

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

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**Psychosocial correlates of alcohol use and reduction for individuals with hepatitis C.**

Perzynski AT, McCormick R, Webster NJ, et al. J Stud Alcohol Drugs. 2011 Sep;72(5):787-98.  
<http://www.ncbi.nlm.nih.gov/pubmed/21906506>

**OBJECTIVE:** Patients with hepatitis C virus (HCV) are advised to refrain from alcohol consumption. A questionnaire was developed to measure concepts associated with alcohol use for individuals with HCV. **METHOD:** Subjects with HCV (N = 527) completed a telephone survey. Eligible respondents had screened negative for current abuse/dependence disorders (Alcohol Use Disorders Identification Test [AUDIT]  $\leq 10$ ). Measures of personality, self-efficacy, knowledge, readiness, coping styles, stigma, and symptoms were examined for associations with alcohol use. **RESULTS:** Factor analysis supported a measurement structure of 105 items in 35 subdomains. A total of 26 subdomains had significant bivariate associations with alcohol use. Higher self-efficacy for resisting drinking in social situations was associated with lower alcohol use ( $r = -.68, p < .001$ ), as was knowledge of alcohol and HCV ( $r = -.27, p < .001$ ). Although agreeableness and marital status are typically associated with lower current drinking in samples of those with alcohol use problems, in our study agreeableness ( $\beta = .13, p < .01$ ) and marital status ( $\beta = .08, p < .05$ ) were modestly associated with higher current drinking. The final multivariate  $R^2$  was .55. **CONCLUSIONS:** The pattern of associations suggests the importance of the social aspects of drinking for drinking decisions. Existing brief interventions will need to be tailored to a contextualized psychosocial model for medical patients with HCV and AUDIT scores  $\leq 10$  to optimize effectiveness. Such future interventions should emphasize the potential medical hazards of drinking for persons with HCV, the maintenance of social relationships in the absence of alcohol use, and strategies for building confidence for resisting drinking in specific situations.

**Occult HCV or delayed viral clearance from lymphocytes of Chronic HCV genotype 3 patients after interferon therapy.** Muazzam AG, Qureshi S, Mansoor A, et al. Genet Vaccines Ther. 2011 Sep 6;9(1):14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21892969>

**BACKGROUND:** A recently discovered occult HCV entity reported by various investigators seems to be highly controversial. Especially, the clinical significance of these findings remains uncertain. For optimal outcome of antiviral therapy, investigation of occult HCV needs a broad-

based probe in order to investigate the results of viral therapy and its host/viral interaction. The current study was aimed at determining the prevalence of occult HCV in peripheral blood lymphocytes of predominantly genotype 3 HCV-infected patients after completion of antiviral therapy and to investigate long term outcomes in the presence or absence of PBMC positivity. **METHOD:** A total of 151 chronic, antiHCV and serum RNA-positive patients were enrolled in the study. Patients with a complete virological response at the end of treatment were screened for the presence of viral RNA in their PBMCs and were followed for up to one year for the presence of serum and PBMC viral genomic RNA. **RESULTS:** Out of 151 patients, 104 (70%) responded to the prescribed interferon treatment and showed viral-clearance from serum. These were screened for the presence of genomic RNA in their PBMCs. Sixteen samples were PBMC-positive for viral RNA at the end of treatment (EOT). All these patients had also cleared the virus from peripheral blood cells after the 6-12 month follow-up study. **CONCLUSION:** True occult hepatitis C virus does not exist in our cohort. Residual viremia at the EOT stage merely reflects a difference in viral kinetics in various compartments that remains a target of immune response even after the end of antiviral therapy and is eventually cleared out at the sustained viral response (SVR).

**Efficacy of the Protease Inhibitor BI 201335, Polymerase Inhibitor BI 207127, and Ribavirin in Patients with Chronic HCV infection.** Zeuzem S, Asselah T, Angus P, et al. Gastroenterology. 2011 Sep 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21925126>

**BACKGROUNDS & AIMS:** Therapeutic regimens are being developed for patients with hepatitis C virus (HCV) infection that do not include the combination of peginterferon alfa and ribavirin. We investigated the antiviral effect and safety of BI 201335 (an inhibitor of the NS3/4A protease) and BI 207127 (an inhibitor of the NS5B non-nucleoside polymerase) with ribavirin. **METHODS:** Thirty-two treatment-naïve patients with chronic HCV genotype-1 infection were randomly assigned to groups that were given 400 mg or 600 mg BI 207127, 3 times each day (TID), plus 120 mg BI 201335 once daily and 1000-1200 mg ribavirin per day for 4 weeks. The primary efficacy endpoint was virological response (HCV RNA <25 IU/mL at week 4). Thirty-two patients received treatment; 31 completed all 4 weeks of assigned combination therapy. **RESULTS:** In the group given BI 207127 400 mg TID, the rates of virologic response were 47%, 67%, and 73% at days 15, 22, and 29; a higher rate of response was observed in patients with genotype-1b, compared with genotype-1a infections. In the group given BI 207127 600 mg TID, the rates of virologic response were 82%, 100%, and 100%, respectively, and did not differ among genotypes. One patient in the group given 400 mg TID had virologic breakthrough ( $\geq 1$  log<sub>10</sub> rebound in HCV RNA) at day 22. The most frequent adverse events were mild gastrointestinal disorders, rash, and photosensitivity. There were no severe or serious adverse events; no patients discontinued therapy prematurely. **CONCLUSIONS:** The combination of the protease inhibitor BI 201335, the polymerase inhibitor BI 207127, and ribavirin has rapid and strong activity against HCV genotype-1 and does not cause serious adverse events.

**Female patients in fertile age with chronic hepatitis C, easy genotype, and persistently normal transaminases have a 100% chance to reach a sustained virological response.**

Floreani A, Cazzagon N, Boemo DG, et al. Eur J Gastroenterol Hepatol. 2011 Sep 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21915057>

**BACKGROUND:** Patients with chronic hepatitis C and persistently normal alanine transaminase levels have recently been included in the guidelines for antiviral treatment. **AIM:** To evaluate the efficacy of PEG-interferon  $\alpha$ -2a and weight-based ribavirin doses in patients with these characteristics in a single Italian centre. **MATERIALS AND METHODS:** Patients with chronic hepatitis C and at least three normal alanine transaminase values over a 12-month period were offered a treatment with PEG-interferon  $\alpha$ -2a 180 mg/week and ribavirin (800 mg/day for weight <60 kg; 1000 mg/day for weight >60 and <75 kg; 1200 mg/day for weight >75 kg) for 24 weeks (according to genotype 2 or 3) or for 48 weeks (according to genotype 1 or 4). Each patient at baseline underwent liver stiffness (LS) examination using Fibroscan. Data were analysed according to the intention-to-treat criteria. **RESULTS:** A total of 227 patients (55 men, 172 women) were enrolled into the study: 65 (28.6%) had genotype 1, 144 (63.4%) genotype 2, nine (4.0%) genotype 3 and nine (4.0%) genotype 4. Patients with genotype 2 or 3 (N=153 with easy genotypes) were allocated in group 1 and those with genotype 1 or 4 (N=74 with difficult genotypes) in group 2. According to the LS measurement, patients were classified as follows: 159 (70.0%) presented absent or mild fibrosis (LS=2.5-7.0 kPa), 61 (26.9%) patients had significant fibrosis (LS=7.1-9.5) and seven (3.1%) patients had severe fibrosis (LS >9.6). Twelve patients (5.3%) dropped out within 4 months because of side-effects, whereas 215 patients completed the study. Overall, 13 patients were considered nonresponders (5.7%) and six patients (2.6%) were relapsers to the therapy. The sustained virological response (SVR) rate was 85.4% and it was higher in 'easy' genotypes (2 or 3) compared with 'difficult' genotypes (1 or 4) (92.2 vs. 74.3%, P<0.001). No statistical difference was found in the SVR rate between patients presenting absent or mild fibrosis as against those with significant fibrosis. Multivariate analysis, including factors correlated with SVR, showed that easy genotype and female sex are significantly associated with a SVR. **CONCLUSION:** Patients with chronic hepatitis C and persistently normal transaminases have an 85.4% chance to clear the virus with conventional antiviral treatment. Female patients in fertile age with easy genotypes have a 100% chance to reach a SVR.

**Response-guided telaprevir combination treatment for hepatitis C virus infection.** Sherman KE, Flamm SL, Afdhal NH, et al. N Engl J Med. 2011 Sep 15;365(11):1014-24.

<http://www.ncbi.nlm.nih.gov/pubmed/21916639>

**BACKGROUND:** Patients with chronic infection with hepatitis C virus (HCV) genotype 1 often need 48 weeks of peginterferon-ribavirin treatment for a sustained virologic response. We designed a noninferiority trial (noninferiority margin, -10.5%) to compare rates of sustained virologic response among patients receiving two treatment durations. **METHODS:** We enrolled patients with chronic infection with HCV genotype 1 who had not previously received treatment. All patients received telaprevir at a dose of 750 mg every 8 hours, peginterferon alfa-2a at a dose of 180  $\mu$ g per week, and ribavirin at a dose of 1000 to 1200 mg per day, for 12 weeks (T12PR12), followed by peginterferon-ribavirin. Patients who had an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) were randomly assigned after week

20 to receive the dual therapy for 4 more weeks (T12PR24) or 28 more weeks (T12PR48). Patients without an extended rapid virologic response were assigned to T12PR48. **RESULTS:** Of the 540 patients, a total of 352 (65%) had an extended rapid virologic response. The overall rate of sustained virologic response was 72%. Among the 322 patients with an extended rapid virologic response who were randomly assigned to a study group, 149 (92%) in the T12PR24 group and 140 (88%) in the T12PR48 group had a sustained virologic response (absolute difference, 4 percentage points; 95% confidence interval, -2 to 11), establishing noninferiority. Adverse events included rash (in 37% of patients, severe in 5%) and anemia (in 39%, severe in 6%). Discontinuation of all the study drugs was based on adverse events in 18% of patients overall, as well as in 1% of patients (all of whom were randomly assigned) in the T12PR24 group and 12% of the patients randomly assigned to the T12PR48 group ( $P < 0.001$ ).

**CONCLUSIONS:** In this study, among patients with chronic HCV infection who had not received treatment previously, a regimen of peginterferon-ribavirin for 24 weeks, with telaprevir for the first 12 weeks, was noninferior to the same regimen for 48 weeks in patients with undetectable HCV RNA at weeks 4 and 12, with an extended rapid virologic response achieved in nearly two thirds of patients.

**Relationship between adherence to hepatitis C virus therapy and virologic outcomes: a cohort study.** Lo Re V 3rd, Teal V, Localio AR, Amorosa VK, Kaplan DE, Gross R. *Ann Intern Med.* 2011 Sep 20;155(6):353-60.

<http://www.ncbi.nlm.nih.gov/pubmed/21930852>

**BACKGROUND:** Adherence to therapy with pegylated interferon and ribavirin for hepatitis C virus (HCV) infection has been incompletely examined. **OBJECTIVE:** To evaluate the relationship between adherence to HCV therapy and early and sustained virologic response, assess changes in adherence over time, and examine risk factors for nonadherence. **DESIGN:** Retrospective cohort study. **SETTING:** National Veterans Affairs Hepatitis C Clinical Case Registry. **Patients:** 5706 HCV-infected patients (genotypes 1, 2, 3, or 4) with at least 1 prescription for both pegylated interferon and ribavirin between 2003 and 2006 and HCV RNA results before and after treatment initiation. **MEASUREMENTS:** Adherence was calculated over 12-week intervals by using pharmacy refill data. End points included early virologic response (decrease of  $\geq 2$  log<sub>10</sub> HCV RNA at 12 weeks) and sustained virologic response (undetectable HCV RNA 24 weeks after the end of treatment). **RESULTS:** Early virologic response increased with higher levels of adherence to ribavirin therapy over the initial 12 weeks (patients with HCV genotype 1 or 4, 25 of 68 [37%] with  $\leq 40\%$  adherence vs. 1367 of 2187 [63%] with 91% to 100% adherence [ $P < 0.001$ ]; patients with HCV genotype 2 or 3, 12 of 18 [67%] with  $\leq 40\%$  adherence vs. 651 of 713 [91%] with 91% to 100% adherence [ $P < 0.001$ ]). Among patients with HCV genotype 1 or 4, sustained response increased with higher adherence to ribavirin therapy over the second, third, and fourth 12-week intervals. Results were similar for adherence to interferon therapy. Mean adherence to therapy with interferon and ribavirin decreased by 3.4 and 6.6 percentage points per 12-week interval, respectively ( $P$  for trend  $< 0.001$  for each drug). Patients who received growth factors or thyroid medications during treatment had higher mean adherence to antiviral therapy. **LIMITATION:** This was an observational study without standardized timing for outcome measurements. **CONCLUSION:** Early and sustained virologic responses increased with higher levels of adherence to interferon and ribavirin therapy. Adherence to therapy with both antivirals decreased over time, but more so for ribavirin.

**Low risk for hepatitis C seroconversion in methadone maintenance treatment.** Peles E, Schreiber S, Rados V, Adelson M. *J Addict Med.* 2011 Sep;5(3):214-20.

<http://www.ncbi.nlm.nih.gov/pubmed/21844836>

**OBJECTIVES:** To study the risk factors for seroconversion to hepatitis C virus (HCV) infection since admission to methadone maintenance treatment (MMT) and to characterize the seronegative admitted group. **METHODS:** All 657 patients admitted to our MMT clinic in Tel Aviv, Israel, between 1993 and 2008 were prospectively followed up. Those who were HCV negative (n = 271) with >1 HCV tests (n = 207) were included for seroconversion analyses. **RESULTS:** Proportions of ever drug injectors, benzodiazepine abuse, and former USSR immigrants were higher among HCV sera-positive versus sera-negative patients on admission to MMT. The incidence of HCV seroconversion in MMT was 2/100 person years [py] (25 seroconversions, 1133.9 py). Seroconversion rates were higher among 44 younger patients (<30 years: 9.6/100 vs 1.4/100 py, P < 0.0005), among 103 patients with positive urine results to benzodiazepines (3.6/100 vs 1/100 py, P = 0.005), among 118 patients who injected the drugs (3.9/100 vs 1/100 py, P = 0.003), and among 43 patients who dropped out and were readmitted to the MMT (4.3/100 vs 1.7/100 py, P = 0.04). There was a trend of higher seroconversion among 61 females (P = 0.1), among 62 patients with no children (P = 0.1), and among those having hepatitis B antigen (n = 7; P = 0.09). Variables that predicted seroconversion were drug injection, benzodiazepine abuse, and being younger at admission to MMT. Being a former USSR immigrant did not predict seroconversion. **CONCLUSIONS:** The HCV seroconversion rate of patients in MMT is low, also, for former USSR immigrants. The predictors for seroconversion were only admission variables (younger age at admission to MMT, ever drug injector, and having positive urine to benzodiazepines at MMT admission). Specific intervention to eliminate seroconversion is needed for these high-risk groups.

**Impact of Hispanic or Asian Ethnicity on the Treatment Outcomes of Chronic Hepatitis C: Results From the WIN-R Trial.** Hu KQ, Freilich B, Brown RS, Brass C, Jacobson IM. *J Clin Gastroenterol.* 2011 Sep;45(8):720-6.

<http://www.ncbi.nlm.nih.gov/pubmed/21836471>

**BACKGROUND AND AIMS:** African American ethnicity is a well-described negative predictor of treatment outcome for chronic hepatitis C (CHC); however, less is known about the influence of Hispanic and Asian ethnicity. The aim of this subanalysis of the Weight-based Dosing of PegInterferon  $\alpha$ -2b and Ribavirin (WIN-R) study was to assess the impact of Asian (n=118), Hispanic (n=289), and white (n=3919) ethnicity on CHC treatment outcomes. **METHODS:** WIN-R was an investigator-initiated trial in which patients with CHC received pegylated interferon  $\alpha$ -2b (1.5  $\mu$ g/kg/wk) plus a fixed ribavirin dose (800 mg/d) or a weight-based ribavirin dose (800 to 1400 mg/d) for 24 or 48 weeks. **RESULTS:** Sustained virologic response was higher in Asian patients than in white patients (56% vs 46%, P=0.041), and higher in Asian and white patients than in Hispanic patients (56% vs 35%, P=0.0001; and 46% vs 35%, P=0.0002, respectively). In genotype 1 patients, sustained virologic response was higher in white and Asian patients than in Hispanic patients (36% and 45% vs 25%, P<0.001 for both comparisons); however, in genotype 2/3 patients, there were no significant differences among ethnic groups. Psychiatric adverse events were less common and anemia was more common in Asians than in white or Hispanic patients. Ribavirin dose reductions were less frequent in Hispanic patients than in white patients, whereas pegylated interferon $\alpha$ -2b dose reductions were

more common in white patients than Hispanic patients. **CONCLUSION:** These observations highlight the importance of ethnicity as an integral component of the tailored treatment approach to CHC.

**Outcomes of chronic hepatitis C therapy in patients treated in community versus academic centres in Canada: Final results of APPROACH (A Prospective study of Peginterferon alfa-2a and Ribavirin at Academic and Community Centres in Canada).** Myers RP, Cooper C, Sherman M, et al. *Can J Gastroenterol.* 2011 Sep;25(9):503-10.

<http://www.ncbi.nlm.nih.gov/pubmed/21912762>

**BACKGROUND:** In patients chronically infected with the hepatitis C virus (HCV), it is not established whether viral outcomes or health-related quality of life (HRQoL) differ between individuals treated at academic or community centres. **METHODS:** In the present observational study, adults with chronic HCV were treated with peginterferon alfa-2a 180 µg/week plus ribavirin at 45 Canadian centres (16 academic, 29 community). The primary efficacy end point was sustained virological response (SVR). Other outcome measures included HRQoL (assessed using the 36-item Short-Form Health Survey), health resource use, and workplace productivity and absences within a 60-day interval. **RESULTS:** In treatment-naïve patients infected with HCV genotype 1, significantly higher SVR rates were achieved in those treated at academic (n=54) compared with community (n=125) centres (52% versus 32% [P=0.01]), although rates of dosage reduction and treatment discontinuation were similar across settings. SVR rates among patients infected with genotype 2/3 were similar between academic (n=59) and community (n=100) centres (64% versus 67% [P=0.73]). Following antiviral therapy, patients with genotype 1 who achieved an SVR (n=67) had significantly higher mean scores on the physical (P=0.005) and mental components of the 36-item Short-Form Health Survey (P=0.043) compared with those without an SVR (n=111). In contrast, HRQoL scores were similar in HCV genotype 2/3 patients with and without an SVR. There were no differences in workplace productivity or absences between patients with and without an SVR. The most frequently used health care resources by all patients were visits and phone calls to hepatitis nurses, and general practice or walk-in clinics. **CONCLUSION:** Patients infected with HCV genotype 1 achieved higher SVR rates when treated at academic rather than community centres in Canada. The reasons for this difference require additional investigation.

**Association of hepatitis C virus infection and malnutrition-inflammation complex syndrome in maintenance hemodialysis patients.** Tsai HB, Chen PC, Liu CH, et al. *Nephrol Dial Transplant.* 2011 Sep 5. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21896499>

**BACKGROUND:** Patients undergoing maintenance hemodialysis (MHD) have a significantly higher prevalence of hepatitis C virus (HCV) infection and malnutrition-inflammation complex syndrome (MICS). In the present study of Taiwanese MHD patients, we determined the clinical characteristics and influence of HCV infection on MICS by calculation of the malnutrition-inflammation score (MIS). **METHODS:** This was a prospective longitudinal study performed at a single hemodialysis (HD) center in Taiwan from September 2007 through March 2008. The study enrolled 58 patients (38%) in the active HCV group and 95 patients (62%) in the non-HCV group. The two or three weekly HD sessions of all patients were followed for 7 months. The MIS was assessed using 10 components, 7 from the conventional subjective global assessment of nutrition and 3 additional elements, body mass index, serum albumin and total iron-binding

capacity. **RESULTS:** HD vintage and total MIS score were greater in patients with active HCV. The active HCV group had significantly longer dialysis vintage and lower total cholesterol but higher total MIS score than the non-HCV group. The MIS 5 score, a measure of major comorbid conditions (including number of years on dialysis), was also significantly higher in the active HCV group. **CONCLUSION:** MHD patients with active HCV infections have more severe MICS-associated metabolic and physiological disease than MHD patients without active HCV infection.

**Low doses of the novel caspase-inhibitor GS-9450 leads to lower caspase-3 and -8 expression on peripheral CD4+ and CD8+ T-cells.** Arends JE, Hoepelman AI, Nanlohy NM, et al. *Apoptosis*. 2011 Sep;16(9):959-66. doi: 10.1007/s10495-011-0620-2.

<http://www.ncbi.nlm.nih.gov/pubmed/21667042>

Chronic hepatitis C virus (HCV) infection is characterized by increased rates of apoptotic hepatocytes and activated caspases have been shown in HCV-infected patients. GS-9450, a novel caspase-inhibitor has demonstrated hepatoprotective activity in fibrosis/apoptosis animal models. This study evaluated the effects of GS-9450 on peripheral T-cell apoptosis in chronic HCV-infected patients. As sub study of the GS-US-227-0102, a double-blind, placebo-controlled phase 2a trial evaluating the safety and tolerability of GS-9450, apoptosis of peripheral CD4+ and CD8+ T-cells was measured using activated caspase-3, activated caspase-8 and CD95 (Fas). Blood samples were drawn at baseline, day 14 after therapy and at 5 weeks off-treatment follow-up in the first cohort of 10 mg. In contrast to the placebo-treated patients, GS-9450 caused a median of 46% decrease in ALT-values from baseline to day 14 in all treated patients (median of 118-64 U/l) rising again to a median of 140 U/l (19%) at 5 weeks off-treatment follow-up. In GS9450-treated patients, during treatment and follow-up, percentages of activated caspase-3+ and caspase-8 expression tended to decrease, in contrast to placebo-treated patients. Interestingly, compared to healthy controls, higher percentages of caspase-3 and caspase-8 positive CD4+ and CD8+ T-cells were demonstrated in HCV-infected patients at baseline. Decreased ALT-values were observed in all HCV-infected patients during treatment with low dose of the caspase-inhibitor GS-9450 accompanied by a lower expression of caspase-3 and -8 on peripheral T-cells. Furthermore, at baseline percentages of activated caspase-3, activated caspase-8 and CD95+ T-cells were higher in chronic HCV-infected patients compared to healthy controls.

**The determination of GGT is the most reliable predictor of nonresponsiveness to interferon-alpha based therapy in HCV type-1 infection.** Weich V, Herrmann E, Chung TL, et al. *J Gastroenterol*. 2011 Sep 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21912897>

**BACKGROUND:** The critical analysis of baseline factors has been found to be useful to predict virologic nonresponse (NR), relapse, or sustained virologic response (SVR) in patients infected with hepatitis C virus (HCV) who receive antiviral therapy. In the present retrospective study we tried to find out whether gamma-glutamyltranspeptidase (GGT) may be one of the baseline factors which are of special predictive power. We analyzed, in patients with different treatment outcomes, the predictive power of established baseline factors either in combination with GGT or by evaluating the predictive value of GGT independently. **METHODS:** Individual data from 632 patients chronically infected with HCV type 1 (n = 561) or type 2/3 (n = 71) were analyzed. All patients had received their first course of antiviral therapy and were treated with pegylated

interferon  $\alpha$ -2a or -2b plus ribavirin. **RESULTS:** In patients with HCV type 1, a multivariate multinomial logistic regression analysis identified low GGT ( $p < 0.0001$ ), high cholesterol ( $p < 0.0001$ ), age  $\leq 40$  years ( $p < 0.0001$ ), high alanine aminotransferase ( $p = 0.0006$ ), low viremia ( $p = 0.0014$ ), and absence of cirrhosis ( $p = 0.0164$ ) as independent predictors. While these baseline factors heralded improved virologic response, high GGT, in contrast, was significantly associated with NR ( $p < 0.0001$ ). A strong correlation was found between  $\log(10)$  GGT and a scoring variable S ( $r = -0.26$  for prediction of SVR,  $p < 0.001$ ;  $r = 0.11$  for prediction of NR,  $p = 0.016$ ) summarizing predictive information from other baseline factors. **CONCLUSIONS:** These findings prove the predictive sensitivity of GGT as an independent indicator of nonresponsiveness even at levels that are slightly above the normal range. This new predictive parameter may help to improve individualized therapy in HCV type-1 infection.

**Response to antiviral therapy in patients with genotype 3 chronic hepatitis C: fibrosis but not race encourages relapse.** Shoeb D, Rowe IA, Freshwater D, et al. Eur J Gastroenterol Hepatol. 2011 Sep;23(9):747-53.

<http://www.ncbi.nlm.nih.gov/pubmed/21691208>

**BACKGROUND AND AIMS:** We completed a retrospective analysis of patients with genotype 3 hepatitis C virus (HCV) undergoing therapy in four UK centres with large populations of patients from the Indian subcontinent. **MATERIALS AND METHODS:** Notes on all patients treated with pegylated interferon and ribavirin were reviewed and factors that influenced the response were examined. **RESULTS:** Six hundred and four patients with genotype 3 HCV were studied, of whom 299 were Asians. Median age was 43 years, 65% were men and 24% had cirrhosis. Overall, 457 (76%) patients achieved sustained virological response (SVR). By multivariable analysis it was found that ethnicity was not associated with an impaired response but age, cirrhosis and diabetes were significantly associated with a reduced SVR, the likelihood of a response was reduced by 25% per 10-year increment in age, by 59% among individuals with cirrhosis and by 62% among individuals with diabetes mellitus. Most patients who did not achieve an SVR relapsed (15%) rather than failing to achieve an end of treatment response. **CONCLUSION:** The response to antiviral therapy in genotype 3 HCV is not affected by South Asian (vs. Caucasian) ethnicity, but age, cirrhosis and diabetes reduce the response. Treatment failure most often is due to relapse.

**Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in Asian patients.** Sinn DH, Kim YJ, Lee ST, et al. J Gastroenterol Hepatol. 2011 Sep;26(9):1374-9. doi: 10.1111/j.1440-1746.2011.06744.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21501223>

**BACKGROUND AND AIMS:** A single nucleotide polymorphism near the interleukin-28B (IL28B) gene has been shown to predict hepatitis C virus (HCV) treatment response. We aim to determine the role of the IL28B genotype in Asian patients. **METHODS:** A total of 118 patients (all Korean, 55 patients with genotype 1 infection and 63 patients with genotype 2 infection) were consecutively enrolled and analyzed. **RESULTS:** The sustained virological response (SVR) rate was 74% (87/118), while 26 patients (22%) relapsed and five patients were non-responders (4%). For rs8099917, the frequencies of major homozygotes (TT), heterozygotes (GT), and minor homozygotes (GG) were 0.85, 0.14 and 0.01, respectively. Of the 55 patients with HCV genotype 1 infection, the SVR rate was 67% and 44% ( $P = 0.19$ ) and the non-response rate was 2% and 22% ( $P = 0.015$ ) for the major allele and minor or hetero allele, respectively. Of

the 63 patients with HCV genotype 2 infection, the SVR rate was 80% and 100% ( $P = 0.13$ ) and the non-response rate was 4% and 0% ( $P = 0.55$ ) for major allele and hetero allele, respectively. **CONCLUSIONS:** The IL28B genotype may help identify non-responding patients in HCV genotype 1, but not in HCV genotype 2. Because of the high frequency of favorable alleles and the low frequency of non-response, the IL28B polymorphism may play a smaller role in Asian patients.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**Alteration of hepatic nuclear receptor-mediated signaling pathways in HCV patients with and without a history of alcohol drinking.** Wu C, Gilroy R, Taylor R, et al. *Hepatology*. 2011 Sep 2. doi: 10.1002/hep.24645. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21898497>

The current study tests a hypothesis that nuclear receptor signaling is altered in chronic hepatitis C patients and that the altered pattern is alcohol drinking history specific. The expression of a panel of more than 100 genes encoding nuclear receptors, co-regulators, and their direct/indirect targets was studied in human livers. (1) Gene expression pattern was compared between 15 normal donor livers and 23 HCV genotype 1 positive livers from patients without a drinking history (age, gender, and BMI matched). HCV infection increased the expression of nuclear receptors small heterodimer partner and constitutive androstane receptor (CAR) as well as genes involved in fatty acid trafficking, bile acid synthesis and uptake, and inflammatory response. However, the expression of retinoid x receptor (RXR)  $\alpha$ , peroxisomal proliferator activated receptor (PPAR)  $\alpha$  and  $\beta$  as well as SREBP-1c was decreased in HCV-infected livers. (2) Gene expression pattern was compared in chronic hepatitis C patients with (21) and without (13) a drinking history. Alcohol drinking increased the expression of genes involved in fatty acid uptake, trafficking, and oxidation, but decreased the expression of genes responsible for gluconeogenesis. These changes were consistent with reduced fasting plasma glucose levels and altered expression of upstream regulators that include RXR $\alpha$ , PPAR $\alpha$ , and CAR. (3) The mRNA levels of fibroblast growth factor 21, IL-10, and fatty acid synthase, which are all regulated by nuclear receptors, showed independent correlation with hepatic HCV RNA levels. **Our findings suggest** that those genes and pathways that showed altered expression could potentially be therapeutic targets for HCV infection and/or alcohol drinking-induced liver injury.

**T-lymphocyte subsets in peripheral blood and liver tissue of patients with chronic hepatitis B and C.** Dimitropoulou D, Karakantza M, Tsamandas AC, et al. *In Vivo*. 2011 Sep-Oct;25(5):833-40.

<http://www.ncbi.nlm.nih.gov/pubmed/21753143>

**AIM:** To evaluate the immune response in peripheral blood and liver tissue, through the measurement of T-cell subsets, in patients with chronic hepatitis B (CHB) and C (CHC).

**PATIENTS AND METHODS:** Thirty-four patients with CHB (21 with active HBV infection and 13 inactive HBV carriers) and 20 patients with CHC were included in the study. We also evaluated 21 biopsies from patients with active CHB infection and 20 patients with CHC. We measured CD3, CD4, CD8 and CD4/CD8 ratio in peripheral blood and liver tissue. **RESULTS:** We found no differences in the numbers of all T-lymphocyte subpopulations between patients with active HBV infection and inactive carriers. We found a significant increase in the absolute numbers of CD3(+), CD4(+) and CD8(+) T-lymphocytes in CHC compared to CHB patients

( $p=0.005$ ,  $p=0.034$  and  $p<0.0001$  respectively). There was a significant increase in the number of CD3(+) and CD8(+) T-lymphocytes in the area of portal tracts ( $p=0.012$  and  $p=0.009$  respectively) and lobules ( $p=0.011$  and  $p=0.01$  respectively) in patients with CHC compared to those with CHB. In both groups there was a direct correlation between CD3(+) cells in portal tracts and HAI score ( $r=0.783$ ,  $p=0.008$ ), while we noted a correlation between CD8(+) cells in portal tracts and HAI score only in patients with CHC. Interface hepatitis correlated to CD3(+) cells in lobules of patients with CHC and CHB but a direct relationship between CD8(+) cells and HAI score was found only in those with CHC. **CONCLUSION:** Insufficient cellular immune response is critical for the ineffective virus clearance and liver damage in chronic hepatitis B, while in chronic hepatitis C, immune response, as represented by CD8(+) T-cells, is present in the peripheral blood and the liver. However, there is an immunological escape of HCV, which seems to survive in the presence of an adequate immune response. The significant correlation between portal and periportal CD8(+) T-lymphocyte expression and interface hepatitis may be considered evidence of the occurrence of cytotoxic immune-mediated toxicity.

**Prohibitin is overexpressed in Huh-7-HCV and Huh-7.5-HCV cells harboring in vitro transcribed full-length hepatitis C virus RNA.** Dang SS, Sun MZ, Yang E, et al. *Virology*. 2011 Sep 6;83(1):424. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21896168>

**BACKGROUND:** Currently, up-regulated proteins and apoptosis in hepatitis C is a hot topic in exploring the pathogenic mechanism of Hepatitis C Virus(HCV). Some recent studies shows that prohibitin is overexpressed in cells expressing HCV core proteins, and up-regulated prohibitin is also found in human hepatoma cell line HCC-M, lung cancer, prostate cancer, and other cancers. Prohibitin is an important member of the membrane protein superfamily, and it plays a role of molecular chaperones in mitochondrial protein stability. Meanwhile, it has a permissive action on tumor growth or acts as an oncosuppressor. Based on our previously established the in vitro HCV cell-culture system (HCVcc), here we aimed to investigate the different expression profiles of prohibitin in Huh-7-HCV and Huh-7.5-HCV cells; **METHODS:** The total cellular RNA of Huh-7, Huh-7.5, Huh-7-HCV and Huh-7.5-HCV cells were extracted, and then the first-strand cDNA was reversely transcribed. The expression of prohibitin at the mRNA level was assessed by real-time PCR with GAPDH as the control. Furthermore, the expression of prohibitin at the protein level was evaluated by western blot with GAPDH as an internal control; **RESULTS:** Our results of real-time PCR showed that the mRNA expression level of prohibitin in Huh-7-HCV cells was 2.09 times higher than that in Huh-7 cells, while, the mRNA level of prohibitin in Huh-7.5-HCV cells was 2.25 times higher than that in Huh-7.5 cells. The results of western blot showed that the protein expression level of prohibitin in Huh-7-HCV cells was 2.38 times higher than that in Huh-7 cells, while the protein expression of prohibitin in Huh-7.5-HCV cells was 2.29 times higher than that in Huh-7.5 cells; **CONCLUSIONS:** The expression of prohibitin was relatively high in Huh-7-HCV and Huh-7.5-HCV cells harboring in vitro transcribed full-length HCV RNA.

**Antiviral combination therapy with peginterferon and ribavirin does not induce a therapeutically resistant mutation in the HCV core region regardless of genetic polymorphism near the IL28B gene.** Toyoda H, Kumada T, Hayashi K, et al. *J Med Virol*. 2011 Sep;83(9):1559-64. doi: 10.1002/jmv.22145.

<http://www.ncbi.nlm.nih.gov/pubmed/21739446>

An association has been reported between genetic polymorphism near IL28B gene and the prevalence of mutation of hepatitis C virus (HCV) core region residue 70, both of which have been associated with a lack of virologic response to antiviral combination therapy with peginterferon (PEG-IFN) and ribavirin. This study investigated whether PEG-IFN/ribavirin combination therapy induces amino acid (AA) mutation at residue 70 of HCV and whether genetic polymorphism near IL28B gene affects it. AA substitutions at residue 70 of the HCV core region were measured and compared before and after combination therapy in 65 non-responders and 88 relapsers to the combination therapy. In three patients in whom both wild-type AA (arginine) and mutant-type AA (glutamine or histidine) were detected at residue 70 before treatment, only mutant-type AA was identified after treatment. In two patients who had wild-type AA solely before treatment, both wild-type and mutant-type AAs were identified at residue 70 after treatment. In five patients, in whom the AA had changed at residue 70 between before and after treatment, four patients carried the TT genotype at a polymorphic locus (rs8099917) near the IL28B gene and one carried the TG/GG genotype. No difference was found in the prevalence of this change of AA at residue 70 between the TT and the TG/GG genotype. Antiviral combination therapy with PEG-IFN and ribavirin does not appear to induce mutation of HCV core region residue 70 regardless of genetic polymorphism near the IL28B gene in Japanese patients infected with HCV genotype 1b.

**Cell-to-Cell Contact with Hepatitis C Virus-Infected Cells Reduces Functional Capacity of Natural Killer Cells.** Yoon JC, Lim JB, Park JH, Lee JM. J Virol. 2011 Sep 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21937646>

The distinct feature of hepatitis C virus (HCV) infection is high incidence of chronicity. The reason for chronic HCV infection has been actively investigated, and impairment of innate and adaptive immune responses against HCV is proposed as a plausible cause. Whereas functional impairment of HCV-specific T cells is well characterized, the role and functional status of natural killer (NK) cells in each phase of HCV infection are still elusive. We therefore investigated whether direct interaction between NK cells and HCV-infected cells modulates NK cell function. HCV-permissive human hepatoma cell lines were infected with cell-culture-generated HCV virions and cocultured with primary human NK cells. Cell-to-cell contact between NK cells and HCV-infected cells reduced NK cells' capacity to degranulate and lyse target cells, especially in the CD56(dim) NK cell subset. The decrease in degranulation capacity was correlated with downregulated expression of NK cell activating receptors such as NKG2D and NKp30 on NK cells. The ability of NK cells to produce and secrete interferon (IFN)- $\gamma$  also diminished after exposure to HCV-infected cells. The decline of IFN- $\gamma$  production was consistent with the reduction of NK cell degranulation. In conclusion, cell-to-cell contact with HCV-infected cells negatively modulated functional capacity of NK cells, and the inhibition of NK cell function was associated with downregulation of NK activating receptors on NK cell surfaces. These observations suggest that direct cell-to-cell interaction between NK cells and HCV-infected hepatocytes may impair NK cell function in vivo and thereby contribute to the establishment of chronic infection.

**Prevalence of immunity to hepatitis viruses A and B in a large cohort of HIV/HCV-coinfected patients, and factors associated with HAV and HBV vaccination.** Winnock M, Bani-Sadr F, Pambrun E, et al. *Vaccine*. 2011 Sep 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21920402>

Hepatitis A (HAV) and B (HBV) vaccination is strongly recommended for HIV-infected patients, especially those with hepatitis C coinfection. The aim of this study was to determine the prevalence of antibodies directed against HAV and HBV in a large cohort of HIV/HCV-coinfected patients, and to identify factors associated with HAV and HBV vaccination.

**PATIENTS AND METHODS:** We studied 1175 HIV/HCV-coinfected patients enrolled in the ANRS CO13 HEPAVIH cohort, whose HAV and HBV serostatus was known. **RESULTS:** 1056 patients (89.9%) have been tested for anti-HBc IgG, anti-HBs, and HbsAg. Only 10.9% of patients had received HBV vaccination and 70% of the patients with no HBV immunity (231/265) had never received HBV vaccination. In multivariate analysis, male sex (OR 2.0, 95% CI 1.1-3.8; p=0.02), a higher level of school education (OR 2.5, 95% CI 1.3-4.5; p=0.003), a higher CD4 cell nadir (OR 1.05, 95% CI 1.009-1.103; p=0.018) and no cirrhosis (OR 2.7, 95% CI 1.2-6.4; p=0.02) were associated with HBV vaccination. Only 368 patients (31.3%) were tested for immunity to HAV. Despite a frequent lack of HAV immunity (48.3%), a low rate of HAV vaccination (6%) was observed. In multivariate analysis, a higher level of school education (OR 3.6, 95% CI 1.03-12.4; p=0.045) was the only factor associated with HAV vaccination. HAV screening rates and HAV and HBV vaccination rates were low in this population of HIV/HCV-coinfected patients. The benefits of routine HAV and HBV screening, vaccination and post-vaccination testing should be emphasized.

**Hip bone geometry in HIV/HCV-co-infected men and healthy controls.** Walker Harris V, Sutcliffe CG, Araujo AB, et al. *Osteoporos Int*. 2011 Sep 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21901477>

People with both HIV and hepatitis C are more likely than those with HIV alone to have wrist, hip, and spine fractures. We compared hip strength between HIV/HCV-co-infected men and healthy men and found that HIV/HCV-co-infected men had decreased hip strength due to lower lean body mass. **INTRODUCTION:** Hepatitis C co-infection is a risk factor for fragility fracture among HIV-infected populations. Whether bone strength is compromised in HIV/HCV-co-infected patients is unknown. **METHODS:** We compared dual-energy x-ray absorptiometry (DXA)-derived hip geometry, a measure of bone strength, in 88 HIV/HCV-co-infected men from the Johns Hopkins HIV Clinic to 289 men of similar age and race and without HIV or HCV from the Boston Area Community Health Survey/Bone Survey. Hip geometry was assessed at the narrow neck, intertrochanter, and shaft using hip structural analysis. Lean body mass (LBM), total fat mass (FM), and fat mass ratio (FMR) were measured by whole-body DXA. Linear regression was used to identify body composition parameters that accounted for differences in bone strength between cohorts. **RESULTS:** HIV/HCV-co-infected men had lower BMI, LBM, and FM and higher FMR compared to controls (all p < 0.05). At the narrow neck, significant differences were observed between HIV/HCV-co-infected men and controls in bone mineral density, cross-sectional area, section modulus, buckling ratio, and centroid position. After adjustment for race, age, smoking status, height, and weight, only buckling ratio and centroid position remained significantly different between cohorts (all p < 0.05). Substituting LBM, FM,

and FMR for weight in the multivariate model revealed that differences in LBM, but not FM or FMR, accounted for differences in all narrow neck parameters between cohorts, except buckling ratio and centroid position. **CONCLUSION:** HIV/HCV-co-infected men have compromised hip strength at the narrow neck compared to uninfected controls, which is attributable in large part to lower lean body mass.

**Clinical variables identify seronegative HCV co-infection in HIV-infected individuals.**

Bharti AR, Letendre SL, Wolfson T, et al. J Clin Virol. 2011 Sep 14. [Epub ahead of print]  
<http://www.ncbi.nlm.nih.gov/pubmed/21924674>

**BACKGROUND:** A substantial number of people living with HIV (PLWH) are co-infected with Hepatitis C Virus (HCV) but have a negative screening HCV antibody test (seronegative HCV infection, or SN-HCV). **OBJECTIVE:** To identify a concise set of clinical variables that could be used to improve case finding for SN-HCV co-infection among PLWH. **STUDY DESIGN:** Two hundred HIV-infected participants of the CHARTER study were selected based on 7 clinical variables associated with HCV infection but were HCV seronegative. Data were analyzed using Fisher's exact tests, receiver-operating characteristic (ROC) curves, and logistic regression. **RESULTS:** Twenty-six (13%) participants had detectable HCV RNA. SN-HCV was associated with a history of IDU, elevated ALT and AST, low platelets, black ethnicity, and undetectable HIV RNA in plasma. Each of these clinical variables, except for abnormal AST, remained independently associated with SN-HCV in a multivariate logistic regression analysis. A composite risk score correctly identified SN-HCV with sensitivity up to 85% and specificity up to 88%. **CONCLUSIONS:** In a substantial minority of PLWH, seronegative HCV viremia can be predicted by a small number of clinical variables. These findings, after validation in an unselected cohort, could help focus screening in those at highest risk.

**Successful treatment of acute hepatitis C virus in HIV positive patients using the European AIDS Treatment Network guidelines for treatment duration.** Dorward J, Garrett N, Scott D, Buckland M, Orkin C, Baily G. J Clin Virol. 2011 Sep 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21924673>

**BACKGROUND:** The incidence of acute hepatitis C virus (HCV) in HIV-positive patients is rising. Recent studies summarized by the European AIDS Treatment Network (NEAT)(1) show that pegylated interferon alpha (PEG-IFN $\alpha$ ) and ribavirin can lead to a sustained virological response (SVR) in approximately 60-80% of patients. Controversy remains on when to start treatment and whether 24 or 48 weeks of treatment lead to better outcomes. **OBJECTIVES:** To assess the effectiveness of a treatment strategy for acute HCV infection in HIV-positive patients, in which patients with undetectable HCV RNA at 4 weeks (rapid virological response, RVR) receive 24 weeks, while those without receive 48 weeks of PEG-IFN $\alpha$  and ribavirin, as per the NEAT guidelines. **STUDY DESIGN:** A retrospective cohort study of HIV-positive patients diagnosed with acute HCV infection between December 2006 and May 2010. Those who received acute treatment with PEG-IFN $\alpha$  and ribavirin had HCV RNA levels monitored and outcomes evaluated. For patients who did not receive acute treatment, the reason for deferral and most recent available HCV RNA were recorded. **RESULTS:** Twenty-two patients received acute treatment with PEG-IFN $\alpha$  and ribavirin. Twelve patients achieved RVR and had 24 weeks treatment, 10 patients had no RVR and had 48 weeks treatment. Two patients discontinued treatment (due to adverse effects [AEs] and failure to suppress HCV RNA sufficiently at 12

weeks). All 20 patients who completed treatment had SVR. **CONCLUSION:** Our high SVR rate of 91% supports the new NEAT treatment duration recommendations.

**HIV and hepatitis C coinfection: pathogenesis: microbial translocation.** Page EE, Nelson M, Kelleher P. *Curr Opin HIV AIDS*. 2011 Sep 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21918438>

**PURPOSE OF REVIEW:** Human immune deficiency virus (HIV)-1 and hepatitis C virus (HCV) coinfecting individuals progress more rapidly to fibrosis than their HCV mono-infected counterparts. Increased microbial translocation in HIV-1/HCV coinfection may play an important role. **RECENT FINDINGS:** The mechanisms of accelerated liver fibrosis in HIV-1/HCV coinfection are complex. Products of microbial translocation may promote liver fibrosis either by direct interaction with Kupffer cells and hepatic stellate cells (HSCs) or indirectly via induction of systemic immune activation and activation-induced apoptotic cell death. HIV-1 enteropathy is associated with increased microbial translocation and systemic immune activation. Mechanisms that underlie increased microbial translocation include direct effects of HIV-1 infection on epithelial barrier function and alteration in intestinal permeability secondary to inflammatory cytokines and CD4 T-cell depletion. Risk of liver fibrosis is increased in HIV-1/HCV coinfection and associated with reduced CD4 T-cell counts and raised lipopolysaccharide levels and/or depletion of hepatic Kupffer cells. **SUMMARY:** Large-scale longitudinal clinical studies are needed to confirm the importance of microbial translocation in promotion of hepatic fibrosis. If microbial translocation is a significant contributory factor to hepatic fibrosis, targeted interventions against microbial products may improve clinical outcomes.

**HIV-1 co-infection and morphine co-exposure severely dysregulate HCV-induced hepatic pro-inflammatory cytokine release and free radical production: increased pathogenesis coincides with uncoordinated host-defenses.** El-Hage N, Dever SM, Fitting S, Ahmed T, Hauser KF. *J Virol*. 2011 Sep 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21900165>

Co-infection with human immunodeficiency virus type-1 (HIV-1) and hepatitis C virus (HCV) is a global pandemic that is more severe in injection drug users because they have a higher risk for acquiring both viruses. The roles of inflammatory cytokines and oxidative stress were examined in HIV-1 and HCV co-infected human hepatic cells. Morphine (the bioactive product of heroin), HIV-1 Tat and gp120(MN) proteins, and X4 HIV-1(LAI/IIIB) and R5 HIV-1(SF162) isolates were used to study the mechanisms of disease progression in HCV (JFH1) infected Huh7.5.1 cell populations. HCV increased tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) release, and augmented production of reactive oxygen species (ROS), nitric oxide (NO) and 3-nitrotyrosine (3-NT) in Huh7.5.1 cells. Morphine preferentially affected R5-tropic, but not X4-tropic, HIV-1 interactions with Huh7.5.1 cells. HIV-1 proteins or isolates increased cytokine release in HCV-infected cells, while adding morphine to co-infected cells caused complex imbalances, significantly disrupting cytokine secretion depending on the cytokine, morphine concentration, exposure duration, and particular pathogen involved. Production of ROS, NO and 3-NT increased significantly in HCV and HIV-1 co-infected cells, while exposure to morphine further increased ROS. The proteasome inhibitor MG132 significantly decreased oxyradicals, cytokine levels, and HCV protein levels. Our findings indicate that hepatic inflammation is increased by combined exposure to HCV and HIV-1, that the ubiquitin-proteasome system and NF- $\kappa$ B contribute to key aspects of the response, and that morphine further exacerbates the

disruption of host-defenses. **The results** suggest that opioid abuse, and HIV-1 co-infection each further accelerate HCV-mediated liver disease by dysregulating immune defenses.

**Management of end-stage liver disease in HIV/hepatitis C virus co-infection.** Spengler U. Curr Opin HIV AIDS. 2011 Sep 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21918437>

**PURPOSE OF REVIEW:** Highly active antiretroviral therapy has improved prognosis of HIV infection and substantially reduced the incidence of opportunistic diseases. However, hepatitis viruses and HIV share the same routes of transmission. Thus, chronic viral hepatitis is found frequently in HIV-infected patients. Antiretroviral drugs do not directly interact with the hepatitis C virus (HCV), so that end-stage liver disease (ESLD) in HCV/HIV co-infected patients has become a leading clinical problem in many co-infected patients. **RECENT FINDINGS:** This review summarizes up-to-date guidelines in the management of ESLD and specifically addresses issues of cirrhosis in HCV/HIV co-infection. The most recent advances in the treatment of typical complication of ESLD such as esophageal varices (updated guidelines), variceal hemorrhage (early use of transjugular intrahepatic portosystemic shunt), ascites (updated guidelines), hepatorenal syndrome (vasopressor therapy, deleterious effects of beta-blockers), spontaneous bacterial peritonitis (primary prophylaxis) and hepatic encephalopathy (use of rifaximin) are discussed. This review also provides a basic outline on liver transplantation in HCV/HIV co-infected patients. **SUMMARY:** Thus, physicians involved in the management of ESLD in HCV/HIV co-infected patients will find a comprehensive overview over current treatment strategies in ESLD of HIV-positive patients as well as a valuable collection of pivotal references on the most recent advances in the treatment of ESLD due to HCV/HIV co-infection.

**Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS.** Vivithanaporn P, Nelles K, Deblock L, Newman SC, Gill MJ, Power C. J Neurol Sci. 2011 Sep 17. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21925684>

Previous studies have reported that hepatitis C virus (HCV) co-infection worsens neurocognitive status among individuals with human immunodeficiency virus (HIV)-1 infection. We assessed the prevalence of neurologic disorders and the severity of HIV-associated neurocognitive impairment among HIV-infected individuals in two centralized HIV clinics in Alberta, Canada from 1998 to 2010 based on their HCV serostatus. Of 456 HIV-infected persons without concurrent substance abuse, 91 (20.0%) were HCV seropositive. Of 58 neurologic disorders identified in the cohort, HIV/HCV co-infected individuals exhibited a higher prevalence of multiple neurologic disorders compared to HIV-infected individuals (60.4% vs. 46.6%,  $p<0.05$ ) and a higher frequency of seizures (28.6% vs. 17.8%,  $p<0.05$ ). Unlike HIV mono-infected persons, the risk of seizures was independent of immune status in HIV/HCV co-infected individuals ( $p<0.05$ ). Symptomatic HIV-associated neurocognitive disorders (sHAND) were more severe among HIV/HCV co-infected persons ( $p<0.05$ ). HCV co-infection was associated with an increased mortality rate (24.2% vs. 14.5%,  $p<0.05$ ) with a mortality hazard ratio of 2.38 after adjusting for demographic and clinical variables. **Our results** indicate that the presence of HCV co-infection among HIV-infected individuals increased neurologic disease burden and risk of death, underscoring HCV's capacity to affect the nervous system and survival of HIV-infected persons.

**The Impact of Hepatitis C Coinfection on Kidney Disease Related to Human Immunodeficiency Virus (HIV): A Biopsy Study.** George E, Nadkarni GN, Estrella MM, et al. *Medicine (Baltimore)*. 2011 Sep;90(5):289-95.

<http://www.ncbi.nlm.nih.gov/pubmed/21857365>

Approximately 1 in 4 individuals infected with the human immunodeficiency virus (HIV) in the United States is coinfecting with the hepatitis C virus. Both conditions increase the risk for the development and progression of kidney disease. The effect, however, of coexisting HIV and hepatitis C infection on the spectrum and progression of kidney disease is not well known. To compare the clinical features, histopathologic kidney diagnoses, and proportion of individuals progressing to end-stage kidney disease (ESKD), we reviewed the clinical records of HIV-infected individuals with and without hepatitis C coinfection who underwent ultrasound-guided percutaneous kidney biopsies between February 7, 1995, and March 30, 2009. Of the 249 HIV-infected individuals included in this study, 58% were coinfecting with hepatitis C. Coinfecting individuals were older (mean age,  $46 \pm 7$  vs.  $44 \pm 10$  yr, respectively;  $p < 0.01$ ) and more likely to have used illicit drugs (85% vs. 14%, respectively;  $p < 0.01$ ) compared to HIV-infected individuals without hepatitis C. HIV-associated nephropathy was the most common histopathologic diagnosis in both groups. Immune-complex glomerulonephritides (ICGNs), including lupus-like nephritis, postinfectious glomerulonephritis, membranous glomerulopathy, membranoproliferative glomerulonephritis, IgA nephropathy, and nonspecific ICGNs, occurred more frequently in individuals coinfecting with hepatitis C than in those not coinfecting (22% vs. 11%, respectively;  $p = 0.02$ ). Although the proportion of those who died was similar between the 2 groups, hepatitis C coinfection was independently associated with a greater risk of progression to ESKD (hazard ratio, 1.81; 95% confidence interval, 1.09-2.99;  $p = 0.02$ ). **The current study demonstrates** that coinfection with hepatitis C in individuals infected with HIV predisposes these individuals to immune-complex glomerulonephritides and is associated with increased risk of ESKD in the biopsied population.

**The role of insulin resistance in HIV/hepatitis C virus-coinfecting patients.** Eslam M, López-Cortés LF, Romero-Gomez M. *Curr Opin HIV AIDS*. 2011 Sep 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21934619>

**PURPOSE OF REVIEW:** Insulin resistance, HIV, antiviral drugs and hepatitis C virus (HCV) infection contribute to a complex interaction involving the metabolic syndrome. The objective of this review was to explore the meaning of insulin resistance in HIV-HCV-coinfecting patients and how it may impact on sustained virological response (SVR) and disease progression. **RECENT FINDINGS:** In the HIV/HCV coinfection setting, insulin resistance seems to be associated with a reduction in rapid virological response and SVR to pegylated interferon and ribavirin, both in naive and treatment experienced patients. A recent meta-analysis demonstrated insulin resistance impairs SVR rate with an odds ratio 0.47 (95% confidence interval 0.31-0.71). However, many confounding factors may promote contradictory results. Prevalence of insulin resistance depends on surrogate markers of insulin resistance and the threshold for defining impaired insulin sensitivity. For example, homeostasis model for the assessment of insulin resistance may be influenced by both methods of insulin measurement and interpretation. Insulin sensitizers, lifestyle changes and improvement in the use of protease inhibitors should be evaluated in the management of coinfecting patients. **SUMMARY:** Insulin resistance is common finding in patients with HIV/HCV coinfection, with wide clinical consequences including progression of hepatic fibrosis and reduction in the response to antiviral treatment. Our understanding of this

relationship continues to improve. More prospective studies are required to improve future management.

**Alterations in Immune Function are Associated with Liver Enzyme Elevation in HIV and HCV Co-infection after Commencement of Combination Antiretroviral Therapy.** Cameron

BA, Emerson CR, Workman C, Kelly MD, Lloyd AR, Post JJ. J Clin Immunol. 2011 Sep 20.

[Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21932111>

The cause of liver enzyme elevation during combination antiretroviral therapy in people with human immunodeficiency virus and hepatitis C virus co-infection is unclear. We followed 12 subjects (five with alanine transaminase elevation) for 24 weeks after combination antiretroviral therapy commencement. Immune responses against hepatitis C virus, human immunodeficiency virus and other viruses were assessed by interferon- $\gamma$  ELISpot. Plasma cytokines, chemokines and anti-hepatitis C virus antibody levels were measured. Those with liver enzyme elevation had higher ELISpot responses both against hepatitis C virus non-structural regions and other viral antigens, and their anti-hepatitis C virus antibody levels were consistently higher, suggesting that reconstitution of both hepatitis C virus-specific and non-hepatitis C virus-specific immune responses may be associated with liver transaminase elevation during combination antiretroviral therapy.

**The effect of hepatitis C treatment and HIV coinfection on the disease burden of hepatitis C among injecting drug users in Amsterdam.** Matser A, Urbanus A, Geskus R, et al.

Addiction. 2011 Sep 15. doi: 10.1111/j.1360-0443.2011.03654.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21919987>

**AIMS:** The HCV disease burden among injecting drug users (IDUs) is determined by HCV incidence, the long latency period of HCV, competing mortality causes, presence of coinfection, and HCV treatment uptake. We examined the effect of these factors and estimated the HCV disease burden in Amsterdam. **DESIGN:** A Markov model was developed, incorporating HCV and HIV, to simulate progression of HCV infection from its acute phase to HCV-related liver disease (i.e. decompensated cirrhosis and hepatocellular carcinoma). The model was parameterised with data from the Amsterdam Cohort Studies, surveillance studies, and literature. **FINDINGS:** During the 1970s, the HCV prevalence among IDUs in Amsterdam increased from <30% to >50%. From 2011 to 2025, the HCV-related disease prevalence will accordingly rise by 36%, from 57 cases (95% range 33-94) to 78 (95% range 43-138) respectively. In total, 945 (95% range 617-1309) individuals will develop HCV-related liver disease. This burden would have been 33% higher in the absence of HIV, resulting in 1219 cases (95% range 796-1663). In Amsterdam, 25% of HIV-negative IDUs receive successful HCV treatment, reducing the cumulative disease burden by 14% to 810 (95% range 520-1120). Further reduction of 36% can be achieved by improving treatment, resulting in 603 cases (95% range 384-851).

**CONCLUSIONS:** The HCV burden among IDUs in Amsterdam has been reduced by a high competing mortality rate, particularly caused by HIV infection, and to a smaller extent by HCV treatment. Improved HCV treatment is expected to contribute to reduce the future HCV disease burden.

**In vitro antiviral activities of extracts derived from *Daucus maritimus* seeds.** Miladi S, Abid N, Debarnot C, et al. Nat Prod Res. 2011 Sep 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21895456>

The antiviral activities of extracts from *Daucus maritimus* seeds were investigated against the reverse transcriptase of human immunodeficiency virus (HIV) type 1 and a panel of RNA-dependent RNA polymerases of dengue virus, West Nile virus (WNV) and hepatitis C virus (HCV). The extracts showed moderate to potent inhibition rates against the four viral polymerases. The ethyl acetate extract exhibited a potent inhibitory effect against WNV's RdRp, with an IC(50) value of 8 µg mL(-1). The F (2) fraction exhibited potent inhibitory activity against WNV and HCV's RdRps, with IC(50) values 1 and 5 µg mL(-1), respectively. The P (2) fraction also showed potent inhibitory effects on WNV and HCV's RdRps, with IC(50) values 2.7 and 4 µg mL(-1), respectively. The results suggest that these extracts are candidates for the development of new anti-WNV RpDp and anti-HCV RpDp agents.

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EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Soluble Urokinase Plasminogen Activator Receptor is Associated With Progressive Liver Fibrosis in Hepatitis C Infection.** Berres ML, Schlosser B, Berg T, Trautwein C, Wasmuth HE. J Clin Gastroenterol. 2011 Sep 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21934527>

**BACKGROUND:** Progressive liver fibrosis is the main predictor of disease outcome in chronic hepatitis C viral (HCV) infection. Although the importance of the coagulation cascade has been suggested in liver fibrogenesis, the role of the fibrinolytic pathway is yet unclear. **GOAL:** We evaluated the association of serum levels of the fibrinolysis-associated soluble urokinase plasminogen activator receptor (suPAR) with the severity of liver fibrosis in HCV infection. **STUDY:** suPAR serum levels were assessed in 146 chronically HCV-infected patients of 2 independent cohorts (64 subjects in the screening cohort, 82 in the validation cohort) by enzyme-linked immunosorbent assay and correlated with biopsy-proven histologic stage of liver fibrosis and noninvasive liver fibrosis markers (aspartate transaminase to platelets ratio index score, transient elastography). **RESULTS:** suPAR serum levels were strongly associated with the histologic stage of liver fibrosis in both cohorts ( $P < 0.0001$ ). Although mean suPAR levels in patients with F1 and F2 fibrosis were not different from healthy control subjects, they were significantly increased at higher stages of liver fibrosis (F3 and F4,  $P < 0.0001$ ). suPAR values had a high diagnostic specificity and sensitivity to differentiate mild/moderate fibrosis (F1/F2) from severe fibrosis (F3/F4) with an area under curve of 0.774 ( $P = 0.0001$ ) and for the differentiation of noncirrhosis from cirrhosis (F1/F2/F3 vs. F4, area under curve 0.791,  $P = 0.0001$ ). SuPAR serum levels were also strongly correlated to the noninvasive fibrosis markers aspartate transaminase to platelets ratio index score ( $r = 0.52$ ) and transient elastography ( $r = 0.44$ , both  $P < 0.0001$ ). **CONCLUSIONS:** Serum suPAR levels were robust markers of liver fibrosis in 2 cohorts with a comparable diagnostic accuracy for prediction of severe liver fibrosis as established noninvasive marker.

**Public Health Implications of Rapid Hepatitis C Screening With an Oral Swab for Community-Based Organizations Serving High-Risk Populations.** Drobnik A, Judd C, Banach D, Egger J, Konty K, Rude E. *Am J Public Health.* 2011 Sep 22. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21940910>

**OBJECTIVES:** Between April and September of 2009 we evaluated the accuracy of the OraQuick hepatitis C virus (HCV) rapid antibody test and assessed its feasibility for use by community-based organizations (CBOs) serving populations at high risk for HCV in New York City. **METHODS:** We compared the results of screening by OraQuick (oral swab) and enzyme immunoassay (EIA; blood draw). We performed ribonucleic acid polymerase chain reaction testing for discordant results. We also assessed research staff perceptions through a survey and focus group. **Results:** Overall, 97.5% of OraQuick and EIA results matched. Testing of discordant samples indicated that the rapid test was more likely than the EIA to provide a correct diagnosis. Research staff preferred the rapid test and identified challenges that would be overcome with its use. CBOs could benefit from increased testing capacity, and clients might benefit from more rapid access to education, counseling, and referrals. **CONCLUSIONS:** OraQuick's accuracy is comparable to the EIA. The oral swab rapid test could help HCV screening programs reach individuals unaware of their status and expand testing into nonclinical settings such as mobile units.

**The cost-effectiveness of HCV antiviral treatment for injecting drug user populations.** Martin NK, Vickerman P, Miners A, et al. *Hepatology.* 2011 Sep 2. doi: 10.1002/hep.24656. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21898506>

**BACKGROUND & AIMS:** Injecting drug use is the main risk of hepatitis C virus transmission in most developed countries. HCV antiviral treatment (peginterferon- $\alpha$ +ribavirin) has been shown to be cost-effective for patients with no reinfection risk. We examined the cost-effectiveness of providing antiviral treatment for injectors (IDUs) as compared to treating ex/non-IDUs or no treatment. **METHODS:** A dynamic model of HCV transmission and disease progression was developed, incorporating: a fixed number of antiviral treatments allocated at the mild HCV stage over 10 years, no retreatment after treatment failure, potential reinfection, and three baseline IDU HCV prevalence scenarios (20%, 40%, and 60%). We performed a probabilistic cost-utility analysis estimating long-term costs and outcomes measured in Quality Adjusted Life Years (QALYs) and calculating the incremental cost-effectiveness ratio (ICER) comparing treating IDUs, ex/non-IDUs or no treatment. **RESULTS:** Antiviral treatment for IDUs is the most cost-effective option in the 20% and 40% baseline chronic prevalence settings, with ICERs compared to no treatment of £521 and £2,539 per QALY saved, respectively. Treatment of ex/non-IDUs is dominated in these scenarios. At 60% baseline prevalence treating ex/non-IDUs is slightly more likely to be the more cost-effective option (with an ICER compared to no treatment of £6,803), and treating IDUs dominated due to high reinfection. A sensitivity analysis indicates these rankings hold even when IDU sustained viral response rates as compared to ex/non-IDUs are halved. **CONCLUSIONS:** Despite the possibility of reinfection, the model suggests providing antiviral treatment to IDUs is the most cost-effective policy option in chronic prevalence scenarios less than 60%. Further research on how HCV treatment for injectors can be scaled up, and its impact on prevalence is warranted.

**Comparison of 8 diagnostic algorithms for liver fibrosis in hepatitis C: New algorithms are more precise and entirely non-invasive.** Boursier J, de Ledinghen V, Zarski JP, et al. Hepatology. 2011 Sep 2. doi: 10.1002/hep.24654. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21898504>

**BACKGROUND:** The SAFE and Bordeaux Algorithms (BA), which cross-check Fibrotest with APRI or Fibroscan, are very accurate but provide only a binary diagnosis of significant fibrosis (SAFE or BA for Metavir  $F \geq 2$ ) or cirrhosis (SAFE or BA for F4). Therefore, in clinical practice, physicians have to apply the algorithm for  $F \geq 2$ , then, when needed, the algorithm for F4 ("Successive algorithms"). We aimed to evaluate Successive SAFE, Successive BA, and a new, non-invasive, detailed classification of fibrosis. **METHODS:** 1785 patients with chronic hepatitis C, liver biopsy, blood fibrosis tests and Fibroscan (in 729 patients) were included. The most accurate synchronous combination of Fibroscan with a blood test (FibroMeter) provided a new detailed (6 classes) classification (FM+FS). **RESULTS:** Successive SAFE had significantly ( $p < 10^{-3}$ ) lower diagnostic accuracy (87.3%) than individual SAFE for  $F \geq 2$  (94.6%) or SAFE for F4 (89.5%), and required significantly more biopsies (70.8% vs 64.0% or 6.4%, respectively,  $p < 10^{-3}$ ). Similarly, Successive BA had significantly ( $p \leq 10^{-3}$ ) lower diagnostic accuracy (84.7%) than individual BA for  $F \geq 2$  (88.3%) or BA for F4 (94.2%), and required significantly more biopsies (49.8% vs 34.6% or 24.6%, respectively,  $p < 10^{-3}$ ). The diagnostic accuracy of FM+FS classification (86.7%) was not significantly different from those of Successive SAFE or BA. However, this new classification required no biopsy. **CONCLUSION:** SAFE and BA for significant fibrosis or cirrhosis are very accurate. However, their successive use induces a significant decrease in diagnostic accuracy and a significant increase in required liver biopsy. A new fibrosis classification that synchronously combines two fibrosis tests was as accurate as Successive SAFE or BA, while providing an entirely non-invasive (0% liver biopsy) and more precise (6 vs 2 or 3 fibrosis classes) fibrosis diagnosis.

**Fast DNA and protein microarray tests for the diagnosis of hepatitis C virus infection on a single platform.** Ember SW, Schulze H, Ross AJ, et al. Anal Bioanal Chem. 2011 Sep 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21881881>

Hepatitis C virus (HCV) is a major cause of chronic liver disease and liver cancer, and remains a large health care burden to the world. In this study we developed a DNA microarray test to detect HCV RNA and a protein microarray to detect human anti-HCV antibodies on a single platform. A main focus of this study was to evaluate possibilities to reduce the assay time, as a short time-to-result (TTR) is a prerequisite for a point-of-care test. Significantly reducing hybridisation and washing times did not impair the assay performance. This was confirmed first using artificial targets and subsequently using clinical samples from an HCV seroconversion panel derived from a HCV-infected patient. We were able to reduce the time required for the detection of human anti-HCV antibodies to only 14 min, achieving nanomolar sensitivity. The protein microarray exhibited an analytical sensitivity comparable to that of commercial systems. Similar results were obtained with the DNA microarray using a universal probe which covered all different HCV genotypes. It was possible to reduce the assay time after PCR from 150 min to 16 min without any loss of sensitivity. Taken together, these results constitute a significant step forward in the design of rapid, microarray-based diagnostics for human infectious disease, and show that the protein microarray is currently the most favourable candidate to fill this role.

## **The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference\*.**

Hatzakis A, Wait S, Bruix J, et al. *J Viral Hepat.* 2011 Sep;18 Suppl 1:1-16. doi: 10.1111/j.1365-2893.2011.01499.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21824223>

Worldwide, the hepatitis B virus (HBV) and the hepatitis C virus (HCV) cause, respectively, 600,000 and 350,000 deaths each year. Viral hepatitis is the leading cause of cirrhosis and liver cancer, which in turn ranks as the third cause of cancer death worldwide. Within the WHO European region, approximately 14 million people are chronically infected with HBV, and nine million people are chronically infected with HCV. Lack of reliable epidemiological data on HBV and HCV is one of the biggest hurdles to advancing policy. Risk groups such as migrants and injecting drug users (IDU) tend to be under-represented in existing prevalence studies; thus, targeted surveillance is urgently needed to correctly estimate the burden of HBV and HCV. The most effective means of prevention against HBV is vaccination, and most European Union (EU) countries have universal vaccination programmes. For both HBV and HCV, screening of individuals who present a high risk of contracting the virus is critical given the asymptomatic, and thereby silent, nature of disease. Screening of migrants and IDUs has been shown to be effective and potentially cost-effective. There have been significant advances in the treatment of HCV and HBV in recent years, but health care professionals remain poorly aware of treatment options. Greater professional training is needed on the management of hepatitis including the treatment of liver cancer to encourage adherence to guidelines and offer patients the best possible outcomes. Viral hepatitis knows no borders. EU Member States, guided by the EU, need to work in a concerted manner to implement lasting, effective policies and programmes and make tackling viral hepatitis a public health priority.

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## **LIVER CANCER**

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**Factors affecting prognosis of small hepatocellular carcinoma in Taiwanese patients following hepatic resection.** Ko CJ, Chien SY, Chou CT, Chen LS, Chen ML, Chen YL. *Can J Gastroenterol.* 2011 Sep;25(9):485-91.

<http://www.ncbi.nlm.nih.gov/pubmed/21912759>

**BACKGROUND:** Small hepatocellular carcinoma (HCC) affects millions of individuals worldwide. Surveillance of high-risk patients increases the early detection of small HCC.

**OBJECTIVE:** To identify prognostic factors affecting the overall survival (OS) and recurrence-free survival (RFS) of patients with small HCC. **METHODS:** The present prospective study enrolled 140 Taiwanese patients with stage I or stage II small HCC. Clinical parameters of interest included operation type, tumour size, tumour histology, Child- Pugh class, presence of hepatitis B surface antigen and liver cirrhosis, hepatitis C status, alpha-fetoprotein, total bilirubin and serum albumin levels, and administration of antiviral and salvage therapies. **RESULTS:**

Tumour size correlated significantly with poorer OS in patients with stage I small HCC (P=0.014); however, patients with stage II small HCC experienced a significantly poorer RFS (P=0.033). OS rates did not differ significantly between patients with stage I and stage II small HCC. Tumour margins, tumour histology and cirrhosis did not significantly affect OS or RFS (P>0.05). **DISCUSSION:** Increasing tumour size has generally been associated with poorer prognoses in cases of HCC. The present study verified the relationship between small HCC tumour size and OS; however, a reduction in OS with increasing tumour size was demonstrated

for patients with stage I - but not for stage II - small HCC. **CONCLUSION:** Patients with stage II small HCC may benefit from aggressive surveillance for tumour recurrence and appropriate salvage treatment. Further studies are needed for additional stratification of stage I patients to identify those at increased risk of death.

**Tumor-related factors do not influence the prognosis of solitary hepatocellular carcinoma after partial hepatectomy.** Kobayashi T, Itamoto T, Tashiro H, et al. J Hepatobiliary Pancreat Sci. 2011 Sep;18(5):689-99.

<http://www.ncbi.nlm.nih.gov/pubmed/21445633>

**BACKGROUND/PURPOSE:** Although many factors related to the tumor or the hepatic functional reserve may affect the outcome of partial hepatectomy for hepatocellular carcinoma (HCC), these factors have not yet been intensively investigated in patients with solitary HCC. The purpose of this study is to determine the clinicopathological factors influencing the long-term outcomes of partial hepatectomy for solitary HCC. **METHODS:** Data on 266 consecutive patients with a solitary HCC who underwent curative hepatectomy between 1997 and 2006 were analyzed with regard to prognosis. **RESULTS:** Overall survival rates at 3, 5, and 10 years were 89.5, 79.6, and 56.1%, respectively. The significant independent predictors for overall survival included hepatitis C virus infection, liver cirrhosis, and prolonged prothrombin activity. Disease-free survival rates at 3, 5, and 10 years were 51.7, 41.1, and 20.4%, respectively. The significant independent predictors for disease-free survival included elevated levels of aspartate amino transferase, decreased platelet counts, presence of liver cirrhosis, and prolonged prothrombin activity. Tumor-related factors such as tumor size and microscopic vascular invasion were not significant predictors of overall or disease-free survival. **CONCLUSIONS:** The long-term outcomes of patients with a solitary HCC who underwent partial hepatectomy mainly depended on the background liver status but not on tumor-related factors; this suggests that partial hepatectomy is a remarkably effective antitumor therapy. If the hepatic functional reserve is within the permissible range, partial hepatectomy should be considered as the treatment of choice for patients with a solitary HCC.

**Hepatitis C Virus-Induced Cancer Stem Cell-like Signatures in Cell Culture and Murine Tumor Xenografts.** Ali N, Allam H, May R, et al. J Virol. 2011 Sep 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21937640>

Hepatitis C virus (HCV) infection is a prominent risk factor for the development of hepatocellular carcinoma (HCC). Similar to most solid tumors, HCCs are believed to contain poorly differentiated cancer stem-like cells (CSCs) that initiate tumorigenesis and confer resistance to chemotherapy. In these studies, we demonstrate that expression of HCV subgenomic replicon in cultured cells results in acquisition of CSC traits. These traits include enhanced expression of DCAMKL-1, Lgr5, CD133,  $\alpha$ -fetoprotein, cytokeratin-19 (CK19), Lin28 and c-Myc. Conversely, curing of the replicon from these cells results in diminished expression of these factors. The putative stem cell marker, DCAMKL-1, is also elevated in response to the overexpression of a cassette of pluripotency factors. The DCAMKL-1-positive cells isolated from hepatoma cell lines by fluorescence activated cell-sorting (FACS) form spheroids in matrigel. The HCV RNA abundance and NS5B level is significantly reduced by the siRNA-led depletion of DCAMKL-1. We further demonstrate that HCV replicon-expressing cells initiate distinct tumor phenotypes compared to the tumors initiated by parent cells lacking the replicon. This HCV-induced phenotype is characterized by high-level expression/co-expression of

DCAMKL-1, CK19,  $\alpha$ -fetoprotein, and active c-Src. The results obtained by the analysis of liver tissues from HCV-positive patients and liver tissue microarray reiterate these observations. **In conclusion**, chronic HCV infection appears to predispose cells on the path of acquiring cancer stem cell-like traits by inducing DCAMKL-1, hepatic progenitor and stem cell-related factors. The DCAMKL-1 also represents a novel cellular target for combating HCV-induced hepatocarcinogenesis.

**Frequency of Elevated Hepatocellular Carcinoma (HCC) Biomarkers in Patients With Advanced Hepatitis C.** Sterling RK, Wright EC, Morgan TR, et al. Am J Gastroenterol. 2011 Sep 20. doi: 10.1038/ajg.2011.312. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21931376>

**OBJECTIVES:** Prospective studies of serum hepatocellular carcinoma (HCC) biomarkers in patients with advanced hepatitis C are lacking. The aim of this study was to determine the frequencies and performance of elevated  $\alpha$ -fetoprotein (AFP), AFP-L3, and des- $\gamma$ -carboxy prothrombin (DCP) levels as HCC biomarkers in advanced hepatitis C. **METHODS:** Patients in the HALT-C Trial were tested every 3 months for 42 months. Screening ultrasound was performed every 12 months. Levels of biomarkers were compared in patients in whom HCC did or did not develop. **RESULTS:** In all, 855 patients were evaluated; HCC developed in 46. Among patients without HCC, 73.2% had AFP consistently <20, 24.5% had at least one AFP between 20 and 199, and 2.3% had at least one AFP value  $\geq$ 200 ng/ml; 73.7% had DCP consistently <90, 11.6% had at least one DCP between 90 and 149, and 14.7% had at least one DCP value  $\geq$ 150 mAU/ml. AFP-L3  $\geq$ 10% was present at least once in 9.0% and in 17.1% of those with AFP  $\geq$ 20 ng/ml. Among all patients with elevated biomarkers, a diagnosis of HCC was made in 0-31.6% (depending on the biomarker and cutoff) during the subsequent 24 months. AFP  $\geq$ 200 ng/ml had the highest specificity (99%), but sensitivity was  $\leq$ 20%. DCP  $\geq$ 40 mAU/ml had the highest sensitivity (76%), but specificity was  $\leq$ 58%. Independent predictors of elevated AFP were gender (female), race (Black), more advanced disease, and HCC. Elevated DCP was associated with more advanced disease and HCC. **CONCLUSIONS:** Mild-moderate elevations in total AFP and DCP but not in AFP-L3 occur frequently in patients with chronic hepatitis C and advanced fibrosis, are related to factors other than HCC, and are poor predictors of HCC.

**Hepatocellular carcinoma in HIV hepatitis C virus.** Puoti M, Rossotti R, Garlaschelli A, Bruno R. Curr Opin HIV AIDS. 2011 Sep 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21934618>

**PURPOSE OF REVIEW:** Recent data showed that in some settings with adequate resources liver diseases rank first among the causes of death in persons living with HIV (PLHIV). Although liver decompensation is the first cause of hepatic death in PLHIV, hepatocellular carcinoma (HCC) is also emerging as one of the causes of hepatic death in PLHIV. This review analyzes the main data published on HCC in PLHIV in the last 3 years. **RECENT FINDINGS:** HCC is more common in persons living with HIV than in general population. In PLHIV with a late diagnosis of HCC, less treatable cases and lower survival were described in retrospective studies. New treatment strategies are available for advanced HCC but there are few data available on PLHIV and some open issues. Nevertheless, screening of HIV-infected patients suspected to have cirrhosis seems to be useful and is mandatory in PLHIV and hepatitis C virus (HCV) induced cirrhosis. Together with screening of patients at risk and an early diagnosis, aggressive treatment of the neoplasia including treatment of relapses and maintenance of HIV

suppression are the best management strategies for HCC in PLHIV. The role of liver transplantation remains controversial. **SUMMARY:** In the last years, HCC is becoming an important issue in PLHIV. Prevention, screening, and treatment strategies for HCC need to be included in the management of PLHIV.

**The Core/E1 domain of hepatitis C virus genotype 4a in Egypt does not contain viral mutations or strains specific for hepatocellular carcinoma.** Zhang X, Ryu SH, Xu Y, et al. J Clin Virol. 2011 Sep 16. [Epub ahead of print]  
<http://www.ncbi.nlm.nih.gov/pubmed/21925935>

**BACKGROUND:** Hepatitis C virus (HCV) infection is a well-documented etiological factor for hepatocellular carcinoma (HCC). As HCV shows remarkable genetic diversity, an interesting and important issue is whether such a high viral genetic diversity plays a role in the incidence of HCC. Prior data on this subject are conflicting. **OBJECTIVES:** Potential association between HCV genetic mutations or strain variability and HCC incidence has been examined through a comparative genetic analysis merely focused on a single HCV subtype (genotype 4a) in a single country (Egypt). **STUDY DESIGN:** The study focused on three HCV sequence datasets with explicit sampling dates and disease patterns. An overlapping HCV Core/E1 domain from three datasets was used as the target for comparative analysis through genetic and phylogenetic approaches. **RESULTS:** Based on partial Core/E1 domain (387bp), genetic and phylogenetic analysis did not identify any HCC-specific viral mutations and strains, respectively. **CONCLUSIONS:** The Core/E1 domain of HCV genotype 4a in Egypt does not contain HCC-specific mutations or strains. Additionally, sequence errors resulting from the polymerase chain reaction, together with a strong evolutionary pressure on HCV in patients with end-stage liver disease, have significant potential to bias data generation and interpretation.