics, a specialist consultant has a vital role in determining whether a patient should receive HCV treatment. These findings support the development of patient-level interventions targeted at identifying and managing comorbidities and contraindications and fostering greater involvement of specialists in the care of HCV.

**Syringe exchange programs --- United States, 2008.** Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2010 Nov 19;59(45):1488-91.

<http://www.ncbi.nlm.nih.gov/pubmed/21085091>

Persons who inject drugs should use a new, sterile needle and syringe for each injection. Syringe exchange programs (SEPs) provide free sterile syringes and collect used syringes from injection-drug users (IDUs) to reduce transmission of bloodborne pathogens, including human immunodeficiency virus (HIV), hepatitis B virus, and hepatitis C virus (HCV). As of March 2009, a total of 184 SEPs were known to be operating in 36 states, the District of Columbia (DC), and Puerto Rico (North American Syringe Exchange Network [NASEN], unpublished data, 2009). Of these, 123 (67%) SEP directors participated in a mail/telephone survey conducted by NASEN and Beth Israel Medical Center (New York, New York) that covered program operations for the calendar year 2008. To characterize SEPs in the United States, this report summarizes the findings from that survey and compares them with previous SEP survey results from the period 1994--2007. In 2008, the 123 SEPs reported exchanging 29.1 million syringes and had budgets totaling \$21.3 million, of which 79% came from state and local governments. Most of the SEPs reported offering preventive health and clinical services in addition to basic syringe exchange: 87% offered HIV counseling and testing, 65% offered hepatitis C counseling and testing, 55% offered sexually transmitted disease screening, and 31% offered tuberculosis screening; 89% provided referrals to substance abuse treatment. Providing comprehensive prevention services and referrals to IDUs, such as those offered by many SEPs, can help reduce the spread of bloodborne infections and should increase access to health care and substance abuse treatment, thus serving as an effective public health approach for this population.

**Evaluation of acute hepatitis C infection surveillance --- United States, 2008.** *MMWR Morb Mortal Wkly Rep.* 2010 Nov 5;59(43):1407-10. Centers for Disease Control and Prevention (CDC).

<http://www.ncbi.nlm.nih.gov/pubmed/21048562>

Hepatitis C virus (HCV) infection affects nearly 4 million persons and causes an estimated 12,000 deaths each year in the United States. For the 10-year period from 2010 to 2019, the direct medical cost of chronic HCV infection is projected to exceed \$10.7 billion, the societal cost of premature mortality attributed to HCV infection is projected to be \$54.2 billion, and the cost of morbidity from disability associated with HCV infection is projected to be \$21.3 billion. The Institute of Medicine recently recommended a comprehensive evaluation of the national hepatitis B and C surveillance system. Complete and timely surveillance data are essential for early identification and response to outbreaks and for implementation of evidence-based prevention strategies. To assess these attributes, CDC compared acute hepatitis C surveillance data reported in 2008 from the National Notifiable Diseases Surveillance System (NNDSS) and the Emerging Infections Program (EIP), which conducts enhanced surveillance for acute hepatitis C in selected states. This report summarizes the results of that analysis, which indicated that 26 (22%) of 120 cases reported from EIP-funded sites were missing from NNDSS. Data on race and major HCV risk factors were missing from 22% and 60% of reports in NNDSS, compared with 8% and 25% of reports in EIP, respectively. The mean duration between diagnosis and reporting of the case to the state health department was 30 days (range: 0-298 days) in NNDSS compared with 19 days (range: 0-350 days) in EIP sites. These findings underscore that enhanced surveillance for acute hepatitis C improves the completeness and timeliness of the data.

**Fatigue and depressive symptoms associated with chronic viral hepatitis patients. health-related quality of life (HRQOL).** Karaivazoglou K, Iconomou G, Triantos C, et al. *Ann Hepatol*. 2010 Oct 1;9(4):419-27.

<http://www.ncbi.nlm.nih.gov/pubmed/21057161>

**BACKGROUND AND RATIONALE:** It is well established that chronic viral hepatitis (CVH) negatively affects patients' health-related quality of life (HRQOL). The aim of the present study was to assess the extent to which fatigue and depressive symptoms are associated with CVH patients. **HRQOL. METHODS:** Eighty-four adult CVH outpatients [45 with hepatitis B virus (HBV) and 39 with hepatitis C virus (HCV) infection] participated in the study. The Short Form-36 Health Survey (SF-36), the Beck Depression Inventory-II (BDI-II) and the Fatigue subscale of the Functional Assessment of Cancer Therapy-Anemia Scale (FACT-F) were used to assess HRQOL, depression and fatigue, respectively. **RESULTS:** All aspects of HRQOL perceived by CVH patients were significantly impaired compared to the general population, as a comparison with Greek population-based normative data revealed. HBV patients presented similar HRQOL with HCV patients. Clinical parameters including infection activity, fibrosis stage or inflammation grade, as well as depressive symptoms and fatigue were found to be significantly associated with HRQOL. Multivariate analyses showed that older age ( $p < 0.001$ ) and higher fatigue scores ( $p < 0.001$ ) were the variables most closely associated with the physical HRQOL, whereas higher rates on depressive symptoms ( $p < 0.0005$ ) and fatigue ( $p < 0.020$ ) scales were the variables most closely associated with the mental HRQOL. **CONCLUSIONS:** In conclusion, CVH is associated with impaired HRQOL. Fatigue and impaired psychological functioning is associated with diminished HRQOL in CHV, independent of the disease etiology. Consequently, management of fatigue and depressive symptoms should be considered a priority, in order to improve HRQOL in CVH patients..

**Transfusion-transmissible viral infections among US military recipients of whole blood and platelets during Operation Enduring Freedom and Operation Iraqi Freedom.** Hakre S, Peel SA, O'Connell RJ, et al. *Transfusion*. 2010 Oct 7. doi: 10.1111/j.1537-2995.2010.02906.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20946199>

**BACKGROUND:** Current US military clinical practice guidelines permit emergency transfusions of non-Food and Drug Administration (FDA)-compliant freshly collected blood products in theaters

of war. This investigation aimed to characterize the risks of transfusion-transmitted infections (TTIs) associated with battlefield transfusions of non-FDA-compliant blood products. **STUDY DESIGN AND METHODS:** US Service members who received emergency transfusion products in Iraq and Afghanistan (March 1, 2002-September 30, 2007) were tested for hepatitis C virus (HCV), human immunodeficiency virus (HIV), and hepatitis B virus (HBV) infections using reposed pre- and posttransfusion sera. Selected regions of viral genomes from epidemiologically linked infected recipients and their donors were sequenced and compared. **RESULTS:** Of 761 US Service members who received emergency transfusion products, 475 were tested for HCV, 472 for HIV, and 469 for HBV. One transfusion-transmitted HCV infection (incidence rate of 2.1/1000 persons) was identified. The pretransfusion numbers (prevalence per 1000 persons) were HCV-four (8/1000), HIV-zero (0/1000), chronic HBV-two (4 /1000), and naturally immune (antibody to HBV core antigen)-nine (19/1000). **CONCLUSION:** One HCV TTI was determined to be associated with emergency blood product use. The pretransfusion HCV and HBV prevalence in transfusion recipients, themselves members of the potential donor population, indicates better characterization of the deployed force's actual donor population, and further investigations of the TTI prevalence in these donors are needed. These data will inform countermeasure development and clinical decision making.

**Patients' perceptions of information and support received from the nurse specialist during HCV treatment.** Grogan A, Timmins F. *J Clin Nurs.* 2010 Oct;19(19-20):2869-78. doi: 10.1111/j.1365-2702.2010.03239.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20846231>

**AIM:** To identify patients' perceptions of support received from the nurse specialist during Hepatitis C virus (HCV) treatment. **BACKGROUND:** HCV is a worldwide health problem. However, it is a treatable disease and treatment success rates are high. Unfortunately, treatment comes with a multitude of adverse side effects and patients require informational and psychological support from specialist nurses while on treatment. To date, there is little nursing research on support received from this specialist nursing care. **DESIGN:** This study used a quantitative descriptive design. **METHOD:** A 59-item questionnaire collected data from 106 patients with a diagnosis of HCV attending a HCV outpatient clinic. **RESULTS:** Overall, patients were very satisfied with support received. Advice on contraception was well received. However, many patients did not feel supported with regard to advice on sleep management. There were no statistically significant differences between overall satisfaction and gender, age, genotype and risk factor. However, there were significant correlations found between support received and reported genotype. Those patients presenting with genotype 1, who are mostly infected through blood or blood products, indicated that they require more support in relation to information on side effects of treatment, quality of life and support groups. Specific approaches to support and advice for this cohort may need to be incorporated into current services.

**CONCLUSION:** Results of this study reinforce the need for the ongoing use of specialist nurse services and development of this service where no such facilities exist. In addition, the service may need to further recognise and support the information and psychological needs of patients with differing modes of HCV infection. **RELEVANCE TO CLINICAL PRACTICE:** Findings provide information to practising nurse specialists about patient's views of information and support received from nurse specialists in HCV treatment centres and identify where deficits exist.

**Guidance for clinical trials for children and adolescents with chronic hepatitis C.** Wirth S, Kelly D, Sokal E, et al. *J Pediatr Gastroenterol Nutr.* 2010 Nov 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21076340>

Most children with chronic hepatitis C are infected vertically, have a low natural seroconversion rate, and carry a lifetime risk of cirrhosis and cancer. Affected children are usually asymptomatic, and

histological findings are mild with a low risk of progression, although 5% develop significant liver disease in childhood. The use of combination treatment with pegylated interferon- $\alpha$  and ribavirin has changed the outcome and prognosis for this disease, with approximately 60% of children achieving sustained viral clearance. Combination therapy is not ideal for children because pegylated interferon is administered subcutaneously, impairs growth velocity, and both interferon and ribavirin have significant adverse effects that affect compliance. In addition, approximately 50% of children infected with genotype 1 do not respond to therapy. Thus, additional treatment options are required including improvement in dosing, reduction in the length of treatment, and evaluation of new drugs, such as protease inhibitors, which could be more effective for patients infected with genotype 1. The primary goal of treatment is to eradicate the infection. The future clinical trial design should ensure that any new drugs demonstrate noninferiority to the present standard regimen in both children and adults. The measure for documenting substantial improvement above present therapy should be increased viral clearance rate or the same clearance rate, with a shorter duration of treatment and/or fewer adverse effects. We do not believe there is any need for a placebo arm because approved therapy is available and new treatments can be compared with present therapy. Safety measures should include the standard recommended laboratory investigations, growth parameters, quality-of-life or psychological measures, and a requirement for long-term follow-up for up to 5 years.

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## LIVER CANCER

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**Steatohepatic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH.** Salomao M, Yu WM, Brown RS Jr, Emond JC, Lefkowitz JH. *Am J Surg Pathol.* 2010 Nov;34(11):1630-6. <http://www.ncbi.nlm.nih.gov/pubmed/20975341>

In explant livers with chronic hepatitis C (HCV-C) we have noted a distinctive histologic variant that we have termed steatohepatic hepatocellular carcinoma (SH-HCC) with features resembling non-neoplastic steatohepatitis, including large droplet steatosis, ballooning of malignant hepatocytes, Mallory-Denk bodies, inflammation, and pericellular fibrosis. This study was undertaken to further describe the characteristics and prevalence of this histologic variant in HCV-C and any possible association with underlying risk factors for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). We selected two 2-year periods (mid-2003 to mid-2005 and 2007 to 2008), from which selected explant livers with HCV-C and HCC were examined to determine the characteristics and frequency of SH-HCC. The underlying cirrhotic liver was also reassessed for steatosis and evidence of steatohepatitis. Clinical records were consulted for concomitant NAFLD and NASH risk factors. The SH-HCC variant was found in a total of 22 of 62 HCC cases (35.5%). Fourteen of the 22 patients with SH-HCC (63.6%) had at least one known risk factor for NAFLD/NASH including diabetes (6 of 22, 27.3%), obesity (6 of 22, 27.3%), hypertension (11 of 22, 50%), and hyperlipidemia (5 of 22, 27.8%). In 14 of the 22 cases (63.6%) of SH-HCC, the non-neoplastic liver showed changes of NAFLD/NASH superimposed on otherwise typical features of HCV-C. In conclusion, in our series of HCV-C explants, approximately one-third of HCCs show a distinctive histological variant termed SH-HCC. Underlying risk factors for NAFLD and for NASH were identified in 63.6% of our cases. Moreover, non-neoplastic tissue in HCV-C explants showed changes of NAFLD/NASH in 63.6% of cases. **These results suggest** a possible NAFLD/NASH pathway leading to SH-HCC in the setting of HCV-C which requires further investigation in the future.

**Synergistic Effect of Celecoxib on 5-fluorouracil-induced Apoptosis in Hepatocellular Carcinoma Patients.** Bassiouny AR, Zaky A, Neenaa HM. Ann Hepatol. 2010 Oct 1;9(4):410-8. <http://www.ncbi.nlm.nih.gov/pubmed/21057160>

**BACKGROUND:** Cyclooxygenase-2 (COX-2) enzyme over expression is reported in many human HCC cell line studies and is linked to tumor cell resistance to chemotherapy-induced apoptosis. We hypothesized that adding a COX-2 inhibitor would improve the therapeutic benefits in patients with HCC. COX-2 is often increased and involved in drug resistance and poor prognosis. **METHOD:** Between January 2001 and December 2007, 15 patients with MDR-positive-HCC from 34 HCC patients based on tissue and serum liver of glypican-3 and fitting the preset eligibility criteria, were treated with a combination regimen with intravenous infusion of (5-FU) 750 mg once per week, 100mg/day cyclophosphamide (Endoxan) and 400 mg/day celecoxib taken orally in divided doses, while the rest of the patients received only 5-FU and Endoxan. Twenty-one patients (62%) had liver disease associated with hepatitis C virus (HCV) and 5 patients with hepatitis B virus (62%).

**RESULTS:** We found that celecoxib reduced P-glycoprotein with activation of caspase-3 and marked regression of tumor sizes. Sera angiogenic factors (VEGF & bFGF) levels measurement in HCC patients indicated that, the sera levels of both angiogenic factors were reduced significantly ( $p < 0.05$ ) after treatment. Based on the tumor markers AFP & Glypican-3, 11 of the patients had a PR (11/15), including 3 patients who had normalization of AFP, and four patients had CR (4/15).

**CONCLUSIONS:** These data suggest that the combination of 5-FU, Endoxan and Celecoxib is highly effective palliative regimen for patients with HCC with good performance status (score  $\geq 3$ ). The study suggests a framework for Celecoxib-based combination treatment of HCC.

**Impact of viral load of hepatitis C on the incidence of hepatocellular carcinoma: A population-based cohort study (JPHC Study).** Ishiguro S, Inoue M, Tanaka Y, et al. Cancer Lett. 2010 Oct 28. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21035947>

Impact of viral load of HCV on the incidence of hepatocellular carcinoma was investigated using a population-based cohort consisting of 20,794 Japanese. A total of 114 newly arising cases of hepatocellular carcinoma were diagnosed during follow-up. Compared to the hepatitis virus-negative group, the hazard ratio (HR) of developing hepatocellular carcinoma was 35.8-fold higher in HCV monoinfection (95% confidence interval [CI], 20.7-62.7). A titer-dependent increase in risk was not identified. The risk was 3.86-fold higher (CI; 1.73-8.62) for genotype 1 than genotype 2. Our findings suggest that HCV viremia strongly influences the occurrence of hepatocellular carcinoma without titer-dependence.

**Increased risk for malignant neoplasms among patients with cirrhosis.** Kalaitzakis E, Gunnarsdottir SA, Josefsson A, Björnsson E. Clin Gastroenterol Hepatol. 2010 Oct 25. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21029788>

**BACKGROUND & AIMS:** It is not clear how cirrhosis affects the risks for hepatocellular carcinoma (HCC) and non-HCC cancers, which are rare among these patients. We assessed the risk for malignant neoplasms in patients with cirrhosis. **METHODS:** Patients diagnosed with cirrhosis in Gothenburg, Sweden from 1994 to 2005 were identified and linked to the National Cancer and Death registers. We studied data from 1019 patients with cirrhosis: 68% men, 48% with alcoholic liver disease (ALD), 10% with hepatitis C (HCV), and 12% with HCV+ALD. Standardized incidence ratios for malignant neoplasms were calculated (corrected for sex, age, and calendar year according to data from the general Swedish population). The follow-up period was 3290 person-years. **RESULTS:** Overall, 114 (11%) patients developed HCC; HCC occurred more frequently among patients with HCV than other diseases ( $P < 0.05$ ). HCC risk did not differ among patients with HCV, with or without ALD ( $P > 0.05$ ). Compared to the general population, cirrhotics had

increased risk for HCC (26-fold); cholangiocarcinoma (13-fold); and esophageal (8-fold), pancreatic (5-fold), and colorectal and lung cancers (each 4-fold). The risk for cholangiocarcinoma increased mainly among patients with non-ALD cirrhosis, whereas the risk for extrahepatic malignancies increased mainly among patients with ALD and cirrhosis. **CONCLUSION:** The overall risk for non-HCC malignancies is more than 2-fold greater for patients with cirrhosis (mostly in biliary and gastrointestinal malignancies) than of the general population. The risk for non-HCC cancers differs between patients ALD and non-ALD cirrhosis. The increased risk for HCC among patients with cirrhosis is associated with HCV; it is the same among patients with HCV, with or without ALD.

**Prognostic significance of circumferential cell surface immunoreactivity of glypican-3 in hepatocellular carcinoma.** Yorita K, Takahashi N, Takai H, et al. *Liver Int.* 2010 Oct 21. doi: 10.1111/j.1478-3231.2010.02359.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20964802>

**BACKGROUND:** GC33 is a recently developed monoclonal antibody against human glypican-3 (GPC3), which is significantly upregulated in hepatocellular carcinoma (HCC). GC33 recognizes a GPC3 ectodomain and shows significant antitumour activity in vivo. Thus, humanized GC33 antibody may be a promising tool for treating HCC having cell surface GPC3 expression. **Aims:** This study aims to determine the specificity, subcellular localization and prognostic impact of GPC3 immunoreactivity detected by GC33 in HCC clinical specimens. **METHODS:** Immunohistochemical analysis was performed for 194 cases of resected HCC and prognostic analysis was performed for 185 eligible cases. Two antigen retrieval methods (autoclave and protease pretreatments) were used for immunohistochemistry and compared. The immunoscore system reflecting circumferential membranous GPC3 immunoreactivity was developed using either the autoclave or protease methods. The GPC3 mRNA level was analysed by quantitative real-time reverse transcription-polymerase chain reaction. **Results:** GC33 immunostaining after autoclave is a sensitive method and revealed the GPC3 expression ( $\geq 20\%$  of tumour cells) in the majority (77%) of HCC samples tested. Alternatively, protease pretreatment showed lower sensitivity, but was superior for evaluating the intensity and subcellular localization of GPC3. Correlation between immunoscores and the GPC3 mRNA level was also confirmed. Subsequent clinicopathological analysis revealed worse prognoses in HCC patients with circumferential membranous GPC3 immunoreactivity. For HCC patients with hepatitis C virus (HCV) infection in particular, the high membranous GPC3 immunoreactivity was an independent prognostic factor for disease-free survival. **CONCLUSIONS:** Circumferential membranous GPC3 immunoreactivity in HCC indicates poorer prognosis particularly in patients with HCV infection.

**Factors associated with use of ultrasonography screening for hepatocellular carcinoma among hepatitis B or C carriers.** Cho ER, Shin A, Choi KS, Lee HY, Kim J. *Cancer Epidemiol.* 2010 Oct 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20947465>

**OBJECTIVES:** Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are important risk factors for hepatocellular carcinoma (HCC). Yet, there have been few studies on adherence to screening recommendations for groups at high risk for HCC. We assessed whether demographic factors or medical conditions affected screening participation among HBV/HCV carriers. **METHODS:** The study population consisted of 15565 men and women who visited the National Cancer Center, Korea between August 2002 and July 2009. A self-administered questionnaire was used to collect information on demographic characteristics, medical history, including chronic HBV and HCV infection, and health check-up history. HBV surface antigen and HCV antibody levels were measured in serum. **RESULTS:** Among 781 HBV carriers, 596 (76.3%) were aware of their infection and 451 (57.8%) had ever been tested by ultrasonography. Among HCV carriers, 49 of 127 (36.6%) were aware of their infection and 61 (48.0%) had ever been tested

by ultrasonography. Among HBV carriers, male sex (OR, 1.68; 95% CI, 1.22-2.31), family history of liver disease (OR, 2.04; 95% CI, 1.43-2.90), medical history of hyperlipidemia (OR, 2.70; 95% CI, 1.36-5.33), and awareness of infection status (OR, 4.30; 95% CI, 2.99-6.17) were associated with being tested. Among HCV carriers, awareness of infection (OR, 3.77; 95% CI, 1.72-8.26) was significantly associated with being tested by ultrasonography. **CONCLUSION:** Male sex, family history of liver disease, medical history of hyperlipidemia, and awareness of high risk status were associated with being tested by ultrasonography.

**Resveratrol arrests cell cycle and induces apoptosis in human hepatocellular Carcinoma Huh-7 cells.** Liao PC, Ng LT, Lin LT, Richardson CD, Wang GH, Lin CC. J Med Food. 2010 Oct 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20946021>

Resveratrol has been shown to possess anticancer, anti-aging, anti-inflammatory, antimicrobial, and neuroprotective activities. In this study, we examined the antiproliferative properties of resveratrol and its molecular mechanism(s) of action in Huh-7 cells, a new human hepatoma cell line system for hepatitis C virus. Results showed that resveratrol significantly inhibited Huh-7 cell proliferation (50% inhibitory concentration  $IC_{50}$ ; 22.4  $\mu$ g/mL) and effectively induced cell cycle arrest and apoptosis. It up-regulated p21/WAF1 expression in a p53-independent manner, but the expressions of cyclin E, cyclin A, and cyclin-dependent kinase 2 were down-regulated. It also caused an increase in the ratio of pro-apoptotic/anti-apoptotic protein, which was associated with the mitochondrial membrane depolarization and the increase in caspase activity. Resveratrol showed no effect on Fas, Fas ligand, extracellular signal regulated kinase (ERK) 1/2, and p38 expression but down-regulated phospho-ERK and phospho-p38 expression. In addition, resveratrol was noted to trigger autophagic cell death through the increased expression of autophagy-related Atg5, Atg7, Atg9, and Atg12 proteins. These results suggest that resveratrol could be an important chemoprevention agent for hepatoma of hepatitis C virus infection.

**Comparative Analysis of outcome in patients with hepatocellular carcinoma exceeding the Milan criteria treated with liver transplantation versus partial hepatectomy.** Canter RJ, Patel SA, Kennedy T, et al. Am J Clin Oncol. 2010 Oct 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20938319>

**INTRODUCTION:** Proponents of orthotopic liver transplantation (TXP) for the treatment of hepatocellular carcinoma (HCC) advocate expanding the Milan criteria. We performed a matched analysis comparing patients treated with TXP to patients treated with partial hepatectomy (PHX) for HCC exceeding the Milan criteria. **METHODS:** From the United Network for Organ Sharing registry, we identified 92 US patients with HCC exceeding the Milan criteria who underwent TXP between 2002 and 2005. During the same period, 94 patients with similar tumor size criteria underwent PHX at a single center. Data were analyzed using  $\chi^2$ , parametric, nonparametric, and Kaplan-Meier methods. **RESULTS:** TXP patients were more commonly male (82% vs. 65%,  $P = 0.01$ ) and had a higher Model for End Stage Liver Disease score (median 11 vs. 7,  $P < 0.001$ ). Pathologic cirrhosis (79% TXP vs. 38% PHX,  $P < 0.001$ ), particularly secondary to hepatitis C virus (29% TXP vs. 5% PHX,  $P < 0.001$ ), was more common among TXP patients. Mean cumulative tumor size was 10.0 cm (63% exceeding University of California at San Francisco criteria) among PHX patients compared with 6.4 cm (20% exceeding University of California at San Francisco criteria) for TXP patients ( $P < 0.001$ ). With a median follow-up of 34 months (range, 1-86), 3-year survival was similar between the cohorts (66%  $\pm$  10% for TXP vs. 66%  $\pm$  10% for PHX,  $P = 0.97$ ). Cancer deaths (26/37, 70%) were more prevalent among PHX patients, whereas noncancer deaths (25/37, 68%) were common in TXP patients ( $P < 0.001$ ). **CONCLUSIONS:** Among heterogeneous patients with HCC who exceed the Milan criteria, TXP and PHX achieve similar

overall survival. Further study is needed to ensure appropriate patient selection for these disparate therapies.

**Clinical Presentation of Hepatocellular Carcinoma (HCC) in Asian-Americans Versus Non-Asian-Americans.** Wong PY, Xia V, Imagawa DK, Hoefs J, Hu KQ. *J Immigr Minor Health*. 2010 Oct 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20890660>

The incidence of HCC is rising worldwide. Studies on ethnicity-based clinical presentation of HCC remain limited. The aim is to compare the clinical presentation and stage of HCC between Asian-Americans and non-Asian-Americans. This retrospective study assessed ethnicity-based differences in HCC presentation, including demographics, laboratory results, diagnosis of underlying liver disease, and stage of HCC. Of 276 patients, 162 were Asian-Americans and 114 were non-Asian-Americans. Compared to non-Asian-Americans, Asian-Americans had a significantly higher incidence of history of hepatitis B virus (HBV) infection (55.0% vs. 4.9%,  $P < 0.001$ ), family history of HBV infection (12.5% vs. 0.0%,  $P < 0.001$ ) and HCC (15.2% vs. 2.9%,  $P = 0.002$ ), but lower incidence of history of hepatitis C virus (HCV) infection (37.5% vs. 61.6%,  $P < 0.001$ ). At diagnosis of HCC, Asian-American patients had a significantly lower frequency of hepatic encephalopathy (8.9% vs. 29.3%,  $P = 0.001$ ), and ascites (26.7% vs. 57.3%,  $P < 0.001$ ). Asian-Americans had lower Child-Pugh scores (class A: 62.0% vs. 31.4%,  $P < 0.001$ ), and MELD scores ( $9.2 \pm 4.4$  vs.  $12.0 \pm 6.4$ ,  $P = 0.02$ ), and presented with a lower stage of HCC by Okuda staging (I: 43.8% vs. 22.8%,  $P = 0.001$ ). Asian-American patients with HCC presented with a higher incidence of history and family history of HBV infection, lower incidence of hepatic decompensation, lower Child and MELD scores, and an early stage HCC disease.

**Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma.** Singal AK, Freeman DH Jr, Anand BS. *Aliment Pharmacol Ther*. 2010 Oct;32(7):851-8. doi: 10.1111/j.1365-2036.2010.04414.x.

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<http://www.ncbi.nlm.nih.gov/pubmed/20659285>

**BACKGROUND:** Hepatocellular carcinoma (HCC) is third most common cause of tumour-related death in the US with hepatitis C virus (HCV) the most common aetiology. Surgical resection and tumour ablation are curative in patients who cannot be transplanted. With native liver having cirrhosis, HCC recurrence is a potential problem. **AIM:** To perform a systematic review and meta-analysis of studies evaluating efficacy of IFN to prevent HCC recurrence after its curative treatment in HCV-related cirrhosis. **METHODS:** Ten studies ( $n = 645$ , 301 treated with IFN) on the use of IFN after resection or ablation of HCV-associated HCC were analysed.

**RESULTS:** Pooled data showed benefit of IFN for HCC prevention with OR (95% CI) of 0.26 (0.15-0.45);  $P < 0.00001$ . The proportion of patients surviving at 5 years ( $n = 505$  in 6 studies) was in favour of IFN with OR of 0.31 [(95% CI 0.21-0.46);  $P < 0.00001$ ]. Data were homogeneous for HCC recurrence (chi(2) 12.05,  $P = 0.21$ ) and survival (chi(2) 6.93,  $P = 0.44$ ). The benefit of IFN was stronger with sustained virological response compared with nonresponders for HCC recurrence [0.19 (0.06-0.60);  $P = 0.005$ ] and survival [0.31 (0.11-0.90);  $P = 0.03$ ]. **CONCLUSION:** Interferon treatment after curative resection or ablation of HCC in HCV-related cirrhotics prevents HCC recurrence and improves survival.

**Prolonged recurrence-free survival following OK432-stimulated dendritic cell transfer into hepatocellular carcinoma during transarterial embolization.** Nakamoto Y, Mizukoshi E, Kitahara M, et al. Clin Exp Immunol. 2010 Nov 19. doi: 10.1111/j.1365-2249.2010.04246.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21087443>

Despite curative locoregional treatments for hepatocellular carcinoma (HCC), tumour recurrence rates remain high. The current study was designed to assess the safety and bioactivity of infusion of dendritic cells (DCs) stimulated with OK432, a streptococcus-derived anti-cancer immunotherapeutic agent, into tumour tissues following transcatheter hepatic arterial embolization (TAE) treatment in patients with HCC. DCs were derived from peripheral blood monocytes of patients with hepatitis C virus-related cirrhosis and HCC in the presence of interleukin (IL)-4 and granulocyte-macrophage colony-stimulating factor and stimulated with  $0.1 \times 10^6$  KE/ml OK432 for 2 days. Thirteen patients were administered with  $5 \times 10^6$  of DCs through arterial catheter during the procedures of TAE treatment on day 7. The immune-modulatory effects and clinical responses were evaluated in comparison with a group of 22 historical controls treated with TAE but without DC transfer. OK432 stimulation of immature DCs promoted their maturation towards cells with activated phenotypes, high expression of a homing receptor, fairly well-preserved phagocytic capacity, greatly enhanced cytokine production and effective tumoricidal activity. Administration of OK432-stimulated DCs to patients was found to be feasible and safe. Kaplan-Meier analysis revealed prolonged recurrence-free survival of patients treated in this manner compared with the historical controls ( $P = 0.046$ , log-rank test). The bioactivity of the transferred DCs was reflected in higher serum concentrations of the cytokines IL-9, IL-15 and tumour necrosis factor- $\alpha$  and the chemokines CCL4 and CCL11. Collectively, this study suggests that a DC-based, active immunotherapeutic strategy in combination with locoregional treatments exerts beneficial anti-tumour effects against liver cancer.

**Effects of interferon treatment on development and progression of hepatocellular carcinoma in patients with chronic virus infection: A meta-analysis of randomized controlled trials.**

Zhang CH, Xu GL, Jia WD, Li JS, Ma JL, Ge YS. Int J Cancer. 2010 Nov 12. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21077159>

Available literature on the effects of interferon (IFN) treatment on development and progression of hepatocellular carcinoma (HCC) in patients with chronic virus infection reports controversial results. The primary objective of this meta-analysis was to evaluate the effect of IFN on HCC risk in patients with chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, IFN's efficacy on local tumor progression and survival of advanced HCC patients was also assessed. All randomized controlled trials (RCTs) comparing IFN with no antiviral treatment were selected. Finally, we identified eleven RCTs including 1772 patients which met our inclusion criteria to perform this meta-analysis. Our analysis results showed that IFN significantly decreased the overall HCC incidence in HCV-infected patients (relative risk [RR]=0.39; 95% confidence interval [CI]=0.26-0.59;  $p=0.000$ ), subgroup analysis indicated that IFN decreased HCC incidence in HCV-related cirrhotic patients evidently (RR=0.44; 95% CI=0.28-0.68;  $p=0.000$ ); but HCC incidence in non-responders to initial antiviral therapy did not be reduced by maintenance IFN therapy (RR=0.96; 95% CI=0.59-1.56;  $p=0.864$ ). Analysis results also demonstrated that IFN did not significantly affect the overall rate of HCC in HBV-infected patients although there was a trend favoring IFN therapy (RR=0.23; 95% CI=0.05-1.04;  $p=0.056$ ). Besides, IFN did not improve 1-year overall survival of advanced HCC patients significantly (RR=1.61; 95% CI=0.96-2.69;  $p=0.072$ ); however, a quantitative analysis on local tumor progression could not be performed owing to lack of unified definitions among trials included in our study. By this meta-analysis, we conclude that IFN therapy is effective in reducing overall HCC risk in chronic HCV-infected patients; using it in this

subpopulation seems promising but its administration in other subpopulations still requires further exploration.

**Does antiviral therapy for hepatitis B and C prevent hepatocellular carcinoma?** Lok AS. J Gastroenterol Hepatol. 2010 Nov 11. doi: 10.1111/j.1440-1746.2010.06576.x. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21070361>

Approximately 75% to 80% of hepatocellular carcinomas (HCC) worldwide are attributed to chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infection. Thus, effective prevention of HBV and HCV infection and progression from acute HBV and HCV infection to chronic hepatitis, cirrhosis and HCC might prevent as many as 450,000 deaths from HCC each year. The most effective approach to preventing HCC is to prevent HBV and HCV infection through vaccination. Indeed HBV vaccine is the first vaccine demonstrated to prevent cancers. However, a vaccine for HCV is not available and for persons who are chronically infected with HBV or HCV, antiviral therapy is the only option for preventing HCC. Direct evidence supporting a benefit of antiviral therapy on the prevention of HCC has been shown in a few randomized controlled trials. There is abundant evidence that antiviral therapy, in patients with long-term virological response, can improve liver histology providing indirect support that antiviral therapy may prevent HCC by slowing progression of liver disease and possibly even reversing liver damage. Nevertheless, the risk of HCC remains in patients with chronic HBV or chronic HCV infection if treatment is initiated after cirrhosis is established. These data indicate that treatment might be of greater benefit if instituted earlier in the course of chronic hepatitis B or C. Safer, more effective, and more affordable antiviral therapies are needed for both hepatitis B and hepatitis C so more patients can benefit from treatment and more HCCs can be prevented.