



# Caring Ambassadors Program Hepatitis C Newsletter

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December 2011

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## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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**Rationale and design of a randomized controlled trial of directly observed hepatitis C treatment delivered in methadone clinics.** Litwin AH, Berg KM, Li X, Hidalgo J, Arnsten JH. BMC Infect Dis. 2011 Nov 12;11(1):315. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22078241>

**BACKGROUND:** Most methadone-maintained injection drug users (IDUs) have been infected with hepatitis C virus (HCV), but few initiate HCV treatment. Physicians may be reluctant to treat HCV in IDUs because of concerns about treatment adherence, psychiatric comorbidity, or ongoing drug use. Optimal HCV management approaches for IDUs remain unknown. We are conducting a randomized controlled trial in a network of nine methadone clinics with onsite HCV care to determine whether modified directly observed therapy (mDOT), compared to treatment as usual (TAU), improves adherence and virologic outcomes among opioid users.

**METHODS:** We plan to enroll 80 HCV-infected adults initiating care with pegylated interferon alfa-2a (IFN) plus ribavirin, and randomize them to mDOT (directly observed daily ribavirin plus provider-administered weekly IFN) or TAU (self-administered ribavirin plus provider-administered weekly IFN). Our outcome measures are: 1) self-reported and pill count adherence, and 2) end of treatment response (ETR) or sustained viral response (SVR). We will use mixed effects linear models to assess differences in pill count adherence between treatment arms (mDOT v. TAU), and we will assess differences between treatment arms in the proportion of subjects with ETR or SVR with chi square tests. Of the first 40 subjects enrolled: 21 have been randomized to mDOT and 19 to TAU. To date, the sample is 77% Latino, 60% HCV genotype-1, 38% active drug users, and 27% HIV-infected. Our overall retention rate at 24 weeks is 92%, 93% in the mDOT arm and 92% in the TAU arm.

**DISCUSSION:** This paper describes the design and rationale of a randomized clinical trial comparing modified directly observed HCV therapy delivered in a methadone program to on-site treatment as usual. Our trial will allow rigorous evaluation of the efficacy of directly observed HCV therapy (both pegylated interferon and ribavirin) for improving adherence and clinical outcomes. This detailed description of trial methodology can serve as a template for the development of future DOT programs, and can also guide protocols for studies among HCV-infected drug users receiving methadone for opiate dependence.

**Viral kinetics during the first weeks of pegylated interferon and ribavirin treatment can identify patients at risk of relapse after its discontinuation: new strategies for such patients?** Milan M, Boninsegna S, Scribano L, et al. *Infection*. 2011 Nov 18. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22095532>

**BACKGROUND:** Pegylated interferon (PEG-IFN) and ribavirin is the most effective treatment for chronic hepatitis C virus (HCV) hepatitis, but the rate of sustained virological response (SVR) remains approximately 50%, and 15-20% of all treated patients have a virological relapse after completing the treatment. Studies on the SVR have failed to discriminate between non-responders and relapsers. **AIMS:** To identify the risk factors for relapse among patients with an end-of-treatment response (ETR). **METHODS:** We retrospectively analyzed 281 patients consecutively treated with PEG-IFN and ribavirin with a follow-up period of at least 24 weeks. The baseline details collected on each patient included demographic data, histological features, and biochemical profiles. **RESULTS:** Forty-six patients (16.4%) relapsed during the first 6 months of follow-up after discontinuing the therapy. Relapser patients were significantly older, had more steatosis, fibrosis, and showed significantly lower rapid virological response (RVR) rates compared with SVR patients. By logistic regression analysis, only the absence of RVR was found to be significantly associated with relapses in both subgroups of patients with genotypes 1 and 4 ( $p < 0.004$ ) and those with genotypes 2 and 3 ( $p < 0.006$ ). Severe fibrosis was also predictive of relapsing disease, but only for genotypes 2 and 3 patients ( $p < 0.003$ ). During the treatment, serum HCV-RNA decreased more rapidly in patients with SVR compared to non-responder and relapser patients ( $p < 0.001$ ). Interestingly, relapser patients exhibited an intermediate serum HCV-RNA decay during the first 4 weeks of therapy. **CONCLUSION:** Among HCV patients treated with PEG-IFN and ribavirin, the absence of RVR was the most important independent predictor of relapse, independent of the HCV genotype. In the subgroup of genotypes 2 and 3 patients, the severity of fibrosis was also an important factor associated with the relapse rate.

**Reducing Peg-IFN doses causes later virologic response or no response in HCV genotype 1 patients treated with Peg-IFN alfa-2b plus ribavirin.** Oze T, Hiramatsu N, Song C, Yakushijin T, et al. *J Gastroenterol*. 2011 Nov 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22109353>

**BACKGROUND:** The timing to the first undetectable hepatitis C virus (HCV) RNA level is strongly associated with sustained virologic response in pegylated interferon (Peg-IFN) plus ribavirin combination therapy for patients with chronic hepatitis C (CH-C) with genotype 1. This study was conducted to clarify the impact of drug exposure to Peg-IFN on the timing of HCV RNA negativity in Peg-IFN plus ribavirin combination therapy for CH-C patients with genotype 1. **METHODS:** A total of 1409 patients treated with Peg-IFN alfa-2b plus ribavirin were enrolled and classified into four categories according to the Peg-IFN dosage. Furthermore, 100 patients were extracted from each Peg-IFN dosage category to adjust for characteristic factors, using the propensity score method. **RESULTS:** Peg-IFN exposure was dose-dependently associated with the timing of HCV RNA negativity ( $p \leq 0.001$ ). The HCV RNA negative rate at week 4 decreased from 12% with a Peg-IFN dose of  $>1.5 \mu\text{g}/\text{kg}/\text{week}$  to 1-3% with a dose of  $<1.5 \mu\text{g}/\text{kg}/\text{week}$  ( $p \leq 0.001$ ), and at week 12 the rate had decreased from 44% with a dose of  $\geq 1.2 \mu\text{g}/\text{kg}/\text{week}$  to 18% with a dose of  $<1.2 \mu\text{g}/\text{kg}/\text{week}$  ( $p = 0.001$ ). Treatment failure (patients without a 1-log decrease of HCV RNA at week 4 or a 2-log decrease of HCV RNA at week 12,

or positive at week 24) was found in 54-66% of patients given  $<1.2 \mu\text{g/kg/week}$  ( $p \leq 0.001$ ), and these patients accounted for 64% of the non-responders. **CONCLUSIONS:** The timing of HCV RNA negativity depends significantly on the Peg-IFN dose. Reducing the Peg-IFN dose can induce a later virologic response or non-response in HCV genotype 1 patients treated with Peg-IFN plus ribavirin.

**Long-term clinical course of decompensated alcoholic cirrhosis: a prospective study of 165 patients.** Alvarez MA, Cirera I, Solà R, Bargalló A, Morillas RM, Planas R. J Clin Gastroenterol. 2011 Nov-Dec;45(10):906-11.

<http://www.ncbi.nlm.nih.gov/pubmed/21814145>

**BACKGROUND:** Prognosis of decompensated alcoholic cirrhosis is based mainly on studies that included patients with different severities of liver disease and did not recognize either hepatitis C virus epidemic or changes in clinical management of cirrhosis. **AIM:** To define the long-term course after the first hepatic decompensation in alcoholic cirrhosis. **METHODS:** Prospective inclusion at the start point of decompensated cirrhosis of 165 consecutive patients with alcoholic cirrhosis without known hepatocellular carcinoma hospitalized from January 1998 to December 2001 was made. Follow-up was maintained until death or the end of the observation period (April 1, 2010). **RESULTS:** The patients were followed for 835.75 patient years. Median age was 56 years (95% confidence interval: 54-58). Baseline Child-Pugh score was 9 (95% CI: 8-9), and model for end-stage liver disease (MELD) was 13.8 (95% CI: 12.5-14.7). Ascites was the most frequent first decompensation (51%). During follow-up, 99 (60%) patients were abstinent, hepatocellular carcinoma developed in 18 (11%) patients, and 116 patients died (70%). Median overall survival was 61 months (95% CI: 48-74). Median survival probability after onset of hepatic encephalopathy (HE) was only 14 months (95% CI: 5-23). Age, baseline MELD, albumin, development of HE, and persistence of alcohol use were independently correlated with mortality. **CONCLUSIONS:** Patients with alcoholic cirrhosis show a high frequency of complications. The low mortality rate in our cohort of patients probably reflects the improvement in the management of patients with cirrhosis; it is mainly influenced by baseline MELD, age, HE development, and continued abstinence. Patients who develop HE should be considered for hepatic transplantation.

**Retreatment with telaprevir combination therapy in hepatitis C patients with well-characterized prior treatment response.** Muir AJ, Poordad FF, McHutchison JG, et al. Hepatology. 2011 Nov;54(5):1538-46. doi: 10.1002/hep.24549.

<http://www.ncbi.nlm.nih.gov/pubmed/22045671>

Retreatment with peginterferon alpha and ribavirin (PR) offers a limited chance of sustained virologic response (SVR) in patients who did not achieve SVR with prior PR treatment. This study evaluated the safety and efficacy of telaprevir-based treatment in combination with PR in well-characterized patients who did not achieve SVR in the control arms of three Phase II clinical trials. Patients eligible to enroll in this open-label nonrandomized study either met on-treatment criteria for nonresponse or relapsed after 48 weeks of treatment in the control arm of the three Phase II PROVE studies. The initial protocol was a 24-week regimen: 12 weeks of telaprevir and PR followed by an additional 12 weeks of PR. During the study the protocol was amended to extend PR to 48 weeks for patients with previous null response. All other patients with undetectable hepatitis C virus (HCV) RNA at weeks 4 and 12 received 24 weeks of therapy. Those with detectable HCV RNA at weeks 4 or 12 received a total of 48 weeks of therapy. The

overall SVR rate was 59% (69/117). SVR rates with T12PR were 37% (19/51) in prior null responders, 55% (16/29) in prior partial responders, 75% (6/8) in prior breakthroughs, and 97% (28/29) in prior relapsers. The overall relapse rate was 16% (13/83). Adverse events were similar to those in previous trials with telaprevir, with 9% of patients discontinuing due to an adverse event (most commonly rash and anemia). **CONCLUSION:** This study demonstrated the benefit of retreatment with a telaprevir-based regimen for patients with well-characterized nonresponse (null and partial) or relapse to a prior course of PR treatment.

**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 Nov;23(11):997-1003.

<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.

**The study of relationship between neutropenia and infection during treatment with peginterferon  $\alpha$  and ribavirin for chronic hepatitis C.** Yu JW, Sun LJ, Zhao YH, Kang P, Yan BZ. Eur J Gastroenterol Hepatol. 2011 Nov;23(12):1192-9.

<http://www.ncbi.nlm.nih.gov/pubmed/21971375>

**OBJECTIVE:** Neutropenia is frequent during treatment of chronic hepatitis C (CHC) with peginterferon and ribavirin. It remains unclear whether neutropenia is associated with infection in CHC. The aim was to study the relationship between neutropenia and infection during treatment with peginterferon and ribavirin for CHC. **METHODS:** A retrospective cohort on 399 patients treated with peginterferon  $\alpha$  and ribavirin derived from our hospital database was conducted. The occurrence of infections and their relationship to neutropenia were investigated. Potential risk factors for infection were identified by multivariate analysis. **RESULTS:** During treatment, neutropenia [absolute neutrophil counts (ANC)  $<1.5 \times 10^3/l$ ] occurred in 251 patients, mild neutropenia [ANC (0.75-1.5)  $\times 10^3/l$ ] occurred in 132 patients, moderate neutropenia [ANC (0.50-0.75)  $\times 10^3/l$ ] occurred in 103 patients, and severe neutropenia (ANC  $<0.50 \times 10^3/l$ ) occurred in 16 patients. Eighty infections (20.1%) occurred, 14 infections (17.5%) were defined as severe. There was no significant difference in infection rate between patients with and without moderate and severe neutropenia (21.0%, 25/119 vs. 19.6%, 55/280;  $\chi^2=0.097$ , P=0.755). There was no significant difference in infection rate between patients with and without peginterferon dose modifications (21.5%, 31/144 vs. 19.2%, 49/255;  $\chi^2=0.307$ , P=0.580). In multivariate logistic regression analysis, the independent factors associated with infection were age (P=0.021), diabetes (P=0.004), and cirrhosis (P=0.012). **CONCLUSION:** Infections during treatment with peginterferon  $\alpha$  and ribavirin for CHC are not associated with neutropenia. The independent factors associated with infection are age, diabetes, and cirrhosis.

**The early on-treatment perihepatic lymph node response predicts sustained viral response of anti-hepatitis C virus therapy.** Lin YM, Sheu MJ, Kuo HT, et al. Eur J Gastroenterol Hepatol. 2011 Nov;23(11):990-6.

<http://www.ncbi.nlm.nih.gov/pubmed/21975695>

**BACKGROUND AND AIMS:** In chronic hepatitis C, the change of perihepatic lymph nodal size after antiviral therapy could be a marker of virologic response. Whether the on-treatment nodal manifestations predict virologic responses is unknown. **METHODS:** Patients (n=88) with biopsy-proven chronic hepatitis C received standard doses of bi-therapy for 24 weeks; sequential changes of the perihepatic lymph nodes were evaluated prospectively by ultrasound. Pretreatment and on-treatment factors were analyzed and correlated with sustained virologic response, focusing on early on-treatment nodal changes (12 weeks). **RESULTS:** Perihepatic lymph nodes were prevalent in 75% of the patients; 72 patients (81.8%) achieved sustained viral response. Before treatment, no factor was significantly associated with the nodal prevalence or size. The pretreatment nodal width (mean 5.3 vs. 3.6 mm; P=0.023) and the on-treatment nodal manifestations including a reduction in nodal width at 12 weeks of antiviral treatment (median; 1.05 vs. 0 mm, P=0.029) and a reduction of nodal volume at the end of treatment (24 weeks; median 0.62 vs. -0.01 ml, P=0.015) were significantly correlated with the sustained virologic response. A reduction of nodal width greater than 2.5 mm at 12 weeks always predicts sustained virologic response (100 vs. 77%; P=0.019). **CONCLUSION:** Results confirm the high prevalence of perihepatic lymphadenopathy in patients with chronic hepatitis C. The use of the nodal width measurement in routine ultrasound follow-up may be a simpler early predictor of sustained virologic response during standard bi-therapy.

**Randomised clinical trial: the efficacy of treatment, guided by a shorter duration of response, using peginterferon alfa-2a plus ribavirin for hepatitis C virus other than genotypes 2 or 3.** Lee SS, Sherman M, Ramji A, et al. *Aliment Pharmacol Ther.* 2011 Nov 2. doi: 10.1111/j.1365-2036.2011.04911.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22050141>

**BACKGROUND:** The efficacy of individualised antiviral treatment durations for chronic hepatitis C remains unclear. **AIM:** To evaluate treatment durations based on virological responses at week 4, 8 and 12 of peginterferon alfa-2a plus ribavirin therapy. **METHODS:** Previously untreated patients with HCV genotypes, other than 2 or 3, initiated therapy with peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1400 mg/day. HCV-RNA-negative patients at week 4 rapid virological response (RVR) were randomised to 24 or 48 weeks of treatment; those negative at week 8 were randomised to 36 or 48 weeks; and those who were negative or had a  $\geq 2$ -log drop at week 12 were randomised to 72 or 48 weeks. Sustained virological response (SVR) was defined as undetectable HCV-RNA after 24 weeks of follow-up. **RESULTS:** The study was terminated prematurely due to lagging enrolment. Of 236 patients who started treatment, 195 were randomised at week 4 (n=50), 8 (n=61) or 12 (n=84). Ninety-five per cent of patients had genotype 1. SVR rates were not significantly different between patients randomised to 24 (84%) or 48 weeks (84%) at week 4, to 36 (73%) or 48 weeks (74%) at week 8, or to 48 (49%) or 72 weeks (40%) at week 12. **CONCLUSIONS:** In this predominantly genotype 1 cohort, shortening therapy to 24 weeks in patients with a week-4 response and 36 weeks in those with a week-8 response produced SVR rates that were similar to a 48-week regimen. Lengthening treatment to 72 weeks did not improve SVR rates. Genotype 1 patients with RVR can be treated for 24 weeks.

**Sexual dysfunction in males with hepatitis C virus: Relevance to histopathologic changes and peginterferon treatment.** El-Atrebi KA, El-Atrebi MA, El-Bassyouni HT. *Saudi J Gastroenterol.* 2011 Nov;17(6):406-10.

<http://www.ncbi.nlm.nih.gov/pubmed/22064340>

**BACKGROUND/AIM:** The frequency of sexual dysfunction (SD) is not well known in patients with chronic hepatitis C virus (HCV). In spite of the fact that histological benefits of peginterferon (Peg-IFN)/ribavirin therapy are well established, the effects on sexual health are less certain. To assess the prevalence of the SD and explore its relevance to histopathologic changes and Peg-IFN treatment. **MATERIALS AND METHODS:** The study included 100 HCV males; all the patients completed questionnaires to assess their sexual function before and during the treatment. **RESULTS:** Before treatment, SD was reported only by 12 (19.4%) and 10 (29.4%) patients of early and advanced liver fibrosis, respectively. SD during HCV treatment (with Peg-IFN and ribavirin) for liver fibrosis was significant, as 24 (70.6%) out of 34 (100%) of HCV patients had advanced fibrosis but only 20 (32.3%) out of 62 (100%) patients had early fibrosis and were sexually affected ( $P = 0.01$ ). SD before treatment was found in 22 (22%) patients; 16 (16%) were  $>40$  years old and 6 (6%) patients were  $\leq 40$  years old. SD showed highly significant ( $P = 0.001$ ) difference prior to and during treatment. Pre treatment, 78 (78%) patients denied any SD and only 22 (22%) were sexually affected, while during treatment, the number of patients who were sexually affected rose to 44 (44%). The rest of the group [56 (56%)] did not report any sexual impairment. **CONCLUSION:** SD was noticed during Peg-IFN and ribavirin treatment in patients with advanced liver fibrosis. Age and advanced liver fibrosis

were important factors in inducing SD. This is of key importance for clinical practice as it modifies the management of HCV patients.

**Formulary management of the protease inhibitors boceprevir and telaprevir for chronic hepatitis C virus.** Tungol A, Rademacher K, Schafer JA. J Manag Care Pharm. 2011 Nov;17(9):685-94.

<http://www.ncbi.nlm.nih.gov/pubmed/22050393>

**BACKGROUND:** Hepatitis C virus (HCV) is the most common chronic bloodborne illness in the United States. The incidence of acute hepatitis C in the United States peaked near 50,000 cases in the late 1980s but has stabilized since 2003 to less than 5,000 cases annually. The combination of pegylated interferon (peginterferon) and ribavirin has been the standard recommended treatment for HCV. Protease inhibitors telaprevir and boceprevir were approved by the FDA in May 2011 for the treatment of hepatitis C genotype 1 in combination with peginterferon and ribavirin. **OBJECTIVE:** To review the phase 3 trials for telaprevir and boceprevir and provide managed care considerations. **METHODS:** A MEDLINE review was performed for articles published and available through September 15, 2011, using keywords "boceprevir" or "telaprevir" with an emphasis on phase 3 trials. The literature search was limited to articles in English, clinical trials, randomized controlled trials, and research conducted in humans. Additional information was obtained from the FDA website. **RESULTS:** Three phase 3 trials are available for telaprevir, which provided data that were the basis for FDA approval. Boceprevir demonstrated efficacy and safety in 2 pivotal phase 3 trials. Both agents demonstrated statistically significantly higher rates of virologic response compared with the standard of care involving peginterferons and ribavirin. Telaprevir and boceprevir also demonstrated efficacy in the treatment of patients who had previously failed dual therapy for hepatitis C. Safety concerns for both agents include anemia, drug interactions, skin rashes, and gastrointestinal adverse events. **CONCLUSIONS:** Decision makers have many factors to consider in developing a strategy around hepatitis C. Increased drug costs, patient management, adherence, comparative safety and efficacy, and appropriate utilization management controls are important issues. Payers may consider developing clinical programs to encourage adherence and appropriate use and leverage an appropriate channel to ensure cost-effective therapy.

**Implications of rapid virological response in hepatitis C therapy in the US veteran population.** Hwang EW, Thomas IC, Cheung R, Backus LI. Aliment Pharmacol Ther. 2011 Nov 7. doi: 10.1111/j.1365-2036.2011.04903.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22060887>

**BACKGROUND:** Early predictors of response to hepatitis C virus (HCV) therapy, such as rapid virological response, are valuable for the identification of patients with a higher likelihood of treatment success. **AIM:** To identify predictors of rapid virological response in a real world setting. **METHODS:** Using the VA Clinical Case Registry, we identified patients with HCV mono-infection, without liver transplantation, who initiated peginterferon (PEG-IFN) and ribavirin (RBV) in 2007 or 2008 and had HCV RNA testing for RVR. Significant baseline characteristics from genotype specific univariate analyses were used in backwards stepwise models to identify significant independent predictors of RVR. **RESULTS:** The final cohort consisted of 2424 patients with genotype 1 (G1), 666 patients with genotype 2 (G2), and 419 patients with genotype 3 (G3). Rapid virological response rates were 15% for G1, 71% for G2 and 57% for G3. Sustained virological response rates were significantly higher in patients with

rapid virological response than without, increasing from 18% to 52% in G1, 39% to 71% in G2, and 40% to 60% in G3 ( $P < 0.0001$ ). A baseline HCV RNA  $< 500000$  IU/mL positively predicted RVR across all genotypes studied. In addition, for G1, Black race, Hispanic ethnicity, aspartate aminotransferase/alanine aminotransferase (AST/ALT)  $\geq 0.6$ , ferritin  $\geq 350$  ng/mL, LDL  $< 100$  mg/dL and diabetes; for G2, BMI  $\geq 30$  kg/m<sup>2</sup>, platelets  $< 150$  K/ $\mu$ L, LDL  $< 100$  mg/dL and the use of PEG-IFN alfa-2b; and for G3, AST/ALT  $\geq 1.0$ , all negatively predicted rapid virological response. **CONCLUSION:** We found several novel independent predictors of rapid virological response, including BMI, AST/ALT ratio, ferritin, platelets, LDL, diabetes and type of PEG-IFN prescribed, which may be useful in guiding treatment decisions in routine medical practice.

**Individual-level syringe coverage among Needle and Syringe Program attendees in Australia.** Iversen J, Topp L, Wand H, Maher L. Drug Alcohol Depend. 2011 Nov 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22071120>

**BACKGROUND:** Harm associated with injecting drug use is a significant public health issue and a major cause of morbidity and mortality, with global estimates of 3 million injectors infected with HIV and 8 million living with chronic hepatitis C virus (HCV) infection. Estimates of program coverage are widely used in the context of HIV prevention and are critical in determining the effectiveness of interventions such as Needle and Syringe Programs (NSPs).

**METHODS:** Data from a national cross-sectional study of NSP attendees in Australia were used to estimate individual-level syringe coverage as a proportion of monthly injections covered by a new syringe. Univariate and multivariate logistic regressions modelled associations between demographics, injecting risk, anti-HIV and HCV prevalence and syringe coverage. The median number of syringes retained per NSP attendee per annum was also estimated. **RESULTS:**

Twenty percent of participants had insufficient new syringes for all injections. Syringe reuse (including reuse of one's own syringe) was independently associated with syringe coverage of  $< 100\%$ . Conversely, procurement of syringes from an NSP was independently associated with syringe coverage  $\geq 100\%$ , with a greater protective effect occurring when NSP utilisation was combined with current engagement in opiate substitution therapy. The median number of syringes retained per participant per annum was 720, equivalent to 2 per day. **CONCLUSIONS:** While Australian NSP attendees report high syringe coverage by international standards, prevention efforts could be scaled up. Syringe reuse was associated with syringe coverage of  $< 100\%$ , suggesting the utility of reuse as a proxy for individual-level syringe coverage.

**Impact of IL28B on treatment outcome in hepatitis C virus G1/4 patients receiving response-guided therapy with peginterferon alpha-2a (40KD)/ribavirin.**

Scherzer TM, Stättermayer AF, Strasser M, et al. Hepatology. 2011 Nov;54(5):1518-26. doi: 10.1002/hep.24546.

<http://www.ncbi.nlm.nih.gov/pubmed/22006276>

The IL28B genotype is the most important pretreatment predictor of treatment outcome in patients with chronic hepatitis C. The impact of the rs12979860 genotype on relapse was retrospectively evaluated in genotype 1/4 patients who received response-guided therapy with peginterferon alpha-2a 180  $\mu$ g/week plus ribavirin 1,000/1,200 mg/day in a large, randomized, multicenter study. Patients with a rapid virologic response (RVR: hepatitis C virus [HCV] RNA  $< 50$  IU/mL) at week 4 were treated for 24 weeks; those with a slow virologic response (no RVR

but undetectable HCV RNA or  $\geq 2\text{-log}(10)$  decrease at week 12) were randomized to 48 (group A) or 72 weeks of treatment (group B). Relapse rates were compared by rs12979860 genotype (C/C versus combined T/C or T/T [T/\*]) in patients with confirmed end-of-treatment response and known end-of-follow-up status (sustained virologic response [SVR] or relapse). The rs12979860 genotype was determined for 340/551 study participants. In patients with RVR and C/C or T/\* genotype, relapse rates were similar (10.7% versus 15.2%). In patients randomized to groups A and B, relapse rates were similar in patients with C/C genotype randomized to group A (26.9%) and group B (20.0%). In contrast, relapse rates in T/\* patients differed markedly between groups A and B, overall (42.9% and 18.8%;  $P < 0.025$ , respectively) and in those with low ( $< 400,000$  IU/mL: 37.5% versus 18.8%) and high ( $\geq 400,000$  IU/mL: 45.0% versus 18.8%) baseline viral loads. **CONCLUSION:** The results suggest that the benefits of extended therapy are restricted to patients with a T allele. Relapse rates are highest in patients with T/\* genotype and are markedly higher in slow responders treated for 48 weeks compared with 72 weeks.

**Selenium deficiency is associated with insulin resistance in patients with hepatitis C virus-related chronic liver disease.** Himoto T, Yoneyama H, Kurokohchi K, et al. *Nutr Res.* 2011 Nov;31(11):829-35.

<http://www.ncbi.nlm.nih.gov/pubmed/22118753>

The relationship between selenium (Se) deficiency and insulin resistance has not much been established in persistent hepatitis C virus (HCV) infection, although Se deficiency is often observed in patients with liver cirrhosis. We hypothesized that the decreased serum Se levels were associated with the severity of hepatic fibrosis or insulin resistance in patients with HCV-related chronic liver disease (CLD). To test the hypothesis, 52 patients with HCV-related CLD including chronic hepatitis and liver cirrhosis were enrolled in this study. The severity of hepatic fibrosis was divided into 4 categories (F(1) through F(4)) according to the new Inuyama classification. Insulin resistance was defined by the homeostasis model for assessment of insulin resistance value. Serum Se levels significantly declined in proportion to the severity of hepatic fibrosis and were positively correlated with serum albumin ( $r = 0.372$ ,  $P = .0065$ ) and zinc ( $r = 0.403$ ,  $P = .0081$ ) concentrations. Serum Se levels were also linked to glutathione peroxidase activities in the sera of the enrolled patients ( $r = 0.374$ ,  $P = .0148$ ). By contrast, serum Se levels were inversely correlated with the homeostasis model for assessment of insulin resistance values ( $r = -0.304$ ,  $P = .0338$ ). However, serum Se levels were independent of HCV genotype and loads of HCV-RNA. These findings suggest that Se deficiency was associated with the severity of hepatic fibrosis in patients with HCV-related CLD and that Se deficiency was likely to be one of the factors contributing to insulin resistance in those patients.

**Role of hepatic HCV-RNA level on the severity of chronic hepatitis C and response to antiviral therapy.** Maylin S, Laouéan C, Martinot-Peignoux M, et al. *J Clin Virol.* 2011 Nov 16. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22099210>

**BACKGROUND:** Correlation between hepatic HCV-RNA and serum HCV-RNA, severity of liver disease and response to therapy is poorly known. **OBJECTIVES:** To assess the influence of hepatic HCV-RNA level on severity of liver disease and response to therapy in a large cohort of chronic hepatitis C (CHC) patients. **STUDY DESIGN:** HCV-RNA was measured in frozen liver biopsies and serum samples from 130 CHC patients the day of liver biopsy prior to

treatment. Liver fibrosis was assessed by Ishaq scoring. A Sustained Virological Response (SVR) was observed in 52% of the patients, non-response (NR) in 34%. **RESULTS:** Mean±standard deviation hepatic HCV-RNA level was 7.69±0.67 log(10) copies/mg of liver. Mean serum HCV-RNA level was 6.21±0.72 log(10) copies/ml. There was a correlation between hepatic and serum HCV-RNA in genotype 1 and 4 (p=0.008 and p=0.03) and age (p=0.006). Mean hepatic HCV-RNA was 7.70±0.69 vs 7.67±0.68 log(10) copies/mg of liver, in patients with significant fibrosis vs those with mild fibrosis, respectively (p=0.7); 8.04±0.68; 7.44±0.47; 7.43±0.49 and 7.44±0.71 log(10) copies/mg of liver in genotypes 1, 2, 3 and 4, respectively (p=0.0001); higher in women than in men (p=0.04); 7.60±0.63, 7.71±0.54 and 7.96±0.73 log(10) copies/mg in SVR, relapsers and NR, respectively (p=0.1). Multivariate analysis showed that high hepatic HCV-RNA level was independently associated with genotype and response to therapy was associated with genotype independently from hepatic HCV-RNA level. **CONCLUSIONS:** Hepatic HCV-RNA level was not associated with severity of liver disease. High level was strongly associated with HCV genotype independently from response to therapy.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**Female Sex and IL28B, a Synergism for Spontaneous Viral Clearance in Hepatitis C Virus (HCV) Seroconverters from a Community-Based Cohort.** van den Berg CH, Grady BP, Schinkel J, et al. PLoS One. 2011;6(11):e27555. Epub 2011 Nov 15.

<http://www.ncbi.nlm.nih.gov/pubmed/22110669>

**BACKGROUND AND AIMS:** Since acute hepatitis C virus (HCV) infection is often asymptomatic, it is difficult to examine the rate and determinants of spontaneous clearance. Consequently, these studies are subject to bias, which can potentially lead to biased rates of viral clearance and risk estimates. We evaluated determinants of spontaneous HCV clearance among HCV seroconverters identified in a unique community-based cohort. **METHODS:** Subjects were 106 drug users with documented dates of HCV seroconversion from the Amsterdam Cohort Study. Logistic regression was used to examine sociodemographic, behavioral, clinical, viral and host determinants, measured around acute infection, of HCV clearance. **RESULTS:** The spontaneous viral clearance rate was 33.0% (95% confidence interval (CI) 24.2-42.8). In univariate analyses female sex and fever were significantly associated with spontaneous clearance. The favorable genotypes for rs12979860 (CC) and rs8099917 (TT) were associated with spontaneous clearance, although borderline significant. In multivariate analysis, females with the favorable genotype for rs12979860 (CC) had an increased odds to spontaneously clear HCV infection (adjustedOR 6.62, 95% 2.69-26.13), whereas females with the unfavorable genotype were as likely as men with the favorable and unfavorable genotype to clear HCV. Chronic Hepatitis B infection and absence of HIV coinfection around HCV seroconversion also favor HCV clearance. **CONCLUSIONS:** This study shows that co-infection with HIV and HBV and genetic variation in the IL28B region play an important role in spontaneous clearance of HCV. Our findings suggest a possible synergistic interaction between female sex and IL28B in spontaneous clearance of HCV.

**Serum ferritin levels are associated with a distinct phenotype of chronic hepatitis C poorly responding to pegylated interferon- $\alpha$  and ribavirin therapy.** Lange CM, Kutalik Z, Morikawa K, et al. Hepatology. 2011 Nov 16. doi: 10.1002/hep.24787. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22095909>

Elevated serum ferritin levels may reflect a systemic inflammatory state as well as increased iron storage, both of which may contribute to an unfavorable outcome of chronic hepatitis C. We therefore performed a comprehensive analysis of the role of serum ferritin and their genetic determinants in the pathogenesis and treatment of chronic hepatitis C. To this end, serum ferritin levels at baseline of therapy with pegylated interferon- $\alpha$  and ribavirin or before biopsy were correlated with clinical and histological features of chronic HCV infection, including necroinflammatory activity (N=970), fibrosis (N=980), steatosis (N=886) and response to treatment (N=876). The association between high serum ferritin levels (>median) and the endpoints was assessed by logistic regression. Moreover, a candidate gene as well as a genome-wide association study of serum ferritin were performed. We found that serum ferritin  $\geq$  the sex-specific median was one of the strongest pre-treatment predictors of treatment failure (univariate  $P < 0.0001$ , OR=0.45, 95% CI=0.34-0.60). This association remained highly significant in a multivariate analysis ( $P = 0.0002$ , OR=0.35, 95% CI=0.20-0.61), with an odds ratio comparable to that of IL28B genotype. When patients with the unfavorable IL28B genotypes were stratified according to high vs. low ferritin levels, SVR rates differed by >30% in both HCV genotype 1- and 3-infected patients ( $P < 0.001$ ). Serum ferritin levels were also independently associated with severe liver fibrosis ( $P < 0.0001$ , OR=2.67, 95% CI=1.68-4.25) and steatosis ( $P = 0.002$ , OR=2.29, 95% CI=1.35-3.91) but not with necroinflammatory activity ( $P = 0.3$ ). Genetic variations had only a limited impact on serum ferritin levels. **CONCLUSION:** In patients with chronic hepatitis C, elevated serum ferritin levels are independently associated with advanced liver fibrosis, hepatic steatosis, and poor response to interferon- $\alpha$ -based therapy.

#### **Hepatitis C viral kinetics with the nucleoside polymerase inhibitor mericitabine (RG7128).**

Guedj J, Dahari H, Shudo E, Smith P, Perelson AS. Hepatology. 2011 Nov 16. doi:

10.1002/hep.24788. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22095398>

Mericitabine (RG7128) is a first-in class nucleoside polymerase inhibitor (NPI), which requires intracellular uptake and phosphorylation to two active triphosphates. Mathematical modeling has provided important insights for characterizing HCV-RNA decline and estimating in vivo effectiveness of antiviral agents; however it has not been used to characterize viral kinetics with NPIs. HCV RNA was frequently measured in 32 treatment-experienced patients infected with HCV genotype-1 during and after mericitabine monotherapy for 14 days with 750-mg or 1500-mg administered once (QD) or twice daily (BID). Initial decline of HCV RNA was typically slower than with interferon-alpha or protease inhibitors and 12 patients presented a novel pattern of HCV RNA kinetics characterized by a monophasic viral decline. Viral kinetics could be well fitted by assuming that the effectiveness in blocking viral production gradually increased over time to reach its final value,  $\epsilon(2)$ , consistent with previous accumulation time estimates of intracellular triphosphates.  $\epsilon(2)$  was high with BID dosing (mean 750-mg and 1500-mg: 98.0% and 99.8%,  $P = 0.018$ ) and significantly higher than in patients treated QD (mean QD vs BID: 90% vs 99%,  $P < 10^{-7}$ ). Virus rebounded rapidly upon drug discontinuation, which was attributed to the elimination of active drug and the subsequent decline of drug effectiveness with mean  $t(1/2) = 13.9$  h in the BID regimens. **CONCLUSION:** The observed slower initial decline likely represents the time needed to accumulate intracellular triphosphates and is consistent with in vitro data. When administered BID, mericitabine reached a high, dose-dependent, final effectiveness in blocking viral production, that rapidly dropped upon treatment cessation.

Understanding HCV RNA kinetics with mericitabine could provide valuable insights for combining it with other direct-acting antiviral agents.

**Enhancement of Humoral Immunity in Mice by coupling pUCpGs10 and Aluminium to the HCV Recombinant Immunogen.** Zhan N, Xiu BS, Wang GH, et al. *Virology*. 2011 Nov

4;8(1):507. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22054420>

**AIM:** To investigate the enhancement of humoral immunity when CpG ODN (cytidine phosphate guanosine oligodeoxynucleotides) and aluminium adjuvants are complexed with the HCV (Hepatitis C virus) recombinant immunogen in mice. **METHODS:** After immunizing Balb/c mice with the recombinant HCV antigen adjuvanted with pUCpGs10 and/or aluminium (antigen+CpG+alum, antigen+CpG, antigen+alum, antigen+PBS), enzyme-linked immunosorbent assay (ELISA) was used to measure the specific serum antibody titers of IgG, to determine the neutralization response to various peptide genotypes, and to determine the concentration of IL-6 and IL-10 in supernatants of in vitro cultured splenic lymphocytes. Enzyme-linked immunospot assay (ELISPOT) was used to quantify the non-specific and specific splenic antibody-secreting cells (ASCs), and flow cytometry (FCM) determined the ratio of different splenic lymphocytes. The serum of rabbits immunized with the recombinant pBVGST/HVR1 antigen immunoprecipitated the HCV isolated from 12 patients' serum. **RESULTS:** The sera antibody titers were 1:51200, 1:9051, 1:18102, 1:6400 respectively after the final immunization and demonstrated good neutralization responses to the six gene peptide containing 1a1b2a3a4a and 6a. The aluminium adjuvant increased the population of both specific ASCs ( $P < 0.01$ ) and total ASCs ( $P < 0.05$ ), with a proportional rise in concentrations of CD19+CD27+ ( $P < 0.05$ ), as well as levels of IL-6/IL-10 ( $P < 0.05$ ) in splenic lymphocytes. The results clearly indicated a significantly higher number of CD19+CD38+ splenic lymphocytes with the aluminium and pUCpGs10 adjuvants present compared to the control group  $P < 0.05$ . Anti-HVR1 antibody in induced mice can cross-reactively capture HCV particles (10/12). **CONCLUSIONS:** 1. The aluminium adjuvant induces a potent Th2-biased immune response by increasing both the populations of specific and total ASCs and the ratio of CD19+CD27+ cells. 2. The pUCpGs10 complexed with the aluminium adjuvant boosts the population of plasma cells and increase the efficiency of the immune response. 3. The two adjuvants have synergistic effects on humoral immunity. 4. The recombinant HVR1 protein has the possibility of generating broadly reactive anti-HVR1 antibody.

**Effect of route of delivery on heterologous protection against HCV induced by an adenovirus vector carrying HCV structural genes.** Guan J, Wen B, Deng Y, et al. *Virology*. 2011 Nov 4;8(1):506. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22054309>

**BACKGROUND:** An effective vaccine and new therapeutic methods for hepatitis C virus (HCV) are needed, and a potent HCV vaccine must induce robust and sustained cellular-mediated immunity (CMI). Research has indicated that adenoviral and vaccinia vectors may have the ability to elicit strong B and T cell immune responses to target antigens. **RESULTS:** A recombinant replication-defective adenovirus serotype 5 (rAd5) vector, rAd5-CE1E2, and a recombinant Tian Tan vaccinia vector, rTTV-CE1E2, were constructed to express the HCV CE1E2 gene (1-746 amino acid HCV 1b subtype). Mice were prime-immunised with rAd5-CE1E2 delivered via intramuscular injection (i.m.), intranasal injection (i.n.), or intradermal

injection (i.d.) and boosted using a different combination of injection routes. CMI was evaluated via IFN-gamma ELISPOT and ICS 2 weeks after immunisation, or 16 weeks after boost for long-term responses. The humoral response was analysed by ELISA. With the exception of priming by i.n. injection, a robust CMI response against multiple HCV antigens (core, E1, E2 ) was elicited and remained at a high level for a long period (16 weeks post-vaccination) in mice. However, i.n. priming elicited the highest anti-core antibody levels. Priming with i.d. rAd5-CE1E2 and boosting with i.d. rTTV-CE1E2 carried out simultaneously enhanced CMI and the humoral immune response, compared to the homologous rAd5-CE1E2 immune groups. All regimens demonstrated equivalent cross-protective potency in a heterologous surrogate challenge assay based on a recombinant HCV (JFH1, 2a) vaccinia virus. **CONCLUSIONS:** Our data suggest that a rAd5-CE1E2-based HCV vaccine would be capable of eliciting an effective immune response and cross-protection. These findings have important implications for the development of T cell-based HCV vaccine candidates.

**Serum Cystatin C, a Cysteine Protease Inhibitor, Correlates Negatively with Viral Load in Treatment-Naive Children with Chronic Hepatitis C.** Behairy BE, Saber MA, Elhenawy IA, et al. J Pediatr Gastroenterol Nutr. 2011 Nov 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22064633>

**OBJECTIVES:** Hepatitis C virus (HCV) infection is a serious health problem that establishes a chronic infection in up to 85% of cases. HCV nonstructural (NS) cysteine protease, NS2/3, is required for viral replication in vivo. Cystatin C is a naturally occurring cysteine protease inhibitor in human cells. We aimed to investigate the relation between serum levels of cystatin C and HCV viremia in treatment-naive children with chronic hepatitis C. **METHODS:** Serum cystatin C levels were measured in 27 children with chronic hepatitis C and determined their relation with liver functions, histopathological parameters and hepatitis C viral load. Serum cystatin C was compared with that of 25 age and sex matched healthy controls. **RESULTS:** Cystatin C was significantly higher in patients than that in controls ( $1.4 \pm 0.47$  vs.  $0.99 \pm 0.49$ ;  $P=0.006$ ) and in those with low viremia than in those with moderate viremia ( $1.55 \pm 0.41$  vs.  $0.99 \pm 0.43$ ;  $P=0.013$ ). Cystatin C was not correlated with histopathological findings in liver biopsy ( $P>0.05$  for all). In addition, there was no significant difference of cystatin C levels in patients with normal versus those with elevated transaminases ( $P>0.05$ ). Of importance, cystatin C correlated negatively with viral load ( $P<0.0001$ ). **CONCLUSION:** cystatin C levels correlated negatively with HCV viremia. This finding might reflect a possible inhibitory effect of cystatin C on HCV replication through inhibiting its NS2/3 and tempting for further studies for cystatin C as a possible adjuvant therapy for HCV infection.

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## HIV/HCV COINFECTION

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**PD 404,182 is a virucidal small molecule that disrupts hepatitis C virus and human immunodeficiency virus.** Chamoun AM, Chockalingam K, Bobardt M, et al. Antimicrob Agents Chemother. 2011 Nov 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22083468>

We describe a virucidal small molecule, PD 404,182, effective against hepatitis C virus (HCV) and human immunodeficiency virus (HIV). The median IC(50) values for the antiviral effect of PD 404,182 against HCV and HIV in cell culture are 11  $\mu$ M and 1  $\mu$ M, respectively. The antiviral activity of PD 404,182 is due to physical disruption of virions that is accompanied to

varying degrees (depending on the virus and exposure temperature/time) by release of viral nucleic acids into the surrounding medium. PD 404,182 does not directly lyse liposomal membranes even after extended exposure and shows no attenuation in antiviral activity when pre-incubated with liposomes of various lipid compositions, suggesting that the compound inactivates viruses through interaction with a non-lipid structural component of the virus. The virucidal activity of PD 404,182 appears to be virus-specific as little to no viral inactivation was detected with the enveloped Dengue and Sindbis viruses. PD 404,182 effectively inactivates a broad range of primary isolates of HIV-1 as well as HIV-2 and simian immunodeficiency virus (SIV), and does not exhibit significant cytotoxicity with multiple human cell lines in vitro (CC(50) > 300 µM). The compound is fully active in cervical fluids although exhibiting decreased potency in the presence of human serum, retains its full antiviral potency for over 8 h when in contact with cells and is effective against both cell-free and cell-associated HIV. These qualities make PD 404,182 an attractive candidate microbicide for the prevention of HIV transmission through sexual intercourse.

**Different patterns of dermatological presentations in patients co-infected with human immunodeficiency virus and hepatitis C virus (HCV), and those infected with HCV alone.**

Cunha VS, Meotti C, Oliveira JH, Sprinz E, Alvares-da-Silva MR, Goldani LZ. Clin Exp Dermatol. 2011 Nov 21. doi: 10.1111/j.1365-2230.2011.04217.x. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22103463>

**BACKGROUND:** Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share the same transmission routes. About 30% of HIV-positive patients are co-infected with HCV. Of the various HCV-related extrahepatic events, those involving the skin may be the first sign of infection. **AIM:** To specify the skin presentations in patients co-infected with HIV and HCV (co-infected patients; CP) and compare them with those found in patients with HCV mono-infection (mono-infected patients; MP). **METHODS:** This was a cross-sectional study, in which the studied population consisted of MP and CP from a tertiary hospital in the South of Brazil, who underwent complete skin examination and laboratory tests. **RESULTS:** In total, 201 patients were assessed, of whom 108 were CP, and 93 were MP. Pruritus tended to be more common in MP. MP also had significantly more dermatological conditions (mean of 5.2) than CP (mean of 4.5). In total, 104 different skin diseases were identified. There was a higher prevalence of infectious diseases and pigmentation disorders, such as verruca vulgaris and facial melasma, in CP, whereas trunk and facial telangiectasias, palmar erythema, and varicose veins were more common in MP. **CONCLUSION:** We found a high prevalence of skin conditions both in MP and in CP; however, the patterns of the dermatological conditions were different. CP were found to have significantly fewer skin lesions than MP, but had a higher prevalence of infectious and pigmentation disorders. By contrast, vascular conditions were more common in MP.

**Effects of hepatitis C and HIV on cognition in women: Data from the Women's Interagency HIV Study.** Crystal H, Kleyman I, Anastos K, et al. J Acquir Immune Defic Syndr. 2011 Nov 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22107817>

**OBJECTIVE:** To compare neuropsychological scores in women infected with HIV, women infected with both HIV and hepatitis C, and uninfected subjects. **BACKGROUND:** Some, but not all, studies have demonstrated that dual infection with HCV and HIV has worse effects on

cognition than infection with HIV alone. **DESIGN/METHODS:** The Women's Interagency HIV Study (WIHS) is an ongoing prospective study of the natural history of HIV in women where participants are reevaluated every 6 months. In a cross-sectional analysis, we evaluated the effects of active HIV and HCV-infections on scores on symbol-digit test (SDMT), the Stroop interference test, and trails A and B after controlling for age, ethnicity, education, depression, liver disease, and current or past substance abuse. **RESULTS:** Data were available for 1338 women - 17.8 % had detectable hepatitis C virus and 67% were HIV-seropositive. In fully adjusted general linear models, HCV viremia was not associated with scores on any of the cognitive tests. **CONCLUSION:** In this large sample of women, active HCV infection was not associated with scores on a small battery of neuropsychological tests.

**An interrupted time series evaluation of a hepatitis C intervention for persons with HIV.** Proeschold-Bell RJ, Hoepfner B, Taylor B, et al. AIDS Behav. 2011 Nov;15(8):1721-31.

<http://www.ncbi.nlm.nih.gov/pubmed/21191643>

Accurate HCV knowledge is lacking among high-risk groups, including people with HIV/AIDS (PLWHA). Liver disease primarily due to HCV has emerged as a serious cause of mortality among PLWHA. We used an Interrupted Time Series design to evaluate a social-ecologically based intervention for PLWHA, where an infectious disease clinic serving a six-county intervention area was monitored before (7 months) and after (17 months) intervention onset. The intervention included education of PLWHA and medical providers, HIV/HCV support groups, and adaptation of the patient chart top sheet to include HCV test information. Clinic-level outcomes were assessed prospectively every other week for 2 years by interviewing patients (n = 259) with clinic appointments on assessment days. Abrupt, gradual and delayed intervention effects were tested. Weighted regression analyses showed higher average HCV knowledge and a higher prevalence of patients reporting HCV discussion with their medical providers after intervention onset. A delayed effect was found for HCV awareness, and a gradually increasing effect was found for knowing one's HCV status. Other communities may consider adopting this intervention. Additional HCV interventions for PLWHA with HIV are needed.

**Randomized trial comparing dose reduction and growth factor supplementation for management of hematological side effects in HIV/hepatitis C virus patients receiving pegylated-interferon and ribavirin.** Talal AH, Liu RC, Zeremski M, J Acquir Immune Defic Syndr. 2011 Nov 1;58(3):261-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21876446>

**BACKGROUND:** Pegylated-interferon (PEG-IFN) and ribavirin (RBV), current standard treatment for hepatitis C virus (HCV) infection, are frequently associated with neutropenia and anemia, leading to high treatment discontinuation rates in HIV/HCV-coinfected patients. Our objective was to compare the effectiveness of intervening with hematologic growth factors versus dose reductions of standard HCV therapy for the management of treatment-induced hematologic disorders. **METHODS:** Ninety-two HIV/HCV-coinfected, therapy-naive subjects received PEG-IFN alfa-2b  $1.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{wk}^{-1}$  and RBV  $13 \pm 2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$  for up to 48 weeks. Before treatment initiation, subjects were randomized to subsequently receive growth factors, recombinant human erythropoietin (rHuEPO) and/or granulocyte colony-stimulating factor, or dose reduction (RBV and/or PEG-IFN) for anemia and neutropenia management, respectively. We analyzed the ability of each management strategy to control anemia and neutropenia and the percentage of subjects who achieved a successful treatment outcome according to the different

management strategies. **RESULTS:** During treatment, 43 subjects developed anemia (human erythropoietin, n = 24; dose reduction, n = 19), whereas 25 subjects developed neutropenia (granulocyte colony-stimulating factor, n = 10; dose reduction, n = 15). After the intervention, the increase in both hemoglobin and absolute neutrophil counts did not differ between the 2 side effect management strategies. Sustained response percentages were similar comparing anemic and neutropenic subjects regardless of management strategy (anemia: recombinant human erythropoietin, 29% versus dose reduction, 21%, P = 0.92; neutropenia: granulocyte colony-stimulating factor, 40% versus dose reduction, 20%, P = 0.46). **CONCLUSIONS:** Growth factor supplementation and dose reduction do not seem to differ as management strategies for anemia and neutropenia in HIV/HCV-coinfected individuals treated with PEG-IFN/RBV.

**Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM.** Lambers FA, Prins M, Thomas X, et al. AIDS. 2011 Nov 13;25(17):F21-F27.

<http://www.ncbi.nlm.nih.gov/pubmed/21857492>

**BACKGROUND:** Recent data indicate that seroprevalence of sexually transmitted hepatitis C virus (HCV) infection among MSM is stabilizing in Amsterdam. However, little is known about the incidence of HCV re-infection in MSM who have cleared their HCV infection. We, therefore, studied the incidence of re-infection in HIV-infected MSM who were HCV RNA-negative following HCV treatment of acute primary infection. **METHODS:** Our study population comprised HIV-infected MSM at two large HIV outpatient clinics in Amsterdam, who were previously diagnosed with a sexually transmitted acute HCV infection and tested HCV RNA-negative at the end of treatment. We defined HCV re-infection as detectable HCV RNA in individuals with an undetectable HCV RNA at the end of treatment accompanied by a switch in HCV genotype or clade. Person-time methods were used to calculate the incidence of re-infection. **RESULTS:** Fifty-six persons who became HCV RNA-negative during primary acute HCV treatment were included. Five of the 56 cases relapsed and were not analysed. Eleven persons were re-infected. The incidence of HCV re-infection in this group was 15.2 per 100person-years (95% confidence interval 8.0-26.5). The cumulative incidence was 33% within 2 years. **DISCUSSION:** An alarmingly high incidence of HCV re-infection was found in this group. This high re-infection rate indicates that current prevention measures should be discussed, frequent HCV RNA testing should be continued after successful treatment and, in case of possible relapse, clade typing should be performed to exclude re-infection.

**CXCR3 Expression Elevated on Peripheral CD8(+) Lymphocytes from HIV/HCV Coinfected Individuals.** Kimball P, McDougan F, Stirling R. Viral Immunol. 2011 Nov 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22111598>

HIV/HCV coinfecting patients tend to develop hepatitis C (HCV)-associated liver disorders. Because the chemokine receptor CXCR3 participates in lymphocyte trafficking during hepatic inflammation, it may participate in the escalated liver disorders of coinfecting patients. However, to date, the relative frequency and density of receptor on lymphocytes has not been established. This study compared the CXCR3(+) phenotype under various in vitro conditions between lymphocytes from healthy and coinfecting individuals. Peripheral lymphocytes were stimulated with phytohemagglutinin for 0-7 d and phenotypes were determined by flow cytometry. Secreted cytokines were measured in culture supernatants by ELISA. Phenotypic differences were

observed between groups. CD4(+)CXCR3(+) frequency between groups was equivalent before and during early activation, but increased only among non-infected individuals during late activation ( $p < 0.001$ ). In contrast, CD8(+)CXCR3(+) frequency was consistently greater ( $p < 0.05$ ) among HIV/HCV patients throughout activation. Among those who were non-infected, CD8(+)CXCR3(+) frequency increased ( $p = 0.002$ ) during late activation. However, CD8(+)CXCR3(+) frequency among HIV/HCV patients increased within 24 h of activation ( $p = 0.008$ ), and was nearly universal by late activation ( $p < 0.001$ ). Both groups elaborated Th-1 cytokine profiles; however, coinfecting patients released more inflammatory cytokines ( $p < 0.01$ ) than non-infected individuals. In summary, we demonstrated that CD8(+) lymphocytes from HIV/HCV-infected patients expressed more CXCR3 and showed greater upregulatory ability upon activation. The atypical CXCR3 expression and enhanced Th-1 cytokine elaboration among coinfecting patients could potentially stimulate increased lymphocyte migration during hepatic inflammation.

**Morphine affects HIV-induced inflammatory response without influencing viral replication in human monocyte derived macrophages.** Dave RS. *FEMS Immunol Med Microbiol*. 2011 Nov 3. doi: 10.1111/j.1574-695X.2011.00894.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22066570>

Opiate-abusing individuals are in the top three risk-factor groups for HIV infection. In fact, almost 30% of HIV-infected individuals in the USA are reported to abuse opiates, highlighting the intersection of drugs of abuse with HIV/AIDS. Opiate-abusers are cognitively impaired and suffer from neurological dysfunctions that may lead to high-risk sexual behavior, poor adherence to antiretroviral regimens, and hepatitis-C virus infection. Collectively, these factors may contribute to accelerated HIV CNS disease progression. To understand the role of morphine in disease progression, we sought to determine whether morphine influences HIV-induced inflammation or viral replication in human monocyte-derived macrophages (h-mdms) and MAGI cells infected with HIV and exposed to morphine. Chronic morphine exposure of HIV-infected h-mdms led to significant alterations in secretion of IL-6 and MCP-2. Morphine enhanced IL-6 secretion and blunted MCP-2 secretion from HIV-infected h-mdms. However, exposure of HIV-infected h-mdms to morphine had no effect on TNF- $\alpha$  secretion. Morphine had no effect on later-stages of viral replication in HIV-infected h-mdms. Morphine had a potentially additive effect on the HIV-induced production of IL-6 and delayed HIV-induced MCP-2 production. These results suggest that in HIV-infected opiate abusers an enhanced inflamed CNS might result even when HIV disease is controlled.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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**Rationale, challenges, and participants in a Phase II trial of a botanical product for chronic hepatitis C.** Reddy KR, Belle SH, Fried MW, et al. *Clin Trials*. 2011 Nov 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22058086>

**BACKGROUND:** Chronic hepatitis C is associated with significant morbidity and mortality as a consequence of progression to cirrhosis, hepatocellular carcinoma, and liver failure. Current treatment for chronic hepatitis C with pegylated interferon (IFN) and ribavirin is associated with suboptimal responses and numerous adverse effects. A number of botanical products have been used to treat hepatic disorders. Silymarin, extracted from the milk thistle plant, *Silybum*

marianum (L) Gaertn. (Asteraceae), has been most widely used for various liver disorders, including chronic hepatitis C, B, and alcoholic liver disease. However, the safety and efficacy of silymarin have not been studied systematically in chronic hepatitis C. **PURPOSE:** We describe our strategy for a phased approach for studying the impact of silymarin in hepatitis C, in the context of the unique challenges of botanical product clinical trials and the development of specific and curative antiviral therapy. **METHODS:** This multicenter, randomized, double-masked, placebo-controlled trial was conducted with four clinical centers and a data-coordinating center in the United States, to assess the impact of silymarin therapy in patients with chronic hepatitis C who failed conventional antiviral therapy. **RESULTS:** Key aspects relevant to performing clinical trials of botanical products include early identification of an appropriate product with standard product chemistry, acquisition of pharmacokinetic and dosing information, selection of the appropriate study group, and choosing rigorous outcome variables. Potential limitations Trial participants were chronic hepatitis C patients who were nonsustained virologic responders to IFN-based therapy; therefore, the findings are not generalizable to all hepatitis C populations. Further, alanine aminotransferase, a biochemical liver test, rather than hepatitis viral RNA or liver histology was the primary end point. **CONCLUSIONS:** The challenges identified and addressed during development of this United States multicenter Phase II trial to evaluate silymarin for treatment of patients with chronic hepatitis C infection who had failed to respond successfully to previous IFN-based therapy are common and must be addressed to conduct rigorous trials of botanical products.

**An innovative method to accommodate chinese medicine pattern diagnosis within the framework of evidence-based medical research.** Berle C, Cobbin D, Smith N, Zaslowski C. Chin J Integr Med. 2011 Nov;17(11):824-33. Epub 2011 Nov 6.  
<http://www.ncbi.nlm.nih.gov/pubmed/22057411>

Pattern diagnosis is an integral aspect of Chinese medicine (CM). CM differentiates biomedical diseases into patterns, based upon the patient's symptoms and signs. Pattern identification (PI) is used to diagnose, direct the treatment principle and determine the treatment protocol. Most CM research has used fixed formula treatments for Western-defined diseases with outcomes measured using objective biomedical markers. This article presents an innovative method used in a randomised controlled pilot study using acupuncture for participants with hepatitis C virus. Each participant's CM patterns were identified and quantified at baseline which directed the treatment protocol for the treatment group. Data identified that while each participant expressed different patterns at baseline all participants displayed multiple patterns. Six patterns showed some expression by all 16 participants; Liver (Gan) yin vacuity expressing a group aggregate mean percentage of 47.2, binding depression of Liver qi 46.9, and Liver Kidney (Shen) yin vacuity 45.1. Further sub category gender grouping revealed that pattern ranking changed with gender; Liver yin vacuity (male 53.4%, female 51.93%), binding depression of Liver qi (male 50.0%, female 42.86%) and Liver Kidney yin vacuity (male 42.9%, female 47.96%). The quantification of CM patterns described in this article permitted statistical evaluation of presenting CM patterns. Although this methodology is in its infancy it may have potential use in the integration of PI with rigorous evidence based clinical research. Biomedical markers often do not relate to symptom/signs and therefore this innovative measure may offer an additional CM evaluation

### **Vitamin D: An innate antiviral agent suppressing hepatitis C virus in human hepatocytes.**

Gal-Tanamy M, Bachmetov L, Ravid A, et al. Hepatology. 2011 Nov;54(5):1570-9. doi: 10.1002/hep.24575.

<http://www.ncbi.nlm.nih.gov/pubmed/21793032>

Vitamin D supplementation was reported to improve the probability of achieving a sustained virological response when combined with antiviral treatment against hepatitis C virus (HCV).

**Our aim was** to determine the in vitro potential of vitamin D to inhibit HCV infectious virus production and explore the mechanism(s) of inhibition. Here we show that vitamin D(3) remarkably inhibits HCV production in Huh7.5 hepatoma cells. These cells express CYP27B1, the gene encoding for the enzyme responsible for the synthesis of the vitamin D hormonally active metabolite, calcitriol. Treatment with vitamin D(3) resulted in calcitriol production and induction of calcitriol target gene CYP24A1, indicating that these cells contain the full machinery for vitamin D metabolism and activity. Notably, treatment with calcitriol resulted in HCV inhibition. Collectively, these findings suggest that vitamin D(3) has an antiviral activity which is mediated by its active metabolite. This antiviral activity involves the induction of the interferon signaling pathway, resulting in expression of interferon- $\beta$  and the interferon-stimulated gene, MxA. Intriguingly, HCV infection increased calcitriol production by inhibiting CYP24A1 induction, the enzyme responsible for the first step in calcitriol catabolism.

Importantly, the combination of vitamin D(3) or calcitriol and interferon- $\alpha$  synergistically inhibited viral production. Conclusion: **This study demonstrates** for the first time a direct antiviral effect of vitamin D in an in vitro infectious virus production system. It proposes an interplay between the hepatic vitamin D endocrine system and HCV, suggesting that vitamin D has a role as a natural antiviral mediator. Importantly, our study implies that vitamin D might have an interferon-sparing effect, thus improving antiviral treatment of HCV-infected patients.

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## **EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS**

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### **Rapid Low-cost Detection of Hepatitis C Virus RNA in HCV-infected Patients by Real-time**

**RT-PCR using SYBR Green I.** Shahzamani K, Sabahi F, Merat S, et al. Arch Iran Med. 2011 Nov;14(6):396-400.

<http://www.ncbi.nlm.nih.gov/pubmed/22039844>

**BACKGROUND:** We intend to design and validate a low-cost assay for the detection of hepatitis C virus (HCV) RNA using rapid-cycle RT-PCR. The procedure is performed in a closed system with little risk of contamination allowing PCR and product identification to be performed within one or two hours. **METHODS:** A SYBR Green-based real-time RT-PCR for rapid detection of HCV. Amplicon synthesis was monitored continuously by SYBR Green I, which binds to double stranded DNA during PCR. The PCR products were identified by melting curve analysis. Standard sera with known concentrations of HCV RNA and 150 clinical samples were used to validate our assay. **RESULTS:** The minimum detection level of our assay was less than 50 IU/mL. The results on 100 plasma samples were comparable with commercial assays. **CONCLUSION:** This method is useful for rapid qualitative detection of HCV infection and particularly suitable for routine diagnostic applications.

**Non-invasive predictive score of fibrosis stages in chronic hepatitis C patients based on epithelial membrane antigen in the blood in combination with routine laboratory markers.**

Attallah AM, Abdallah SO, El Sayed AS, et al. *Hepatology*. 2011 Nov;41(11):1075-84. doi: 10.1111/j.1872-034X.2011.00862.x.

<http://www.ncbi.nlm.nih.gov/pubmed/22035384>

**AIM:** The epithelial membrane antigen (EMA) could detect small deposits of liver malignant cells. However, no information exists regarding the use of EMA in patients with chronic hepatitis C (CHC). Therefore, we attempted to evaluate the diagnostic performance of EMA to distinguish patients with different liver fibrosis stages. **METHODS:** Epithelial membrane antigen was identified in sera of 154 CHC patients using Western blot and enzyme linked immunosorbent assay (ELISA). Multivariate discriminant analysis (MDA) and receiver operating characteristic (ROC) curve analyses were used to create a predictive model including EMA in addition to a panel of routine blood markers. A combination algorithm was developed and validated prospectively in 170 CHC additional patients. **RESULTS:** Epithelial membrane antigen at 130 kDa was identified, purified and quantified in sera of CHC patients using ELISA. Based on these encouraging results, we purified and developed a direct ELISA for the quantitation of EMA in sera of CHC. MDA selected a score for the prediction of significant liver fibrosis patients based on measurements of EMA, aspartate aminotransferase to platelet ratio index and albumin. Areas under the ROC curves (AUC) of the score for the three biomarkers were 0.82 for patients with liver fibrosis (F1-F4), 0.86 for significant liver fibrosis (F2-F4), 0.87 for advanced liver fibrosis (F3-F4) and 0.86 for liver cirrhosis (F4). The results of the validation study demonstrated that (74%) of patients could have avoided liver biopsy. **CONCLUSION:** This score was validated for the prediction of liver fibrosis stages and may minimize the need for liver biopsy.

**A Secreted Form of the Asialoglycoprotein Receptor, sH2a, as a Novel Potential Noninvasive Marker for Liver Fibrosis.** Veselkin E, Kondratyev M, Lurie Y, et al. *PLoS One*. 2011;6(11):e27210. Epub 2011 Nov 11.

<http://www.ncbi.nlm.nih.gov/pubmed/22096539>

**BACKGROUND AND AIM:** The human asialoglycoprotein receptor is a membrane heterooligomer expressed exclusively in hepatocytes. A soluble secreted form, sH2a, arises, not by shedding at the cell surface, but by intracellular cleavage of its membrane-bound precursor, which is encoded by an alternatively spliced form of the receptor H2 subunit. Here we determined and report that sH2a, present at constant levels in serum from healthy individuals is altered upon liver fibrosis, reflecting the status of hepatocyte function. **METHODS:** We measured sH2a levels in serum using a monoclonal antibody and an ELISA assay that we developed, comparing with routine liver function markers. We compared blindly pretreatment serum samples from a cohort of 44 hepatitis C patients, which had METAVIR-scored biopsies, with 28 healthy individuals. **RESULTS:** sH2a levels varied minimally for the healthy individuals ( $150 \pm 21$  ng/ml), whereas the levels deviated from this normal range increasingly in correlation with fibrosis stage. A simple algorithm combining sH2a levels with those of alanine aminotransferase allowed prediction of fibrosis stage, with a very high area under the ROC curve of 0.86. **CONCLUSIONS:** sH2a has the potential to be a uniquely sensitive and specific novel marker for liver fibrosis and function.

**Discovery and development of telaprevir: an NS3-4A protease inhibitor for treating genotype 1 chronic hepatitis C virus.** Kwong AD, Kauffman RS, Hurter P, Mueller P. *Nat Biotechnol.* 2011 Nov 8;29(11):993-1003. doi: 10.1038/nbt.2020.

<http://www.ncbi.nlm.nih.gov/pubmed/22068541>

Infection with hepatitis C virus (HCV) is a major medical problem with over 170 million people infected worldwide. Substantial morbidity and mortality are associated with hepatic manifestations (cirrhosis and hepatocellular carcinoma), which develop with increasing frequency in people infected with HCV for more than 20 years. Less well known is the burden of HCV disease associated with extrahepatic manifestations (diabetes, B-cell proliferative disorders, depression, cognitive disorders, arthritis and Sjögren's syndrome). For patients infected with genotype 1 HCV, treatment with polyethylene glycol decorated interferon (peginterferon)  $\alpha$  and ribavirin (PR) is associated with a low (40-50%) success rate, substantial treatment-limiting side effects and a long (48-week) duration of treatment. In the past 15 years, major scientific advances have enabled the development of new classes of HCV therapy, the direct-acting antiviral agents, also known as specifically targeted antiviral therapy for hepatitis C (STAT-C). In combination with PR, the HCV NS3-4A protease inhibitor telaprevir has recently been approved for treatment of genotype 1 chronic HCV in the United States, Canada, European Union and Japan. Compared with PR, telaprevir combination therapy offers significantly improved viral cure rates and the possibility of shortened treatment duration for diverse patient populations. Developers of innovative drugs have to blaze a new path with few validated sign posts to guide the way. Indeed, telaprevir's development was once put on hold because of its performance in a standard IC(50) assay. Data from new hypotheses and novel experiments were required to justify further investment and reduce risk that the drug might fail in the clinic. In addition, the poor drug-like properties of telaprevir were a formidable hurdle, which the manufacturing and formulation teams had to overcome to make the drug. Finally, novel clinical trial designs were developed to improve efficacy and shorten treatment in parallel instead of sequentially. Lessons learned from the development of telaprevir suggest that makers of innovative medicines cannot rely solely on traditional drug discovery metrics, but must develop innovative, scientifically guided pathways for success.

**Directly acting antivirals for hepatitis C and antiretrovirals: potential for drug-drug interactions.** Seden K, Back D. *Curr Opin HIV AIDS.* 2011 Nov;6(6):514-26.

<http://www.ncbi.nlm.nih.gov/pubmed/22001895>

**PURPOSE OF REVIEW:** Boceprevir and telaprevir are directly acting antivirals (DAAs) that have recently been licensed for treatment of hepatitis C virus (HCV) infection. Data in both untreated and previously treated patients indicate a significantly increased sustained virological response (SVR) compared with that observed with conventional therapy. However, the advent of DAA therapy poses specific challenges for HCV treatment in terms of managing drug-drug interactions (DDIs). This review aims to provide a comprehensive summary of DDI with the recently licensed DAAs, including pharmacokinetic data and current recommendations made by the manufacturers and with particular reference to antiretrovirals. Potential for DDIs with the DAAs in clinical development and the mechanisms of interaction are also discussed. **RECENT FINDINGS:** Targeted pharmacokinetic drug interaction studies have demonstrated that both boceprevir and telaprevir are potent inhibitors of the metabolic enzyme cytochrome P4503A4, making them perpetrators of interactions with co-administered medications which are metabolized by this enzyme. In addition, co-administered medications may affect plasma levels

of boceprevir and telaprevir via various mechanisms, some of which remain to be fully elucidated. **SUMMARY:** As a result of DDIs, the concomitant use of some medicines with DAA will be contraindicated, whereas other combinations may require caution, monitoring, or dose modification of the co-administered drug. Management of DDIs with these novel agents will pose a new challenge, and prescriber awareness of the potential for DDIs is fundamental for safe prescribing. Online resources are likely to play a key role in prescriber education and clinical decision-making.

**Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care.** Innes HA, Hutchinson SJ, Allen S, et al. *Hepatology*. 2011 Nov;54(5):1547-1558. doi: 10.1002/hep.24561.

<http://www.ncbi.nlm.nih.gov/pubmed/22045672>

Our objective was to address two shortfalls in the hepatitis C virus (HCV) literature: (1) Few data exist comparing post-treatment liver-related mortality/morbidity in HCV-sustained virologic response (SVR) patients to non-SVR patients and (2) no data exist examining liver-related morbidity among treatment response subgroups, particularly among noncirrhotic SVR patients, a group who in the main are discharged from care without further follow-up. A retrospective cohort of 1,215 previously naïve HCV interferon patients (treated 1996-2007) was derived using HCV clinical databases from nine Scottish clinics. Patients were followed up post-treatment for a mean of 5.3 years. (1) By Cox-regression, liver-related hospital episodes (adjusted hazard ratio [AHR]: 0.22; 95% confidence interval [CI]: 0.15-0.34) and liver-related mortality (AHR: 0.22; 95% CI: 0.09-0.58) were significantly lower in SVR patients, compared to non-SVR patients. (2) Rates of liver-related hospitalization were elevated among all treatment subgroups, compared to the general population: Among noncirrhotic SVR patients, adjusted standardized morbidity ratio (SMBR) up to 5.9 (95% CI: 4.5-8.0); among all SVR patients, SMBR up to 10.5 (95% CI 8.7-12.9); and among non-SVR patients, SMBR up to 53.2 (95% CI: 49.4-57.2). Considerable elevation was also noted among patients who have spontaneously resolved their HCV infection (a control group used to gauge the extent to which lifestyle factors, and not chronic HCV, can contribute to liver-related morbidity), with SMBR up to 26.8 (95% CI: 25.3-28.3).

**CONCLUSIONS:** (1) Patients achieving an SVR were more than four times less likely to be hospitalized, or die for a liver-related reason, than non-SVR patients and (2) although discharged, noncirrhotic SVR patients harbor a disproportionate burden of liver-related morbidity (i.e., up to six times that of the general population). Furthermore, alarming levels of liver-related morbidity in spontaneous resolvers is an important finding warranting further study.

**Hepatitis C virus infection among transmission-prone medical personnel.** Zaaier HL, Appelman P, Frijstein G. *Eur J Clin Microbiol Infect Dis*. 2011 Nov 3. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22045049>

Hepatitis C virus (HCV)-infected physicians have been reported to infect some of their patients during exposure-prone procedures (EPPs). There is no European consensus on the policy for the prevention of this transmission. To help define an appropriate preventive policy, we determined the prevalence of HCV infection among EPP-performing medical personnel in the Academic Medical Center in Amsterdam, the Netherlands. The prevalence of HCV infection was studied among 729 EPP-performing health care workers. Serum samples, stored after post-hepatitis B virus (HBV) vaccination testing in the years 2000-2009, were tested for HCV antibodies. Repeat reactive samples were confirmed by immunoblot assay and the detection of HCV RNA. The

average age of the 729 health care workers was 39 years (range 18-66), suggesting a considerable cumulative occupational exposure to the blood. Nevertheless, only one of the 729 workers (0.14%; 95% confidence interval [CI]: <0.01% to 0.85%) was tested and confirmed to be positive for anti-HCV and positive for HCV RNA, which is comparable to the prevalence of HCV among Amsterdam citizens. Against this background, for the protection of personnel and patients, careful follow-up after needlestick injuries may be sufficient. If a zero-risk approach is desirable and costs are less relevant, the recurrent screening of EPP-performing personnel for HCV is superior to the follow-up of reported occupational exposures.

### **The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S.**

**Primary Care Settings.** Rein DB, Smith BD, Wittenborn JS, et al. *Ann Intern Med.* 2011 Nov 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22056542>

**BACKGROUND:** In the United States, hepatitis C virus (HCV) infection is most prevalent among adults born from 1945 through 1965, and approximately 50% to 75% of infected adults are unaware of their infections. **OBJECTIVE:** To estimate the cost-effectiveness of birth-cohort screening. **DESIGN:** Cost-effectiveness simulation. Data Sources: National Health and Nutrition Examination Survey, U.S. Census, Medicare reimbursement schedule, published sources. Target Population: Adults born from 1945 through 1965 with 1 or more visits to a primary care provider annually. **TIME HORIZON:** Lifetime. Perspective: Societal, health care. Interventions: One-time antibody test of 1945-1965 birth cohort. **OUTCOME MEASURES:** Numbers of cases that were identified and treated and that achieved a sustained viral response; liver disease and death from HCV; medical and productivity costs; quality-adjusted life-years (QALYs); incremental cost-effectiveness ratio (ICER). **RESULTS OF BASE-CASE ANALYSIS:** Compared with the status quo, birth-cohort screening identified 808 580 additional cases of chronic HCV infection at a screening cost of \$2874 per case identified. Assuming that birth-cohort screening was followed by pegylated interferon (pegIFN+R) and ribavirin for treated patients, screening increased QALYs by 348 800 and costs by \$5.5 billion, for an ICER of \$15 700 per QALY gained. Assuming that birth-cohort screening was followed by a direct-acting antiviral, pegIFN+R treatment for treated patients, screening increased QALYs by 532 200 and costs by \$19.0 billion, for an ICER of \$35 700 per QALY saved. **RESULTS OF SENSITIVITY ANALYSIS:** The ICER of birth-cohort screening was most sensitive to sustained viral response rate of antiviral therapy, the cost of therapy, the discount rate and the QALY losses assigned to disease states. **LIMITATION:** Empirical data on screening and direct-acting antiviral treatment in real-world clinical settings are scarce. Conclusion: Birth-cohort screening for HCV in primary care settings was cost-effective.

**Changing trends in viral hepatitis-associated hospitalizations in the American Indian/Alaska native population, 1995-2007.** Byrd KK, Redd JT, Holman RC, Haberling DL, Cheek JE. *Public Health Rep.* 2011 Nov-Dec;126(6):816-25.

<http://www.ncbi.nlm.nih.gov/pubmed/22043097>

**OBJECTIVE:** We described the changing epidemiology of viral hepatitis among the American Indian/Alaska Native (AI/AN) population that uses Indian Health Service (IHS) health care. **METHODS:** We used hospital discharge data from the IHS National Patient Information Reporting System to determine rates of hepatitis A-, B-, and C-associated hospitalization among AI/ANs using IHS health care from 1995-2007 and summary periods 1995-1997 and 2005-2007.

**RESULTS:** Hepatitis A-associated hospitalization rates among AI/AN people decreased from 4.9 per 100,000 population during 1995-1997 to 0.8 per 100,000 population during 2005-2007 (risk ratio [RR] = 0.2, 95% confidence interval [CI] 0.1, 0.2). While there was no significant change in the overall hepatitis B-associated hospitalization rate between time periods, the average annual rate in people aged 45-64 years increased by 109% (RR=2.1, 95% CI 1.4, 3.2). Between the two time periods, the hepatitis C-associated hospitalization rate rose from 13.0 to 55.0 per 100,000 population (RR=4.2, 95% CI 3.8, 4.7), an increase of 323%. The hepatitis C-associated hospitalization rate was highest among people aged 45-64 years, males, and those in the Alaska region. **CONCLUSIONS:** Hepatitis A has decreased to near-eradication levels among the AI/AN population using IHS health care. Hepatitis C-associated hospitalizations increased significantly; however, there was no significant change in hepatitis B-associated hospitalizations. Emphasis should be placed on continued universal childhood and adolescent hepatitis B vaccination and improved vaccination of high-risk adults. Prevention and education efforts should focus on decreasing hepatitis C risk behaviors and identifying people with hepatitis C infection so they may be referred for treatment.

**Motivators and barriers influencing willingness to participate in candidate HCV vaccine trials: Perspectives of people who inject drugs.** Park JN, White B, Bates A, Enriquez J, Liao L, Maher L. *Drug Alcohol Depend.* 2011 Nov 8. [Epub ahead of print]  
<http://www.ncbi.nlm.nih.gov/pubmed/22071117>

**BACKGROUND:** A safe and efficacious vaccine may be the most efficient and cost-effective strategy for controlling the hepatitis C virus (HCV) epidemic among people who inject drugs (PWID) and several candidates are in development. However, little is known about the factors that influence willingness to participate (WTP) in candidate HCV vaccine trials among this group. **METHODS:** HCV seronegative PWID recruited between 2008 and 2010 as part of a prospective observational cohort study in Sydney, Australia were asked whether they would be willing to participate in a future candidate hepatitis C vaccine trial and to provide reasons to explain their decision. **RESULTS:** Of 113 participants, 74% indicated WTP, 15% were unwilling to participate and 11% reported WTP that was contingent on vaccine characteristics and trial design issues. The most commonly reported motivator for hypothetical trial participation was altruism, followed by potential health benefits, financial remuneration, and knowledge gain. Barriers to hypothetical participation included fears about possible harms to health, such as concerns about vaccine safety, side effects, and acquiring HCV from the vaccine; other barriers included mistrust of biomedical research and time constraints. **CONCLUSIONS:** These results may be useful in designing strategies to enhance HCV vaccine trial recruitment and retention and have ethical implications for developing informed consent processes and standards of care.

**Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment.** Harrington PR, Zeng W, Naeger LK. *Hepatology.* 2011 Nov 16. doi: 10.1002/hep.24791. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22095516>

Boceprevir- and telaprevir-based treatments for chronic hepatitis C virus (HCV) infection use specific response-guided therapy (RGT) guidelines. Eligibility for shortened treatment duration is based on achieving Undetectable HCV RNA early during treatment. It is unclear whether a detected HCV RNA level that is below the assay lower limit of quantitation (Detectable/BLOQ)

is comparable to an Undetectable HCV RNA level, particularly regarding RGT decision making. We analyzed data from boceprevir and telaprevir clinical trials to obtain a comprehensive understanding of the frequency and clinical relevance of Detectable/BLOQ HCV RNA measurements. In Phase 3 trials P05216 (boceprevir), C216 (telaprevir) and 108 (telaprevir), Detectable/BLOQ levels were reported for approximately 10-20% of all on-treatment HCV RNA measurements. In P05216 and C216, subjects with Detectable/BLOQ HCV RNA, on average, had a reduced sustained virologic response (SVR) rate compared to subjects with Undetectable HCV RNA at the same on-treatment timepoint. At key RGT timepoints (Week 8 for boceprevir, Week 4 for telaprevir), subjects with Detectable/BLOQ HCV RNA had an approximately 20% lower SVR rate compared to subjects with Undetectable HCV RNA, and this difference widened for later on-treatment timepoints. A similar trend was observed for Study 108, but the differences in SVR rates were more modest, which may be explained by a higher frequency of reported Detectable/BLOQ results. Analyses of Phase 2 boceprevir and telaprevir trials indicated subjects with Detectable/BLOQ HCV RNA at RGT timepoints benefited from extended treatment duration. **CONCLUSIONS:** During boceprevir- and telaprevir-based treatment, subjects with Detectable/BLOQ HCV RNA had a reduced virologic response compared to subjects with Undetectable HCV RNA. Eligibility for shortened treatment duration should be based on patients achieving Undetectable HCV RNA at RGT decision timepoints.

**Predicting clinical outcomes using baseline and follow-up laboratory data from the hepatitis C long-term treatment against cirrhosis trial.** Ghany MG, Kim HY, Stoddard A, et al. *Hepatology*. 2011 Nov;54(5):1527-1537. doi: 10.1002/hep.24550.

<http://www.ncbi.nlm.nih.gov/pubmed/22045670>

Predicting clinical outcomes in patients with chronic hepatitis C is challenging. We used the hepatitis C long-term treatment against cirrhosis (HALT-C) trial database to develop two models, using baseline values of routinely available laboratory tests together with changes in these values during follow-up to predict clinical decompensation and liver-related death/liver transplant in patients with advanced hepatitis C. Patients randomized to no treatment and who had  $\geq 2$ -year follow-up without a clinical outcome were included in the analysis. Four variables (platelet count, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ratio, total bilirubin, and albumin) with three categories of change (stable, mild, or severe) over 2 years were analyzed. Cumulative incidence of clinical outcome was determined by Kaplan-Meier analysis and Cox regression was used to evaluate predictors of clinical outcome. In all, 470 patients with 60 events were used to develop models to predict clinical decompensation. Baseline values of all four variables were predictive of decompensation. There was a general trend of increasing outcomes with more marked worsening of laboratory values over 2 years, particularly for patients with abnormal baseline values. A model that included baseline platelet count, AST/ALT ratio, bilirubin, and severe worsening of platelet count, bilirubin, and albumin was the best predictor of clinical decompensation. A total of 483 patients with 79 events were used to evaluate predictors of liver-related death or liver transplant. A model that included baseline platelet count and albumin as well as severe worsening of AST/ALT ratio and albumin was the best predictor of liver-related outcomes. **CONCLUSION:** Both the baseline value and the rapidity in change of the value of routine laboratory variables were shown to be important in predicting clinical outcomes in patients with advanced chronic hepatitis C.

**Chronic hepatitis c genotype-4 infection: role of insulin resistance in hepatocellular carcinoma.** Mohamed AA, Loutfy SA, Craik JD, M Hashem AG, Siam I. *Virology*. 2011 Nov 1;8:496.

<http://www.ncbi.nlm.nih.gov/pubmed/22044490>

**BACKGROUND:** Hepatitis C virus (HCV) is a major cause of chronic hepatitis and hepatocellular carcinoma (HCC) and different HCV genotypes show characteristic variations in their pathological properties. Insulin resistance (IR) occurs early in HCV infection and may synergize with viral hepatitis in HCC development. Egypt has the highest reported rates of HCV infection (predominantly genotype 4) in the world; this study investigated effects of HCV genotype-4 (HCV-4) on prevalence of insulin resistance in chronic hepatitis C (CHC) and HCC in Egyptian patients. **METHODS:** Fifty CHC patients, 50 HCC patients and 20 normal subjects were studied. IR was estimated using HOMA-IR index and HCV-4 load determined using real-time polymerase chain reaction. Hepatitis B virus was excluded by enzyme-linked immunosorbent assay. Standard laboratory and histopathological investigations were undertaken to characterize liver function and for grading and staging of CHC; HCC staging was undertaken using intraoperative samples. **RESULTS:** HCC patients showed higher IR frequency but without significant difference from CHC (52% vs 40%,  $p = 0.23$ ). Multivariate logistic regression analysis showed HOMA-IR index and International Normalization Ratio independently associated with fibrosis in CHC; in HCC, HbA1c, cholesterol and bilirubin were independently associated with fibrosis. Fasting insulin and cholesterol levels were independently associated with obesity in both CHC and HCC groups. Moderate and high viral load was associated with high HOMA-IR in CHC and HCC ( $p < 0.001$ ). **CONCLUSIONS:** IR is induced by HCV-4 irrespective of severity of liver disease. IR starts early in infection and facilitates progression of hepatic fibrosis and HCC development.

**Enhancement of Canonical Wnt/ $\beta$ -Catenin Signaling Activity by HCV Core Protein Promotes Cell Growth of Hepatocellular Carcinoma Cells.** Liu J, Ding X, Tang J, et al. *PLoS One*. 2011;6(11):e27496. Epub 2011 Nov 15.

<http://www.ncbi.nlm.nih.gov/pubmed/22110662>

**BACKGROUND:** The Hepatitis C virus (HCV) core protein has been implicated as a potential oncogene or a cofactor in HCV-related hepatocellular carcinoma (HCC), but the underlying mechanisms are unknown. Overactivation of the Wnt/ $\beta$ -catenin signaling is a major factor in oncogenesis of HCC. However, the pathogenesis of HCV core-associated Wnt/ $\beta$ -catenin activation remains to be further characterized. Therefore, we attempted to determine whether HCV core protein plays an important role in regulating Wnt/ $\beta$ -catenin signaling in HCC cells. **METHODOLOGY:** Wnt/ $\beta$ -catenin signaling activity was investigated in core-expressing hepatoma cells. Protein and gene expression were examined by Western blot, immunofluorescence staining, RT-qPCR, and reporter assay. **PRINCIPAL FINDINGS:** HCV core protein significantly enhances Tcf-dependent transcriptional activity induced by Wnt3A in HCC cell lines. Additionally, core protein increases and stabilizes  $\beta$ -catenin levels in hepatoma cell line Huh7 through inactivation of GSK-3 $\beta$ , which contributes to the up-regulation of downstream target genes, such as c-Myc, cyclin D1, WISP2 and CTGF. Also, core protein increases cell proliferation rate and promotes Wnt3A-induced tumor growth in the xenograft tumor model of

human HCC. **CONCLUSIONS/SIGNIFICANCE:** HCV core protein enhances Wnt/ $\beta$ -catenin signaling activity, hence playing an important role in HCV-associated carcinogenesis.

**Family history of liver cancer and hepatocellular carcinoma.** Turati F, Edefonti V, Talamini R, et al. *Hepatology*. 2011 Nov 16. doi: 10.1002/hep.24794. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22095619>

Familial clustering of hepatocellular carcinoma (HCC) has been reported frequently among eastern Asiatic countries, where hepatitis B infection is common. Little is known about the relationship between family history of liver cancer and HCC in Western populations. We carried out a case-control study in Italy, involving 229 HCC cases and 431 hospital controls. Data on family history were summarized through a binary indicator (yes/no) and a family history score (FHscore), considering selected family characteristics. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were obtained from unconditional multiple logistic regression models including terms for age, sex, study center, education, tobacco smoking, alcohol drinking, hepatitis B surface antigen and/or anti-hepatitis C virus positivity. We also performed a meta-analysis on family history and liver cancer updated to April 2011 using random-effects models. After adjustment for chronic infection with hepatitis B/C viruses, family history of liver cancer was associated to HCC risk, when using both the binary indicator (OR=2.38, 95% CI, 1.01-5.58) and the FHscore, with increasing ORs for successive score categories. Compared to subjects without family history and no chronic infection with hepatitis B/C viruses, the OR for those exposed to both risk factors was 72.48 (95% CI, 21.92-239.73). In the meta-analysis, based on 9 case-control and 4 cohort studies, for a total of about 3600 liver cancer cases, the pooled relative risk for family history of liver cancer was 2.50 (95% CI, 2.06-3.03). **CONCLUSION:** A family history of liver cancer increases HCC risk, independently of hepatitis. The combination of family history of liver cancer and hepatitis B/C serum markers is associated to an over 70-fold elevated HCC risk.

**Total and high molecular weight adiponectin and hepatocellular carcinoma with HCV infection.** Sumie S, Kawaguchi T, Kuromatsu R, et al. *PLoS One*. 2011;6(11):e26840. Epub 2011 Nov 14.

<http://www.ncbi.nlm.nih.gov/pubmed/22110596>

**BACKGROUND:** Adiponectin is shown to be inversely associated with development and progression of various cancers. We evaluated whether adiponectin level was associated with the prevalence and histological grade of hepatocellular carcinoma (HCC), and liver fibrosis in patients with hepatitis C virus (HCV) infection. **METHODS:** A case-control study was conducted on 97 HCC patients (cases) and 97 patients (controls) matched for sex, Child-Pugh grade and platelet count in patients with HCV infection. The serum total and high molecular weight (HMW) adiponectin levels were measured by enzyme-linked immunosorbent assays and examined in their association with the prevalence of HCC. In addition, the relationship between these adiponectin levels and body mass index (BMI), progression of liver fibrosis, and histological grade of HCC was also evaluated. Liver fibrosis was assessed using the aspartate aminotransferase to platelet ratio index (APRI). **RESULTS:** There were no significant differences in the serum total and HMW adiponectin levels between cases and controls. Moreover, there were no inverse associations between serum total and HMW adiponectin levels and BMI in both cases and controls. On the other hand, serum total and HMW adiponectin levels are positively correlated with APRI in both cases ( $r=0.491$ ,  $P<0.001$  and  $r=0.485$ ,  $P<0.001$ ,

respectively) and controls ( $r=0.482$ ,  $P<0.001$  and  $r=0.476$ ,  $P<0.001$ , respectively). Interestingly, lower serum total (OR 11.76, 95% CI: 2.97-46.66 [ $P<0.001$ ]) and HMW (OR 10.24, CI: 2.80-37.40 [ $P<0.001$ ]) adiponectin levels were independent risk factors of worse histological grade of HCC. **CONCLUSIONS:** Our results suggested that serum total and HMW adiponectin levels were predictors of liver fibrosis, but not prevalence of HCC in patients with HCV infection. Moreover, low these adiponectin levels were significantly associated with worse histological grades.

**The PNPLA3 rs738409 148M/M Genotype Is a Risk Factor for Liver Cancer in Alcoholic Cirrhosis but Shows No or Weak Association in Hepatitis C Cirrhosis.** Nischalke HD, Berger C, Luda C, et al. PLoS One. 2011;6(11):e27087. Epub 2011 Nov 7.

<http://www.ncbi.nlm.nih.gov/pubmed/22087248>

**BACKGROUND:** An isoleucine>methionine mutation at position 148 in the PNPLA3 gene (p.I148M, rs738409) has recently been identified as a susceptibility factor for liver damage in steatohepatitis. Here, we studied whether the PNPLA3 rs738409 polymorphism also affects predisposition to hepatocellular carcinoma (HCC). **METHODS:** We compared distributions of PNPLA3 genotypes in 80 and 81 Caucasian patients with alcoholic and hepatitis C virus (HCV)-associated HCC to 80 and 81 age- and sex-matched patients with alcohol-related and HCV-related cirrhosis without HCC, respectively. PNPLA3 genotypes in 190 healthy individuals from the same population served as reference. Potential confounders obesity, diabetes, HCV genotype and HBV co-infection were controlled by univariate and multivariate logistic regression with forward variable selection. **RESULTS:** PNPLA3 genotypes were in Hardy-Weinberg equilibrium for all study groups. The frequency of the 148M allele was significantly ( $p<0.001$ ) increased in alcoholic cirrhosis with (53.7%) and without HCC (36.2%) but was not different between healthy controls (22.9%) and patients with cirrhosis (25.3%;  $p=0.545$ ) and HCC (30.2%;  $p=0.071$ ) due to hepatitis C. HCC risk was highest in 148M/M homozygous patients with alcoholic liver disease (odds ratio (OR) 16.8 versus healthy controls; 95% confidence interval (CI) 6.68-42.43,  $p<0.001$ ). Finally, multivariate regression confirmed 148M/M homozygosity (OR 2.8; 95%-CI: 1.24-6.42;  $p=0.013$ ) as HCC risk factor in alcoholic cirrhosis. In HCV-related cirrhosis only HCV genotype 1 was confirmed as a HCC risk factor (OR 4.2; 95%-CI: 1.50-11.52;  $p=0.006$ ). **CONCLUSION:** The PNPLA3 148M variant is a prominent risk factor for HCC in patients with alcoholic cirrhosis, while its effects are negligible in patients with cirrhosis due to HCV. This polymorphism provides an useful tool to identify individuals with particularly high HCC risk in patients with alcoholic liver disease that should be taken into account in future HCC prevention studies.

**Risk of Hepatocellular Carcinoma in Diabetic Patients and Risk Reduction Associated With Anti-Diabetic Therapy: A Population-Based Cohort Study.** Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Am J Gastroenterol. 2011 Nov 15. doi: 10.1038/ajg.2011.384. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22085817>

**OBJECTIVES:** Using population-based representative insurance claims data, the risk of developing hepatocellular carcinoma (HCC) among diabetes mellitus (DM) patients, as well as whether DM medications alter the risk of developing HCC were investigated. **METHODS:** From the Taiwan National Health Insurance Research Database, 19,349 newly diagnosed DM patients 20 years and older and 77,396 comparison subjects without DM were identified from

claims from 2000 to 2005. The incidences of HCC at the end of 2008 and the risks associated with hepatitis B and hepatitis C were determined. Whether metformin and thiazolidinediones reduce the risk of developing HCC was also measured. **RESULTS:** The incidence of HCC was twice higher in the DM group compared with the non-DM group (21.0 vs. 10.4 per 10,000 person-years), with an adjusted hazard ratio (HR) of 1.73 (95% confidence interval (CI)=1.47-2.03) using multivariable Cox proportional hazard regression. Male sex, cirrhosis, hepatitis B, and hepatitis C were significant independent factors that predict HCC, with HRs of 2.32, 8.65, 2.52, and 5.61, respectively. In the stratified analysis, the HR increased to 72.4 (95% CI=42.9-122) among patients with DM, cirrhosis, and hepatitis C. HCC risk reduction was greater for diabetics taking metformin than those taking thiazolidinediones (51 vs. 44% reduction). **CONCLUSIONS:** Comorbidity with cirrhosis and/or hepatitis appears to be associated with an extremely increased risk of developing HCC among DM patients. These high-risk patients should be closely monitored for HCC. The use of metformin or thiazolidinediones may reduce the risk of developing HCC.

**The influence of postoperative glycemic control on recurrence after curative resection in diabetics with hepatitis C virus-related hepatocellular carcinoma.** Kaneda K, Uenishi T, Takemura S, et al. *J Surg Oncol.* 2011 Nov 7. doi: 10.1002/jso.22137. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22065536>

**BACKGROUND AND OBJECTIVES:** To elucidate the influence of diabetes on tumor recurrence after curative resection for hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). **METHODS:** A total of 100 patients who underwent curative resection for solitary HCV-related HCC were analyzed. Data from 26 patients with diabetes were compared to those of 74 patients without diabetes. The two groups were matched in terms of presence of cirrhosis, Child-Pugh classification, and tumor size (within 10%). **RESULTS:** Tumor-free survival rates were 45% and 48% at 3 years and 27% and 27% at 5 years in patients with and without diabetes, respectively. No significant difference was observed in the tumor-free survival rates between patients with and without diabetes. Tumor-free survival rates were 66% and 27% at 3 years in patients with normal postoperative glycated hemoglobin (HbA1c) level (HbA1c, <6.5%) and elevated postoperative HbA1c level (HbA1c, ≥6.5%), respectively. Multivariate analysis showed that poor glycemic control (HbA1c, ≥6.5%) was associated with postoperative tumor recurrence in patients with diabetes [odds ratio (OR) = 3.551, 95% confidence interval (CI) = 1.129-11.172, P = 0.030]. **CONCLUSIONS:** Careful control of plasma glucose should be performed to prevent tumor recurrence after curative resection for HCV-related HCC in patients with diabetes.

**Identification of Four Isoforms of Aldolase B Down-regulated in Hepatocellular Carcinoma Tissues by Means of Two-dimensional Western Blotting.** Wang Y, Kuramitsu Y, Takashima M, et al. *In Vivo.* 2011 Nov;25(6):881-6.

<http://www.ncbi.nlm.nih.gov/pubmed/22021680>

**BACKGROUND:** Hepatocellular carcinoma (HCC) is one of the most lethal diseases, and one of the major causes of death in Japan. Our previous research of proteomics for cancerous and paired non-cancerous tissues from patients with HCC with hepatitis C virus infection (HCV-HCC) by means of the combination of two-dimensional gel electrophoresis (2-DE) and liquid chromatography tandem mass spectrometry (LC-MS/MS) reported that four of numerous spots of weaker intensity in cancerous tissues than in paired non-cancerous tissues were identified as four isoforms of liver type aldolase (aldolase B). In the present study, two-dimensional (2-D)

Western blot analysis demonstrated a significantly lower expression of four isoforms of aldolase B in cancerous than in non-cancerous tissues. **CONCLUSION:** Our finding of differences of expression aldolase B isoforms between cancerous and paired non-cancerous tissues for HCV-HCC may be useful for shedding light on some behaviors of aldolase B during hepatocellular carcinogenesis.

**Screening serum biomarkers for early primary hepatocellular carcinoma using a phage display technique.** Zhang Z, Xu L, Wang Z. J Clin Lab Anal. 2011 Nov;25(6):402-8. doi: 10.1002/jcla.20491.

<http://www.ncbi.nlm.nih.gov/pubmed/22086793>

Hepatocellular carcinoma (HCC) occurs mainly in chronically diseased livers following hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Early detection and diagnosis of HCC would be of great clinical benefit. In this study, we used a random phage display peptide library and sera from early-stage primary HCC patients (n = 30) to screen potential serum biomarkers for early primary HCC. Age- and sex-matched patients with HBV and/or HCV infection were used as controls. In the screening phase, 19 out of 20 randomly selected phage clones exhibited specific reaction with purified sera IgG from early primary HCC patients, among them 14 coming from the same phage clone with inserted peptidesequence RGWCRPLPKGEG (named HC1). In the validation phase, phage ELISA results showed that the positive reaction rate of the HC1 phage clone was 91.4% with the early HCC group (n = 70), significantly higher than that with the HBV infection group (20.0%) (n = 70), the HCV infection group (12.9%) (n = 70), the HBV + HCV infection group (24.3%) (n = 70), the cirrhosis group (17.1%) (n = 70), and the healthy control group (10.0%) (n = 70). **In conclusion,** the HC1 mimic peptide showed high diagnostic validity for early primary HCC, and thereby could be a candidate serum biomarker for early primary HCC.

**Decrease in alpha-fetoprotein levels predicts reduced incidence of hepatocellular carcinoma in patients with hepatitis C virus infection receiving interferon therapy: a single center study.** Osaki Y, Ueda Y, Marusawa H, et al. J Gastroenterol. 2011 Nov 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22105231>

**BACKGROUND:** Increasing evidence suggests the efficacy of interferon therapy for hepatitis C in reducing the risk of hepatocellular carcinoma (HCC). The aim of this study was to identify predictive markers for the risk of HCC incidence in chronic hepatitis C patients receiving interferon therapy. **METHODS:** A total of 382 patients were treated with standard interferon or pegylated interferon in combination with ribavirin for chronic hepatitis C in a single center and evaluated for variables predictive of HCC incidence. **RESULTS:** Incidence rates of HCC after interferon therapy were 6.6% at 5 years and 13.4% at 8 years. Non-sustained virological response (non-SVR) to antiviral therapy was an independent predictor for incidence of HCC in the total study population. Among 197 non-SVR patients, independent predictive factors were an average alpha-fetoprotein (AFP) integration value  $\geq 10$  ng/mL and male gender. Even in patients whose AFP levels before interferon therapy were  $\geq 10$  ng/mL, reduction of average AFP integration value to  $< 10$  ng/mL by treatment was strongly associated with a reduced incidence of HCC. This was significant compared to patients with average AFP integration values of  $\geq 10$  ng/mL (P = 0.009). **CONCLUSIONS:** Achieving sustained virological response (SVR) by interferon therapy reduces the incidence of HCC in hepatitis C patients treated with interferon.

Among non-SVR patients, a decrease in the AFP integration value by interferon therapy closely correlates with reduced risk of HCC incidence after treatment.

**FIB-4 Index Is Associated with Hepatocellular Carcinoma Risk in HIV-Infected Patients.**

Park LS, Tate JP, Justice AC, et al. Cancer Epidemiol Biomarkers Prev. 2011 Nov 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22028407>

**BACKGROUND:** Chronic inflammation caused by hepatitis B virus infection, hepatitis C virus infection, and/or heavy alcohol use can lead to fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC). FIB-4 is an index score calculated from platelet count, alanine transaminase, aspartate transaminase, and age that predicts fibrosis and cirrhosis. We hypothesized that high FIB-4 would be associated with development of HCC in HIV-infected persons, who are at high risk due to high prevalence of viral hepatitis and alcohol consumption, and possibly due to HIV infection itself. **METHODS:** Using proportional hazards models, we tested this hypothesis among 22,980 HIV-infected men from the Veterans Aging Cohort Study. We identified incident HCC cases from the Veterans Affairs Central Cancer Registry. **RESULTS:** During follow-up, there were 112 incident HCC diagnoses. The age- and race/ethnic group-adjusted HR was 4.2 [95% confidence interval (CI), 2.4-7.4] for intermediate FIB-4 and 13.0 (95% CI, 7.2-23.4) for high FIB-4, compared with low FIB-4. After further adjustment for enrollment year, CD4 count, HIV-1 RNA level, antiretroviral therapy use, hepatitis B and C virus infection, alcohol abuse/dependency, and diabetes, FIB-4 remained a strong, significant, independent risk factor for HCC. The multivariate-adjusted HR was 3.6 (95% CI, 2.1-6.4) for intermediate FIB-4 and 9.6 (95% CI, 5.2-17.4) for high FIB-4. **CONCLUSIONS:** Calculated from routine, noninvasive laboratory tests, FIB-4 is a strong, independent HCC risk factor in HIV-infected patients. **IMPACT:** FIB-4 might prove valuable as an easily measured index to identify those at highest risk for HCC, even prior to development of clinical cirrhosis.

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**AASLD HIGHLIGHTS - HCV: CLINICAL TRIALS AND THERAPEUTIC DEVELOPMENTS**

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**Efficacy and safety of telaprevir-based regimens in cirrhotic patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure: subanalysis of the REALIZE Phase III study** Dr. Stanislas Pol The Liver Meeting AASLD 2011 #31

**BACKGROUND:** Patients with cirrhosis due to HCV genotype 1 (G1) infection have low rates of sustained virologic response (SVR) with peginterferon/ribavirin (PR). In this REALIZE subanalysis, we assessed the efficacy and safety of telaprevir (TVR, T) plus PR in G1 patients with cirrhosis and prior PR treatment failure. **METHODS:** Patients were randomized to 48 weeks total treatment with PR alone or one of two T/PR regimens: 12 weeks T/PR plus 36 weeks PR alone, or 4 weeks PR alone followed by 12 weeks T/PR and 32 weeks PR alone. Efficacy and safety variables were reanalyzed for patients with and without baseline (BL) cirrhosis; associations were explored between BL variables and other prognostic factors in cirrhotic patients by univariate and multivariate logistic regression analyses. **RESULTS:** Of 662 patients randomized, 578 with complete BL information were included in this analysis. Cirrhotic patients (n=143) were slightly older and more likely to be prior null responders. T/PR was associated with higher SVR rates than PR alone in patients with cirrhosis. Cirrhotic patients had lower SVR rates than non-cirrhotics (except previous relapsers), however the treatment effect of T/PR vs PR

was maintained (Table). In cirrhotic patients receiving T/PR, high BL LDL, high BL ALT or AST and prior PR response were significantly associated with SVR in univariate analyses; the latter two factors also predicted SVR in multivariate analyses ( $p < 0.025$ ). In patients failing a T/PR regimen, there was no association between the presence or level of TVR resistance and stage of fibrosis. Rash, pruritus and anemia ( $Hb < 10$  g/dL) were more frequent in cirrhotic patients receiving T/PR (43%, 55%, 44%, respectively) than PR (27%, 35%, 27%, respectively). Adverse events led to TVR discontinuation in 15% of cirrhotic and 11% of non-cirrhotic patients. **CONCLUSIONS:** T/PR was associated with increased SVR rates versus PR alone irrespective of cirrhosis, even if patients with cirrhosis had lower SVR rates than those without cirrhosis. In cirrhotics, prior response to PR therapy and high BL ALT or AST predicted response to a T/PR regimen.

**Predictors of virologic response with telaprevir-based combination treatment in HCV genotype 1-infected patients with prior peginterferon/ribavirin treatment failure: post-hoc analysis of the Phase III REALIZE study** Dr. Thomas Berg The Liver Meeting AASLD 2011 #32

**BACKGROUND:** The effect of baseline (BL) patient characteristics and on-treatment response at Week 4 and 12 on sustained virologic response (SVR) was investigated in patients who had prior PR treatment failure and received the direct-acting antiviral telaprevir (TVR, T) plus peginterferon alfa-2a (P) and ribavirin (R) in the Phase III REALIZE study. **METHODS:** Patients stratified by prior PR response (relapse vs null/partial) and BL HCV RNA levels ( $<$  or  $\geq 800,000$  IU/mL) were randomized to 48 weeks of treatment comprising: 12 weeks of TVR (750mg q8h) + P (180 $\mu$ g/week) + R (1000-1200mg/day) (either without [T12/PR48] or with [LI T12/PR48] a 4-week PR lead-in) followed by PR, or PR alone (PR48). In this post-hoc analysis, multiple logistic regression analyses explored the prognostic value of BL host and viral factors on SVR. On-treatment response as defined by eRVR (undetectable HCV RNA at Weeks 4 and 12) was also evaluated. **RESULTS:** Of 662 randomized patients, data were available for 578: 28%, 19% and 53% were prior null responders, partial responders or relapsers, respectively; 69% male; 5% black; mean age 51 years; 88% with HCV RNA levels  $\geq 800,000$  IU/mL; and 25% had cirrhosis. Mean low density lipoprotein (LDL) was 2.6 mmol/L. BL factors predictive of SVR are summarized in the table. The effect of fibrosis stage was most prominent in TVR prior non-responders (OR=0.60 (0.45,0.81)) and PR48 relapsers (OR=0.41 (0.20,0.81)). The effect of BL HCV RNA levels was most prominent in PR48 patients, irrespective of type of prior response ( $P < 0.05$ ), but was not significant among TVR patients. When included, eRVR was the strongest predictor of SVR (OR=7.8 (4.7,12.9)). Age, race, ALT/AST, gender, BMI, HOMA-IR, HDL, triglycerides, GGT were not independently predictive of SVR ( $P > 0.05$  for each) in the overall population. **CONCLUSIONS:** TVR added to PR significantly improves SVR rates in HCV genotype 1-infected patients who failed prior PR treatment. Previous response to PR, BL LDL and fibrosis stage remain significant predictors of SVR with TVR-based regimen. On-treatment response (eRVR) was the strongest predictor of SVR when added to the model.

**Once Daily PSI-7977 plus RBV: Pegylated interferon-ALFA not required for Complete Rapid viral response in Treatment-naïve Patients with HCV GT2 or GT3**

Dr. Edward Gane The Liver Meeting AASLD 2011 #34

**BACKGROUND:** PSI-7977, a uridine nucleotide analog, has demonstrated potent on-therapy viral kinetics in combination with pegylated-interferon and ribavirin in HCV GT 1, 2 and 3,

leading to 100% SVR12 in GT 2/3 subjects after a 12 week treatment course (PROTON, EASL 2011) and as monotherapy in HCV GT1 (NUCLEAR, EASL 2011). This may be attributed to its inherent antiviral potency, a lack of pre-existing resistant HCV variants and/or no impact of IL-28b genotype. Thus, this study is designed to determine the optimal duration of pegylated-interferon alfa-2a (PEG), if any, required to achieve SVR in HCV GT2 or GT3 subjects when PSI-7977 is combined with ribavirin (RBV) for 12 weeks. **METHODS:** Treatment-naïve non-cirrhotic patients with HCV GT2 or GT3 were stratified by IL28B SNP (rs12979860) and HCV RNA and randomized to receive PSI-7977 (400 mg) plus RBV for 12 weeks, with PEG for 0, 4, 8, or 12 weeks with 10 subjects per group. Viral dynamics from interferon-containing arms are combined in this analysis through week 4. **RESULTS:** 40 patients were enrolled, mean BL HCV RNA 6.49 log<sub>10</sub>IU/mL, with 42.5% CC genotype at the IL28B SNP. At the time of abstract submission, 34 of the 40 subjects enrolled have results at Week 4, including all 10 of the PEG-free subjects. Week 4 antiviral response rates were similar in the PEG-free and PEG-containing arms as assessed by decline in HCV RNA and proportion of subjects with HCV RNA **CONCLUSIONS:** PSI-7977 with RBV elicited rapid declines in HCV RNA when administered with or without PEG. No viral breakthrough has been observed to date. High on-treatment response and lack of viral resistance, even in the absence of PEG, confirm the high barrier to resistance in this patient population. The potent antiviral efficacy in association with a promising safety profile, support the continued exploration of PSI-7977 with abbreviated interferon duration, as monotherapy, or with other DAA in patients with all HCV genotypes.

**Retreatment with telaprevir/Peg-IFN/RBV after a short exposure to telaprevir in Phase I studies: interim results from a Phase IIIb rollover trial (C219)** Christoph Sarrazin The Liver Meeting AASLD 2011 #35

**BACKGROUND:** C219 is a rollover study evaluating a telaprevir (TVR)-containing regimen for genotype 1 HCV-infected patients who either had treatment failure with peginterferon/ribavirin (Peg-IFN/RBV) alone in the TVR REALIZE trial, or had received at least 1 dose of TVR (alone or in combination with Peg-IFN/RBV) in the Phase I studies, and had not subsequently achieved a sustained virologic response (SVR). An interim analysis was performed at Week 8 to evaluate the antiviral activity and safety of TVR plus Peg-IFN/RBV in patients with previous short-term exposure to TVR. **METHODS:** Nine HCV genotype 1-infected patients (6 subtype 1a, 3 subtype 1b) who had previously received TVR (450mg q8h [n=2], 750mg q8h [n=3], 1250mg q12h [n=3], 750mg q8h plus Peg-IFN [n=1]) for 14 days in Study 101 (n=8) or 103 (n=1) were enrolled in this subsequent study (C219). Six were treatment-experienced prior to Study 101. TVR-resistant variants had been detected by clonal sequence analysis after dosing in Study 101/103 for all patients with available genotypic data (n=8). In Study C219, all 9 patients received TVR 750mg q8h plus Peg-IFN/RBV for 12 weeks, followed by 36 weeks of Peg-IFN/RBV. HCV RNA levels were determined using COBAS TaqMan assay with lower limits of quantification and detection of 25 and 10 IU/mL, respectively. **RESULTS:** All 9 patients completed the Week 8 visit: 56% (n=5) were male, 100% were Caucasian, 100% had baseline HCV RNA  $\geq$ 800,000 IU/mL, 44% (n=4) had cirrhosis, median time since last TVR exposure was 5.7 years (range 4.9-6.0). No TVR-resistant variants were detected by population sequencing before entering Study C219. Patients exhibited a rapid decline in HCV RNA during the first 8 weeks of treatment (Table). One patient had an unconfirmed viral breakthrough at Week 8. All patients with cirrhosis had HCV RNA <25 IU/mL at Week 8. Seven patients (78%) reported an adverse event (AE), all grade 1 or 2 in severity. The most common AEs were fatigue

(n=5), rash events (n=4), influenza-like illness and depression (n=3 each). **CONCLUSIONS:** Among patients with previous TVR exposure, 89% had HCV RNA <25 IU/mL at Week 8 of retreatment with TVR 750mg q8h plus Peg-IFN/RBV, comparable with that seen in patients who were TVR-treatment naïve. The observed safety profile of the TVR regimen was consistent with previous studies.

**SILEN-C3: Treatment for 12 or 24 weeks with BI201335 combined with peginterferon alfa-2a and ribavirin (P/R) in treatment-naïve patients with chronic genotype-1 HCV infection**  
Douglas T. Dieterich The Liver Meeting AASLD 2011 #36

**BACKGROUND AND AIMS:** BI201335 is a highly potent hepatitis C virus (HCV) NS3/4A protease inhibitor given once daily (QD). The trial evaluated the optimal treatment duration of BI201335. **METHODS:** 159 treatment-naïve HCV genotype-1 patients were randomized in this open-label, phase II trial to receive 120 mg QD BI201335 for 12 or 24 weeks, each after 3 days lead-in with P/R. In both groups, P/R was given for 24 weeks. Patients not achieving extended rapid virological response (eRVR), defined as viral load (VL) <25 IU/mL (Roche TaqMan, lower limit of quantification 25 IU/mL) at Week 4 and undetected at Weeks 8-18, continued P/R up to Week 48. **RESULTS:** 71.6% and 82.1% of patients in the 12- and 24-week groups achieved eRVR and stopped all treatment at Week 24. SVR rates were 63% and 71.8% (not significant) in the 12- and 24-week groups, respectively. Similar patient numbers in both groups achieved first undetectable VL within 8 weeks treatment (Table). Undetectable VL at Week 8 correlated closely with SVR. Patients attaining undetectable VL later than Week 8 did not achieve SVR, whereas patients with first negative VL before Week 8 had similar SVR rates, whether treated for 12 or 24 weeks (80.0% and 82.4%). The reduced SVR in the 12-week group was due to a random imbalance of patients who never achieved undetectable VL. Safety and tolerability in the 12- and 24-week groups, respectively, were similar to historical P/R reports, including mild gastrointestinal disorders (57% and 48%), rash or photosensitivity (28% and 25%), and jaundice (3.8% and 5.1%) due to isolated unconjugated hyperbilirubinemia. **CONCLUSIONS:** BI201335 120 mg QD with P/R achieved high efficacy with good safety and tolerability. There was no advantage of 24 weeks over 12 weeks treatment duration of BI201335. Phase III trials testing different doses and durations of BI201335 are ongoing.

**Once-Daily PSI-7977 Plus Peg/RBV in Treatment-naïve Patients with HCV GT1: Robust End of Treatment Response Rates are Sustained Post-treatment** Eric Lawitz The Liver Meeting AASLD 2011 #225

**BACKGROUND:** PSI-7977 (uridine nucleotide analog) is being studied in PROTON, a Phase 2b dose-ranging study of PSI-7977 with pegylated-interferon alfa-2a/ribavirin (PEG/RBV) in patients with HCV genotype 1 (GT1). 98% RVR and 96% cEVR were reported for this GT1 population (EASL 2011). **METHODS:** Treatment-naïve, non-cirrhotic patients with HCV GT1, stratified by IL28B SNP (rs12979860), were randomized 2:2:1 to PSI-7977 200mg, 400mg, or placebo (pbo), plus PEG/RBV for 12 weeks, followed by 12 or 36 weeks PEG/RBV if HCV RNA **RESULTS:** 121 patients were enrolled with mean BL HCV RNA 6.5 log<sub>10</sub> IU/mL and 41% IL28B genotype CC. 48 received PSI-7977 200mg, 47 received 400mg, 26 received pbo, all with PEG/RBV. Safety of PSI-7977 regimens was previously reported and was similar to pbo/PEG/RBV with no new safety events including 4 subjects receiving PSI-7977 400mg who discontinued prior to Wk12 and were **CONCLUSIONS:** PSI-7977 200mg or 400mg QD with PEG/RBV demonstrated potent on-treatment antiviral activity in treatment-naïve patients with

HCV GT1. Greater efficacy of 400mg over 200mg is demonstrated by, three viral breakthroughs (between Wk12 and Wk24 while receiving PEG/RBV) and 1 relapse in the 200mg group, compared with no breakthrough or relapse in the 400mg group. Complete SVR12 data will be presented.

**Treatment with the second generation HCV protease inhibitor BI201335 results in high and consistent SVR rates - results from SILEN-C1 in treatment-naïve patients across different baseline factors** Dr. Mark Sulkowski The Liver Meeting AASLD 2011 #226

**BACKGROUND AND AIMS:** BI201335 is a highly potent and specific HCV NS3/4A protease inhibitor given once daily (QD) with strong antiviral activity in chronic HCV genotype-1 (GT1) infection. **METHODS:** In this double-blind, randomized phase II trial, 429 HCV GT1 treatment-naïve patients were randomized 1:1:2:2 to placebo or BI201335, 120 mg with 3 days lead-in (LI) of PR (120 mg QD/LI), 240 mg QD/LI or 240 mg QD without LI (240 mg QD). In each arm, BI201335 was given for 24 weeks together with PR for 24 or 48 weeks. Viral load (VL) was measured by Roche TaqMan (lower limit of quantification 25 IU/mL), subtype was assessed by NS3/4A sequencing, and IL-28B genotype was collected retrospectively on approximately 50% of patients. Based on slightly reduced response rates in both LI groups of BI201335 (Sulkowski et al, EASL 2011), the 240 mg QD dose has been selected for phase III evaluation (along with 120 mg QD). Comparison of this dose with PR across important patient characteristics is presented. **RESULTS:** Overall, 83.1% of patients treated with BI201335 240 mg QD achieved SVR, compared with 56.3% of patients on PR alone ( $p < 0.0001$ ). The SVR rates were consistently high across a wide range of difficult-to-cure subgroups (Table). Notably, the SVR rate for subtype 1a patients was 82.4% (compared with 46.9% on PR,  $p = 0.0013$ ). All 22 patients (100%) with IL-28B genotype CC who received 24 weeks BI201335 240 mg without LI achieved SVR. The SVR in non-CC patients was also significantly higher (70.8%) compared with PR alone (41.4%,  $p = 0.0162$ ). The percentage of patients achieving eRVR and thus eligible for 24 weeks overall treatment duration was 87.3% with consistently high rates across all subgroups including non-CC patients. **CONCLUSIONS:** BI201335 240 mg once daily in treatment-naïve patients achieved consistently strong and significant eRVR and SVR rates, even in difficult-to-cure patients such as GT1a and IL28B non-CC. The 240 mg once daily treatment is currently being tested, along with 120 mg QD, in phase III trials.

**BMS-790052, A NS5A Replication Complex Inhibitor, Combined with Peginterferon Alfa-2a and Ribivirin in Treatment-Naïve HCV-Genotype 1 or 4 Patients: Phase 2b AI444010 Study Interim Week 12 Results** Christophe Hezode The Liver Meeting AASLD 2011 #227

**BACKGROUND:** BMS-790052 is a 1st-in-class, highly selective NS5A Replication Complex Inhibitor (NS5A RCI) with pM potency and broad genotypic coverage in vitro. Treatment-naïve patients with genotype (GT)-1 chronic HCV (CHC) achieved high rates of SVR after 48 weeks of BMS-790052 + pegIFN $\alpha$ -2 $\alpha$ /ribavirin (P/R) in a Phase 2a study. Phase 2b Week 12 interim results for GT-1 and 4 CHC are reported here. **METHODS:** AI444010 is a randomized, double-blind study in which patients with CHC GT-1 ( $n = 365$ ) or GT-4 ( $n = 30$ ) receive placebo, 20 mg, or 60 mg BMS-790052 + P/R for 24 or 48 weeks. Patients on BMS-790052 with HCV RNA Week 4  $<$  LOQ (25 IU/mL) and Week 10 undetectable [Roche COBAS TaqMan High Pure v2.0] will receive 24 weeks triple therapy or 12 weeks triple therapy then 12 wks P/R. **RESULTS:** For GT-1 both BMS doses had higher response rates compared to PBO. Virologic breakthrough (HCV RNA:  $>$  1 log $_{10}$  increase over nadir or  $\geq$  LOQ after undetectable) occurred in 4% and 8%

in the 20 mg or 60 mg arms, respectively. All GT-4 (19/19) with available Week 12 data treated with BMS 20 or 60 mg were HCV RNA undetectable compared to 50% for PBO (3/6). SAE (6-8%) and D/C to AE (4-5%) were consistent across the 20 mg, 60 mg or PBO groups. There was one death (unrelated per investigator; cause unknown) in the BMS 20 mg arm. AE were those commonly reported for P/R. Grade 3-4 laboratory abnormalities, mean levels of hemoglobin, absolute lymphocytes, absolute neutrophils, ALT, and total bilirubin at Week 12 were consistent across treatment groups, as were the use of erythropoietin (4-6%) and filgrastim (0-3%). Rash (Grade 1-4) was reported in 24%, 22%, and 28%, and led to D/C in 1, 1, and 0 patients for 20 mg, 60 mg or PBO respectively. **CONCLUSIONS:** Once daily BMS-790052 NS5A RCI + P/R resulted in higher rates of early virologic suppression compared to placebo in both GT-1 and 4 CHC. The majority of BMS-790052-treated patients were eligible for 24 weeks of therapy. The AE profile of BMS-790052 + P/R was comparable to P/R + placebo through Week 12.

**A Randomized, Placebo-Controlled Trial of Oral Silymarin (Milk Thistle) For Chronic Hepatitis C: Final Results of the SYNCH Multicenter Study** Michael Fried The Liver Meeting AASLD 2011 #228

**BACKGROUND:** The botanical extract silymarin, commonly known as milk thistle, is a polyphenolic flavonoid with anti-oxidant, anti-inflammatory, and immunomodulatory properties in vitro and is used extensively by patients with chronic liver disease. This trial evaluated the effect of high doses of oral silymarin on disease activity in patients with chronic hepatitis C. **METHODS:** Patients with chronic hepatitis C infection who were previously unsuccessfully treated with interferon-based therapies and with serum ALT activity > 65 IU/L were eligible. Participants were randomly assigned to either placebo or one of two doses of a standardized silymarin preparation (Legalon® 140, Rottapharm Madaus) at 420 or 700 mg administered orally thrice daily for 24 weeks. These doses, 4.5-7.5 times higher than customary, were chosen based on results of a phase I pharmacokinetic study. The prespecified primary endpoint, assessed at the end of therapy, was serum ALT < 45 IU/L (considered to be within the normal range) or ALT < 65 IU/L (<1.5 x ULN), provided this was at least a 50% decline from baseline values. Changes in serum ALT and HCV RNA during treatment, and the relationship of these to study medication adherence, measured by dose counts, and silymarin levels were also examined. **RESULTS:** Four U.S. clinical centers enrolled 154 patients, of whom 138 (90%) completed the endpoint evaluation at week 24. Baseline characteristics were well matched with the exception of a larger proportion of whites in the placebo group. Most participants were male (71%) and the median age was 54 years. Median ALT was 106 IU/L. The mean decline in serum ALT activity at the end of treatment did not differ significantly (p=0.75) across the 3 treatment groups. Only 6 participants (2 in each treatment group, p =1.00) met the primary endpoint. Based on dose cups returned, over 90% of participants met or exceeded an 80% adherence to study medications, despite the substantial pill burden (15 capsules per day). Analysis of serum ALT activity performed by per protocol analysis (those with > 80% adherence) did not demonstrate significant changes in serum ALT activity among the treatment arms. Silymarin treatment at both doses had an adverse event profile comparable to placebo. Pharmacokinetics of silymarin and HCV RNA results are pending. **CONCLUSION:** Although well tolerated, oral silymarin administered at higher than customary doses did not significantly alter biochemical markers of disease activity in patients with chronic hepatitis C who had failed prior treatment with interferon-based regimens. (Funded by National Institutes of Health, NCCAM and NIDDK).

**Follow-up of SVR Durability and Viral Resistance in Patients with Chronic Hepatitis C Treated with Telaprevir-Based Regimens: Interim Analysis of the EXTEND Study**

Dr. Kenneth Sherman, The Liver Meeting AASLD 2011 The Liver Meeting AASLD 2011 #248

**BACKGROUND:** Telaprevir (TVR), a hepatitis C virus (HCV) NS3-4A protease inhibitor, in combination with peginterferon alfa-2a (P) and ribavirin (R) led to higher sustained viral response (SVR) rates than PR in treatment-naïve and treatment-experienced genotype 1 HCV patients. This interim analysis from EXTEND, an ongoing 3-year virology follow-up study, reports SVR durability in patients who had achieved SVR in previous TVR studies, and evolution of HCV variants in patients who had not achieved SVR. **METHODS:** A subset of patients who received at least 1 dose of TVR in an eligible Phase 2 or 3 trial was enrolled. Patients who achieved and who did not achieve SVR were observed for a median of 21 (range: 4-45) and 29 months (range: 7-49), respectively. HCV RNA levels were assessed using COBAS TaqMan<sup>®</sup> HCV Test (v.2.0). NS3 amino acid positions associated with TVR-resistance (36, 54, 155, 156) were analyzed by population sequence analysis. Turnbull estimation was used for time-to-event analyses. The association of HCV RNA levels after treatment failure with the presence of resistant variants was explored by a matched pairs t-Test comparing baseline and follow-up HCV RNA levels for patients that lost or retained resistant variants. **RESULTS:** 99% (220/221) of patients maintained SVR during follow-up: 1 patient had late relapse 44 wks after early study dosing discontinuation, as previously described. 162 patients did not achieve SVR and had sequence data after treatment-failure; 83% (134/162) of patients did not have detectable resistant variants at their last EXTEND visit. More 1b patients (98%) had wild-type virus at their last visit than 1a patients (78%), consistent with observed faster rates of loss of common 1b variants (V36A, T54A, A156S/T) than 1a variants (V36M, R155K). Median time to wild-type was associated with subtype (p<0.05): 8 months for 1a and 4 wks for 1b. Time to loss of detectable resistance did not vary with treatment arm, TVR dosing duration, or non-response type (i.e. on-treatment virologic failure vs. relapse). Viral load after treatment did not appear to be associated with the presence of resistant variants; patients had comparable HCV RNA levels at baseline and follow-up regardless of the presence of resistant variants. **CONCLUSIONS:** In this interim analysis, SVR after TVR-based therapy was durable: 99% of patients maintained undetectable HCV RNA at a median follow-up of 21 months after achieving SVR. Among patients not achieving SVR after TVR-based therapy, variants associated with TVR-resistance were no longer observed in 83% of patients at the time of analysis (median follow-up after treatment failure: 29 months).

**High sustained virologic response following interferon-free treatment of chronic HCV GT1 infection for 4 weeks with HCV protease inhibitor BI201335, polymerase inhibitor BI207127 and ribavirin, followed by BI201335 and PegIFN/ribavirin - the SOUND-C1**

Dr. Stefan Zeuzem The Liver Meeting AASLD 2011 #249

**BACKGROUND:** BI201335 and BI207127 are potent and specific inhibitors of the HCV NS3/4A protease and NS5B RNA-dependent RNA polymerase, respectively. A combination of both compounds with ribavirin (RBV) achieved up to 100% rapid virological response rates (RVR, HCV RNA  $\leq$ 25 IU/mL at week 4) in HCV genotype-1 (GT-1) patients. Here we report results of the follow-on treatment with BI201335 and PegIFN/RBV. **METHODS:** In this open-label trial, 32 treatment-naïve patients were randomised to 4 weeks treatment with 400 (n=15) or 600 mg (n=17) three times a day (TID) BI207127, 120 mg once daily (QD) BI201335 and RBV

(1000/1200 mg daily). Plasma virus load (VL) was measured by Roche COBAS TaqMan assay with a lower limit of quantification of 25 IU/mL. After 4 weeks, patients in both groups were switched to treatment with BI201335 and PegIFN/RBV until week 24. Patients not achieving extended RVR (eRVR; VL  $\leq$ 25 IU/mL at week 4 and undetectable weeks 5-18) obtained PegIFN/RBV until week 48. **RESULTS:** After completion of the 4 week trial period, 11/15 and 17/17 patients achieved RVR at 400 and 600 mg TID of BI207127 (Zeuzem et al, AASLD 2010). One patient experienced VL breakthrough and was switched per protocol to PegIFN/RBV. All remaining patients were switched to BI201335/PegIFN/RBV with only 3/31 patients (all at 400 mg TID) exhibiting quantifiable VL (range: 64-377 IU/mL) at time of switch. The table shows virological response rates following BI201335/PegIFN/RBV treatment. The one breakthrough patient who switched to PegIFN/RBV had undetectable VL at week 24 when he discontinued. The PegIFN sparing treatment was well tolerated with mild to moderate gastrointestinal effects, rashes or photosensitivity representing the most common adverse events (no severe AE, SAE or treatment discontinuations) during that period. The safety and tolerability profile of the BI201335/PegIFN/RBV treatment was consistent with that seen in phase IIb trials of BI201335 (Sulkowski et al, EASL 2011). Complete SVR data will be shown at the meeting. **CONCLUSIONS:** A 4-week PegIFN-free treatment with the NS3/4A inhibitor BI201335, the NS5B polymerase inhibitor BI207127 and RBV, followed by triple therapy of BI201335 with PegIFN/RBV demonstrated very high efficacy (SVR) against HCV genotype-1. A phase IIb trial is ongoing to explore optimized PegIFN-free regimens with BI201335 in combination with BI207127.

#### **Summary of Clinical Virology Findings from Clinical Trials of Telaprevir** Dr. Doug Bartels The Liver Meeting AASLD 2011 #1328

**BACKGROUND:** Telaprevir (TVR, T) in combination with peginterferon and ribavirin (PR) significantly increased sustained viral response (SVR) rates compared to PR alone in Phase 3 studies of treatment-naïve and treatment-experienced genotype 1 HCV patients. Clinical virology analyses were performed to understand the pattern of emergence of HCV substitutions with decreased TVR sensitivity. **METHODS:** Population sequence analysis of the NS3-4A region was performed in patients treated with TVR-based therapy in Phase 3 studies (n=1797) at baseline, and during treatment and follow-up in patients who did not achieve an SVR. On treatment virologic failure was defined as meeting a stopping rule and/or having viral breakthrough. Loss of resistant variants was assessed by Kaplan-Meier. **RESULTS:** NS3 amino acid substitutions V36M/A/L, T54A/S, R155K/T, and A156S/T were determined to emerge frequently among patients treated with T/PR who did not achieve SVR. Prior to treatment, 5% of patients had substitutions at positions V36, T54, R155 or D168. In patients treated with T/PR, resistant substitutions were observed in 18% of patients. The substitutions V36M and R155K/T were observed in 49% and 56% of genotype 1a (G1a) non-SVR patients with the majority containing V36M+R155K. V36A/L (17%), T54A/S (22%), and A156S/T (12%) were observed in non-SVR G1b patients. Emergent substitutions observed in 2% or less of patients included V36G/I, I132V, R155G/M, A156V/F/N or D168N. Emergent resistant substitutions were not observed in 31% of G1a and 55% of G1b non-SVR patients. In patients receiving T/PR, virologic failure rates were low in treatment-naïve (7%) and prior PR relapse (1%) patients, but were higher for prior nonresponder patients (36%). Virologic failure during TVR-based treatment was more common in G1a patients and associated with higher-level TVR-resistant variants. Relapse rates were low in patients who completed the assigned T/PR regimen and were

associated with either lower-level or no resistant substitutions. The pattern of resistant substitutions was consistent between treatment-naïve patients and all categories of PR-experienced patients. After treatment, the commonly occurring resistant substitutions were undetectable with a median time of 10 months for G1a and 3 weeks for G1b patients.

**CONCLUSIONS:** A well-characterized, consistent resistance profile has been established for those patients who did not achieve SVR with a telaprevir-based regimen. Resistant substitutions were observed in 18% of patients who received a telaprevir-based regimen. These resistant substitutions tended to diminish over time in the absence of telaprevir selective pressure.

**Different likelihood of achieving SVR on a telaprevir-containing regimen among null responders, partial responders and relapsers irrespective of similar responses after a peginterferon/ribavirin 4-week lead-in phase: REALIZE study subanalysis**

Dr. Stefan Zeuzem The Liver Meeting AASLD 2011 #1331

**INTRODUCTION:** Prior response characterization (relapsers, partial responders, null responders) has been shown to provide a better prediction of sustained virological response (SVR) with telaprevir (TVR) plus peginterferon (P) and ribavirin (R) than  $<$  or  $\geq 1$  log<sub>10</sub> decline in HCV RNA after 4 weeks of PR lead-in phase in the REALIZE Phase III trial. To determine if refining the  $<$  or  $\geq 1$  log<sub>10</sub> response categories impacts SVR with TVR-based treatment in relapsers, partial responders and null responders, an analysis using smaller intervals of HCV RNA response at Week 4 was conducted. **METHODS:** HCV genotype 1-infected patients were randomized 2:2:1 to treatment with 12 weeks of TVR (750mg q8h) + P (180µg/week) + R (1000-1200mg/day) (either with immediate start [T12/PR48] or with a 4-week PR lead-in [LI T12/PR48]) followed by PR, or placebo/PR alone (Pbo12/PR48), for a total treatment duration of 48 weeks. Stratification was by viral load (HCV RNA  $< 800,000$  or  $\geq 800,000$  IU/mL) and prior PR response (null, partial or relapse). The relationship between five ranges of HCV RNA response after 4 weeks of a PR lead-in phase and SVR was explored in the LI T12/PR48 and PR arms. **RESULTS:** A total of 121 and 239 patients had Week 4 HCV RNA data available in the PR and LI T12/PR48 arms, respectively. Prior relapsers or partial responders with very poor responses at Week 4 of the lead-in phase (0-0.5 log<sub>10</sub>) achieved substantially higher SVR rates than prior null responders with similar responses at this time point (Table, bolded cells). Prior null responders exhibited the widest range of SVR rates to TVR-based treatment (6% to 80%). **CONCLUSIONS:** Among patients with a poor on-treatment response to PR ( $< 1$  log<sub>10</sub> HCV RNA decline at Week 4), prior null responders, as defined in the REALIZE study, were different from prior partial responders and relapsers in their capacity to achieve an SVR with a TVR-containing regimen. This suggests that the exclusive use of a lead-in phase strategy to predict SVR to a TVR-containing regimen in prior treatment-experienced patients may not predict the true likelihood of achieving an SVR and highlights the value of prior response categorization to predict response to TVR.

**Effect of fluvastatin-combined pegylated-interferon/ribavirin combination therapy on chronic hepatitis C** Dr. Chisa Kondo The Liver Meeting AASLD 2011 #1335

**BACKGROUND & AIMS:** The current standard therapy for genotype 1b, high viral load chronic hepatitis C is pegylated-interferon (PEG-IFN)/ribavirin (RBV) combination therapy, but only about 50-60% of cases achieve a sustained viral response (SVR). It indicates the presence of patients in whom it is difficult to eliminate the virus, for which a new therapeutic method has been investigated. Recent reports showed that fluvastatin (FLV), HMG-CoA reductase inhibitor

also known as antihypercholesterolemic agent, inhibit HCV-RNA replication. In order to clarify anti-HCV effect of FLV in vivo, we designed the present prospective randomized controlled study and investigated whether the combination of FLV with PEG-IFN/ribavirin could improve SVR in patients with HCV genotype 1b and high viral load. We also examined both host and viral factors that might affect therapeutic outcome with FLV employing stratified analysis. **METHODS:** A total of 101 chronic hepatitis C patients were randomly allocated to PEG-IFN/RBV combination therapy or PEG-IFN/RBV/FLV combination therapy. Only patients in whom at least 80% of the planned administration could be executed were included in analysis (per protocol analysis). All patients provided written informed consent to participate in the study. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the ethical committee of Nippon Medical School. **RESULTS:** There were 48 and 46 patients in the PEG-IFN/RBV and PEG-IFN/RBV/FLV combination therapy groups, respectively. No apparent difference was noted in the patient background between the two groups. The overall rapid viral response (RVR) rate was 9.7%, early viral response (EVR) rate was 64.5%, end of treatment response (ETR) rate was 69.9%, and SVR rate was 51.6%. The RVR, EVR, ETR, and SVR rates in the group without FLV were 6.7, 62.5, 69.6, and 41.7%, respectively, and those in the group with FLV were 13.0, 67.4, 73.9, and 63.0%, respectively. To identify a factor contributing to SVR in FLV group, multivariate analysis was performed involving the 46 patients. Male and IL28B SNPs (rs8099917) major genotype were extracted as independent factors contributing to SVR. No apparent adverse events associated with concomitant FLV occurred. **CONCLUSIONS:** It was suggested that FLV-combined PEG-IFN/RBV therapy for genotype 1b, high viral load chronic hepatitis C is safe and improves the therapeutic outcome.

### **High Rapid Virologic Response(RVR) with ACH-1625 Daily Dosing plus PegIFN-alpha 2a/RBV in a 28-day Phase 2a Trial**

Dr. Jay Lalezari The Liver Meeting AASLD 2011 #1341  
**BACKGROUND:** ACH-1625, an HCV NS3 protease inhibitor in Phase 2 for treatment of HCV is rapidly and selectively distributed to the liver. A recent Phase 1 trial demonstrated the safety and tolerability of ACH-1625 monotherapy administered once-daily for five days to HCV GT-1 patients. Both the pharmacokinetic and viral kinetic profiles support once-daily dosing and the potential to combine ACH-1625 in an all direct acting antiviral (DAA) combination.

**METHODS:** Double-blind, randomized, placebo-controlled, dose-ranging, parallel-group study with patients assigned to one of three daily doses of ACH-1625 (200, 400, or 800 mg) or placebo for 28-days, administered with PegIFN-alpha 2a/RBV. Treatment naïve patients with chronic HCV, GT-1a or GT-1b infection were randomized and stratified by IL28B status to provide balance among treatment groups. All patients were assessed for RVR (HCV RNA < 25 IU/mL) at Day 28. PK analysis and HCV RNA collection for genotypic analysis was performed.

**RESULTS:** 11 US sites enrolled 64 patients. Most patients were HCV GT-1a (73%) with less frequent GT-1b (25%) and GT-1 (2%). Total 83% of patients enrolled were IL28B CT/TT and 17% were CC. Mean age was 50 and mean BMI 27.6 across treatment groups; Baseline demographics were similar across groups. There were no serious adverse events (SAEs) or discontinuations due to adverse events (AEs). The most commonly reported AEs in patients receiving ACH-1625 were headache, fatigue, nausea, and pain (general), were mild or moderate and were transient. The most common AEs observed were consistent with PegIFN-alfa 2a/RBV administration.

**Assessment of Boceprevir Pharmacokinetic/Pharmacodynamic Relationships for Sustained Viral Response and Occurrence of Anemia from Phase 3 Data** Julie Stone The Liver Meeting AASLD 2011 #1342

**BACKGROUND AND AIMS:** Boceprevir (BOC, VICTRELIS™) is a hepatitis C protease inhibitor approved for treatment of hepatitis C infection in combination with pegylated interferon and ribavirin (PR). The objective was to characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationships for sustained viral response (SVR) and occurrence of anemia in patients from the Phase 3 studies in treatment-naïve (SPRINT-2) and treatment-experienced (RESPOND-2) patients. **METHODS:** PK/PD dataset consisted of 291 patients (from PR control, fixed duration PR + BOC, and response-guided therapy (RGT) PR + BOC arms) with PK data available based on pop PK analysis of sparse concentrations. Anemia was defined as hemoglobin <10 g/dL and SVR as assessed at 24 weeks post-therapy in the primary analyses of SPRINT-2 and RESPOND-2. Multivariate logistic regression models for the event (SVR or anemia) with BOC PK (one of AUC, C<sub>max</sub>, or C<sub>min</sub>) and R AUC as predictors without interaction estimated the Odds Ratio (OR): fold-change in odds (probability of event /probability of no event) over a unit change defined by the 25th to 75th percentile of the Phase 3 PK distribution. OR>1 indicates a positive association of the event with PK. **RESULTS:** The OR estimates for BOC AUC and R AUC from the pooled SPRINT-2 and RESPOND-2 dataset are below. If BOC PK was insignificant for BOC arms only, but significant with BOC placebo data included, an alternate binary BOC parameter (presence versus absence of BOC) was tested. Sensitivity analyses of the influence of other BOC PK measures (C<sub>max</sub>, C<sub>min</sub>), treatment naïve vs experienced, inclusion of RGT arm, inclusion of other covariates yielded generally similar results. **CONCLUSION:** While the presence of BOC was a highly significant predictor of SVR, BOC PK was not significant within the BOC arms, consistent with PK from the 800 mg TID BOC regimen used in Phase 3 being near the top of the exposure-response curve. Ribavirin PK was consistently a highly significant predictor of anemia across all analyses consistent with prior results. The presence of BOC was also a significant predictor of anemia; however, the lack of significance of BOC PK within the BOC arms suggests that reduction of BOC dose would not be an effective strategy for managing anemia.

**Safety and efficacy of Vaniprevir (MK-7009) in combination with Peg-interferon alfa-2a (Peg-IFN) / Ribavirin (RBV) in Genotype 1 treatment experienced HCV-infected Japanese patients** Dr. Norio Hayashi The Liver Meeting AASLD 2011 #1347

**BACKGROUND:** Vaniprevir is a NS3/4A protease inhibitor of the HCV. We have conducted a Phase 2 study to assess the safety and efficacy of vaniprevir in combination with peg-IFN and RBV when administered for 28 days to genotype (GT) 1 HCV-infected Japanese patient who have previously relapsed on therapy with peg-IFN and RBV. **METHODS:** This study was multi-centered, double-blind, and placebo-controlled with vaniprevir given in 3 arms of study at doses of 100 mg, 300 mg, or 600 mg, twice daily in combination with peg-IFN and RBV. The primary objective of the study was to assess the efficacy of vaniprevir by Rapid Viral Response (RVR) at Week 4, and the safety and tolerability of vaniprevir as compared to the control arm up to Week 6. Treatment with peg-IFN and RBV continued up to 72 weeks with investigator's judgment. Pharmacokinetic and viral resistance analyses were also conducted. **RESULT:** A total of 90 patients approximately equally distributed among the 4 arms were enrolled in the study. In the Per Protocol Analysis population (83 patients), RVR rates in all arms with vaniprevir in combination with peg-IFN and RBV were significantly greater than the control arm. (86.4% in

the 100 mg arm, 95.0% in the 300 mg arm, 76.2% in the 600 mg arm and 20.0% in control arm.) All patients were included in the safety analysis. There were no serious adverse events or discontinuations due to adverse events during the 28 days of vaniprevir given in combination with Peg-IFN and RBV and the 14-day follow-up period. Vomiting and constipation were reported at higher rates in the vaniprevir 600 mg arm (26.1% and 17.4%, respectively) than the control arm (both 0.0%). Rates of nausea and diarrhea were also numerically higher in the vaniprevir 600 mg arm than the other arms. Concerning the pharmacokinetics, the geometric mean steady-state AUC<sub>0-24hr</sub> for the 100 mg arm (3.8  $\mu\text{M}\cdot\text{hr}$ ) and 300 mg arm (25.3  $\mu\text{M}\cdot\text{hr}$ ), but not the 600 mg arm (78.5  $\mu\text{M}\cdot\text{hr}$ ) were below the NOAEL of 72  $\mu\text{M}\cdot\text{hr}$ . These data showed higher exposures with vaniprevir in Japanese patients as opposed to non-Japanese patients in other Phase 2 vaniprevir studies. At baseline, there were 2 subjects with detectable vaniprevir resistance associated amino acid variants (RAVs); namely A156T and D168E. No patients experienced virologic failure with detectable RAVs during the vaniprevir dosing period. **CONCLUSION:** Vaniprevir in combination with peg-IFN and RBV has demonstrated efficacy with high RVR rates in GT1 treatment-experienced HCV-infected Japanese patients. Based on cumulative efficacy, safety and tolerability data, vaniprevir at 300 mg twice daily was chosen as the appropriate dose for Phase 3 studies in Japanese patients.

**Hematologic tolerability of high-dose peg-interferon  $\alpha$ -2a and ribavirin during the first 12 weeks of re-treatment for hepatitis C: influence of treated HIV infection** Dr. Philippe Bonnard The Liver Meeting AASLD 2011 #1348

**INTRODUCTION:** Despite the arrival of new anti-hepatitis C virus (HCV) drugs, patients not responding to standard doses of ribavirin and peg-interferon may benefit from higher doses. HIV infection, even when treated, has long been considered an obstacle to increased doses of interferon and ribavirin. **MATERIALS AND METHODS:** We compared hematologic tolerability between HIV/HCV-coinfected patients participating in the ANRS HC20 ETOC trial and HCV-monoinfected patients in the SYREN trial. All the patients received 360  $\mu\text{g}/\text{week}$  peg-interferon  $\alpha$ 2a and a bodyweight-adjusted dose of ribavirin for the first 3 months, following an unsuccessful first course of peg-interferon-ribavirin therapy ( $<2$  log reduction in HCV viral load at Week (W) 12). An algorithm was used for growth factor administration (EPO and G-CSF). **RESULTS:** 49 HIV/HCV-coinfected patients and 98 HCV-monoinfected patients were compared. Most had advanced-stage liver disease (stage F4 in 39% of dually infected patients and 43% of HCV-monoinfected patients; NS). Data are presented in table 1. In coinfecting patients the mean CD4 cell count was  $635\pm 273/\text{mm}^3$  (31%) at enrollment and fell by  $253\pm 179/\text{mm}^3$  between W0 and W12 ( $<200$  CD4/ $\text{mm}^3$  in 12% of patients). However, the CD4 cell percentage remained stable at 37%. **CONCLUSION:** In HIV-HCV-coinfected patients receiving high-dose ribavirin and peg-interferon, rational use of growth factors ensures hematologic tolerability similar to that in HCV-monoinfected patients, even in case of severe hepatic fibrosis. HIV infection does not therefore appear to worsen hematologic tolerability, suggesting that high-dose treatment of HCV infection is an interesting option for combination with telaprevir or boceprevir in order to minimize the risk of resistance selection and increase the sustained virological response rates in non-responders coinfecting patients to prior standard therapy.

**Alisporivir – A Host-targeting Antiviral, Provides Low Viral Breakthrough Rate and High Barrier to Resistance in HCV Genotype 1 Treatment-naïve Patients in the Phase IIb ESSENTIAL Study** Dr. Bin Li The Liver Meeting AASLD 2011 #1350

**BACKGROUND:** Alisporivir (ALV) is an oral host-targeting cyclophilin inhibitor with pan-genotypic anti-HCV activity. In the phase IIb ESSENTIAL study, HCV genotype (GT) 1 treatment-naïve patients receiving ALV in combination with Peg-IFN $\alpha$ 2a/ribavirin (P/R) achieved 76% SVR. Here, we investigate the viral breakthrough (VB) events during the ESSENTIAL study and evaluate the factors associated with VB in ALV-treated patients. **METHODS:** Population sequencing of the entire HCV coding region was performed with samples at baseline and at VB. The HCV NS5A gene was further analyzed using clonal sequencing and pyrosequencing. Phenotypic analysis of NS5A from patient isolates was performed using GT1b replicon shuttle vector in vitro. **RESULTS:** A total of 215 intent-to-treat patients (43 GT1a; 172 GT1b) were treated with ALV in combination with P/R in the ESSENTIAL study. While on full-dose of ALV, 6/215 (2.8%) patients (1 GT1a; 5 GT1b) experienced VB, compared with 4/73 (5.5%) patients in the control (placebo with P/R) arm. No VB was observed until treatment Week 12. In 3 of 6 ALV-treated patients, VB occurred after P/R dose adjustment/stoppage; in 2 of the other 3 VBs, pharmacokinetics analysis revealed suboptimal ALV exposure. Population sequencing of HCV genome did not identify any genotypic change consistently associated with VB, confirmed by clonal sequencing of NS5A, the putative viral target of cyclophilins. A mutation previously reported to be associated with ALV treatment in vitro, D320E in NS5A domain II, was seen at the time of initial VB in 1 patient. However, phenotypic assays demonstrated only a slight (~3-fold) decrease in susceptibility to ALV with GT1b replicons bearing D320E alone or the entire NS5A of the patient isolate. **These data suggest** that the emergence of D320E or viral resistance is not the primary cause of VB. Importantly, a number of mutations that confer resistance to direct-acting antivirals (DAAs) including NS5A inhibitors were seen at baseline for patients who achieved RVR and subsequently SVR24 with ALV, supporting the in vitro data of lack of cross-resistance between ALV and DAAs.

**The pharmacokinetic interaction between the investigational NS3/4A HCV protease inhibitor TMC435 and methadone** Dr. Sivi Ouwerkerk-Mahadevan The Liver Meeting AASLD 2011#1353

**OBJECTIVE:** Some patients infected with hepatitis C virus (HCV) may be undergoing treatment with methadone for opioid dependence. Therefore, methadone is expected to be frequently co-administered with antiviral agents. This Phase I study (TMC435-C110; NCT00915564) evaluated the pharmacokinetic interaction between TMC435 and methadone, both at steady-state. **METHODS:** A Phase I, open-label, single-sequence, drug-drug interaction study was performed in 12 HCV-negative, opioid-dependent subjects receiving stable methadone maintenance therapy. TMC435 (150 mg once daily [QD]) was administered for 7 days in addition to continued stable methadone maintenance therapy. Pharmacokinetics of R- and S-methadone were assessed prior to co-administration with TMC435 and after 7 days of combined therapy. Pharmacokinetics of TMC435 were determined after 7 days of co-administration. All intakes of TMC435 were observed and methadone intakes were observed from 14 days prior to co-administration of TMC435 onwards. Pharmacodynamic assessment of opioid effects (questionnaires and pupillometry) and standard laboratory safety parameters were monitored throughout. **RESULTS:** The majority of subjects were male (10/12) and Caucasian (11/12). Daily methadone doses ranged from 30 to 145 mg (QD) and were not altered during the study. The pharmacokinetics of R- and S-methadone were not affected after 7 days of co-administration with TMC435 (150 mg QD). The ratios (methadone plus TMC435/methadone only) of least

square means (90% confidence intervals) for AUC24h, Cmax, and Cmin of R-methadone were 0.99 (0.91-1.09), 1.03 (0.97-1.09), and 1.02 (0.93-1.12), respectively. These values were 1.03 (0.91-1.16), 1.09 (1.02-1.16), and 1.02 (0.89-1.17) for S-methadone, respectively. Following co-administration, plasma concentrations of TMC435 were within the range observed in other healthy volunteer studies (mean [SD] AUC24h 12110 [7704] ng.h/mL; Cmax 965.7 [429.1] ng/mL; Cmin 152.4 [130.5] ng/mL). In this study, co-administration of TMC435 and methadone was generally safe and well tolerated. During co-administration, no consistent trends in methadone withdrawal or toxicity symptoms were observed. One subject discontinued TMC435 due to Grade 2 rash. **CONCLUSION:** TMC435 has no effect on the pharmacokinetics of methadone following multiple dosing. No a priori dose adjustment is required for methadone when therapy with TMC435 is initiated.

**Less severe flu-like symptoms with PEG-Interferon Lambda in Phase IIb Study of treatment-naïve chronic hepatitis C (CHC) patients** Susan Mathias The Liver Meeting AASLD 2011 #1363

**INTRODUCTION/ PURPOSE:** Flu-like symptoms, including pyrexia, chills, myalgia and arthralgia, are experienced by 30% - 50% of patients undergoing combination interferon Ribavirin (RBV) treatment for chronic hepatitis C (CHC), and contributes to morbidity, inadequate compliance, and early discontinuation. To track the severity and impact of these flu-like symptoms from the patient perspective, a novel patient reported diary, the Hepatitis Physical Symptom Severity Diary (HPSS-D), was developed to assess physical symptoms in clinical trials. **METHODS:** Four items from the HPSS-D comprise the Flu-Like Symptom Index that measures fever, chills, muscle aches and pain, and joint pain. The HPSS-D was developed based on HCV-patient interviews (treatment-naïve and experienced), clinical input and following the FDA's PRO Guidance. Each of the 4 items uses a 0 to 10 response option, where 0 = no symptoms and 10 = the worst symptom or problem imaginable over the past 24 hours. Higher index scores indicate greater symptom severity. The diary was completed at baseline and then for 7 days at weeks 4, 8 and 12 in two Phase 2b studies of treatment-naïve patients comparing pegIFNalpha2a/RBV (pegalfa) to peg-INF Lambda/RBV (peg-lambda) (EMERGE) and peg-alfa to peg-alfa + direct acting antiviral (study AI44010). Data from the Flu-Like Symptom Index for peg-alfa in both studies were combined and compared with data from peg-lambda patients in EMERGE. Mean scores, change from baseline to week 12, and the percent of patients reporting flu-like symptoms were calculated. **RESULTS:** Mean scores for the Flu-Like Symptom Index at week 12 for the peg-alfa group (N=36) increased from baseline by 2.39 (sd=4.95) as compared to 0.83 (sd=5.05) for peg-lambda patients (N=26). The incremental increase for peg-alfa over peg-lambda was 1.83, p=0.16, controlling for the baseline score. The percent of patients reporting any flu-like symptoms was significantly (p < .001) higher for peg-alfa (75%) as compared to peg-lambda patients (27%) at week 12 despite similar rates at study start (peg-alpha: 47%, peg-lambda: 42%). 50% of peg-lambda patients as compared to 82% of peg-alfa patients experienced clinically significant worsening of their flu-like symptoms (estimated as an increase of 2.5 - 3 points). **CONCLUSIONS:** Patient reported outcomes are important parameters to gauge patients' experience with treatment and can be a key predictor of persistence with treatment. Peg-lambda patients reported lower intensity and frequency of flu-like symptoms as compared to peg-alfa patients. Further work to elucidate correlations of flu-like symptoms with discontinuation rates and SVR outcomes should be undertaken.

**Impact of anemia and ribavirin dose reduction on SVR to a telaprevir-based regimen in patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure in the Phase III REALIZE study** Dr. Stuart Roberts The Liver Meeting AASLD 2011 #1368

**BACKGROUND:** In hepatitis C virus (HCV)-infected genotype 1 (G1) treatment-naïve patients treated with telaprevir (TVR) + peginterferon/ribavirin (PR), anemia had no effect on sustained virologic response (SVR). This analysis explored the impact of anemia on SVR following treatment with TVR + PR, or PR alone, in patients with G1 HCV and prior PR treatment failure in the Phase III REALIZE study. **METHODS:** Patients were randomized 2:1:1 and stratified by viral load (<800,000 or ≥800,000IU/mL) and prior PR response (null, partial or relapse). Treatment was 12 weeks of TVR (750mg q8h) + P (180µg/week) + R (1000-1200mg/day) (either without [T12/PR48] or with a 4-week PR lead-in [LI T12/PR48]) followed by PR, or PR alone (PR48), for a total of 48 weeks. Erythropoietin was not allowed. In this exploratory post-hoc analysis, multivariable logistic regression analyses (MLRA) were used to evaluate the impact of baseline (BL) factors on anemia (hemoglobin [Hb] <10g/dL); of anemia as a predictor of SVR; and the association between R dose reduction and SVR. Data from the two TVR arms were pooled. MLRA were conducted separately in the overall population and according to TVR or control treatment. **RESULTS:** The study population (n=662) was characterized as follows: 28%, 19% and 53% were prior null responders, partial responders or relapsers, respectively; 69% male; mean age 51 yrs; 5% black; 26% had cirrhosis; mean BMI 27 kg/m<sup>2</sup>; mean BL Hb 15.4g/dL. 219/530 (41%) and 29/132 (22%) had Hb <10g/dL in the pooled TVR groups and PR48 group, respectively. Factors significantly associated with developing anemia on TVR treatment were older age, lower BMI, lower BL Hb (p<0.0001 for all 3 parameters), more advanced fibrosis (p=0.0369) and G1b vs G1a (p=0.0119). With PR48, older age (p<0.0002) and lower BL Hb (p<0.0001) were associated with anemia. Anemia was a significant predictor of SVR with PR48 (p=0.0310) but not TVR (p=0.18). R dose was reduced due to an adverse event in 133/532 (25%) TVR patients and 16/132 (12%) PR48 patients. SVR rates according to RBV dose reduction are summarized in the table. Transfusions were received by 7% (38/532) of patients in the TVR group vs <1% (1/132) in the PR48 group. **CONCLUSIONS:** In this analysis of patients with G1 HCV and prior PR treatment failure, anemia and ribavirin dose reduction did not appear to have a significant impact on SVR rates on combination triple therapy with TVR plus PR.

**Dual Oral Combination Therapy with the NS5A Inhibitor BMS-790052 and the NS3 Protease Inhibitor BMS-650032 Achieved 90% Sustained Virologic Response (SVR12) in HCV Genotype 1b-Infected Null Responders** Kazuaki Chayama The Liver Meeting AASLD 2011 #LB-4

**BACKGROUND:** Retreatment of patients with chronic HCV infection and prior null response to peginterferon and ribavirin (P/R) with P/R alone or P/R + telaprevir or boceprevir has limited efficacy. Increasing antiviral activity with 2 potent direct-acting antivirals may achieve SVR without P/R in some patients (Lok et al, EASL 2011). The combination of BMS-790052, a first-in-class NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage in vitro, and BMS-650032, a potent inhibitor of NS3 protease with activity vs genotypes 1 and 4 in vitro, was assessed in Japanese null responders. **METHODS:** This ongoing open-label study began with a sentinel cohort of 10 patients with chronic HCV genotype 1 infection and prior null response (<2 log<sub>10</sub> reduction in HCV RNA after 12 weeks) to P/R. Patients received BMS-790052 (60mg QD) and BMS-650032 (initially 600mg BID,

subsequently reduced to 200mg BID) for 24 weeks. The primary endpoint was undetectable HCV RNA 12 weeks post-treatment (SVR12). **RESULTS:** The 10 enrolled patients were all HCV genotype 1b with median baseline HCV RNA of 6.8 log<sub>10</sub> IU/mL and median age of 62 years. Nine patients completed 24 weeks of treatment; 1 patient discontinued after 2 weeks. In all 9 patients who completed treatment, HCV RNA was undetectable from treatment week 8 through post-treatment week 12 (SVR12). In the patient who discontinued, HCV RNA remained undetectable for >24 weeks after discontinuation. There was no viral breakthrough. Polymorphisms associated with resistance to BMS-790052 (L28M, R30Q, L31M, Y93H) and some NS3 protease inhibitors (T54S, Q80L) were detected at baseline in several patients (1 patient had both NS3 and NS5A substitutions) but had no apparent effect on virologic outcomes. Grade 1 diarrhea and headache were the most common adverse events (AE); 3 patients had grade 1/2 transaminase elevations. The 2 serious AEs were hyperbilirubinemia, possibly related to treatments (ie meropenem) for infectious gastroenteritis that led to discontinuation, and pyrexia. **CONCLUSIONS:** Oral combination therapy with BMS-790052 and BMS-650032, without P/R, can achieve rapid and durable viral suppression in null responders with HCV genotype 1b infection. 9/10 subjects completed 24 weeks and achieved SVR12; HCV RNA was undetectable after treatment or discontinuation in all 10 patients. The treatment regimen was safe and well-tolerated.

**TMC435 in combination with peginterferon and ribavirin in treatment-naïve HCV genotype 1 patients: Final analysis of the pillar phase IIb study** Michael Fried The Liver Meeting AASLD 2011#LB-5

**OBJECTIVE:** PILLAR (TMC435-C205; NCT00882908) is an international, Phase IIb, randomized, double-blind study in treatment-naïve patients chronically infected with HCV genotype 1 to assess efficacy and safety of the investigational once daily (QD) oral HCV NS3/4A protease inhibitor TMC435 in combination with peginterferon  $\alpha$ -2a/ribavirin (P/R). **METHODS:** Patients were randomized to 1 of 5 arms: 4 with TMC435 (75 or 150mg QD)/P (180 $\mu$ g/wk)/R (1000-1200mg/day) for 12 or 24 weeks, or 1 with placebo/P/R. In TMC435 arms, total treatment duration was 24 or 48 weeks; a 24 week duration was assigned if HCV RNA <25IU/mL detectable or undetectable at Week 4 and <25 IU/mL undetectable at Weeks 12, 16, and 20. In the control arm patients were treated for 48 weeks. Primary endpoint was sustained virologic response (SVR) at Week 72. **RESULTS:** Significantly higher response rates were observed with TMC435 compared to control. In TMC435 arms, 68-76% of patients achieved RVR, of whom 88-95% achieved SVR24. In addition, 79-86% of TMC435 patients were eligible to complete treatment at Week 24. In consenting patients, distribution of IL28B genotype was 30% CC, 58% CT and 12% TT. In CC, CT and TT patients, respectively, SVR24 rates were 34/35 (97%), 48/60 (80%) and 8/12 (67%) with TMC435 150mg, and 12/12 (100%), 14/28 (50%) and 3/6 (50%) with control. Incidence of discontinuations, adverse events (AEs, including rash, anemia and neutropenia) and serious AEs were similar in TMC435 and control arms. Mild, transient increases in direct and indirect bilirubin, not associated with increases in other hepatic parameters, were observed with TMC435 150mg. **CONCLUSION:** TMC435 75 or 150mg QD in combination with P/R led to significantly higher SVR rates compared to P/R alone, with a 24 week total treatment duration in the majority of patients, and a favorable safety profile. TMC435 150mg QD will be administered in Phase III trials.

### **Once daily Alisporivir interferon (IFN)-free regimens achieve high rates of early HCV clearance in previously untreated patients with HCV genotype (G) 2 or 3**

Prof. Jean-Michel Pawlotsky The Liver Meeting AASLD 2011 #LB-11

Alisporivir (ALV), an oral host-targeting cyclophilin inhibitor, has potent pangenotypic anti-HCV activity with a high barrier to viral resistance. Here we describe the first study investigating ALV as an IFN-free treatment in HCV G2/3 patients. **METHODS:** This international, multicenter, open-label study included 334 G2/3 patients (ratio 3:7), randomized to 5 treatment arms to receive: i) ALV 1000mg QD monotherapy [ALV1000, n=82], ii) ALV 600mg QD+ribavirin (R) [ALV600R, n=84], iii) ALV 800mg QD+R [ALV800R, n=94], iv) ALV 600 mg QD+PegIFN (P) [ALV+P, n=39], or v) PR, n=35. In week (wk) 1, all ALV-treated patients received ALV 600mg BID. Patients in ALV-containing arms with undetectable HCVRNA (<25 IU/mL) at wk 4 remained on initial treatment, while those with detectable HCVRNA continued with ALV+PR triple therapy from wk 6 to wk 24. Early virological efficacy and safety up to wk 8 were analyzed. **RESULTS:** Mean baseline HCVRNA was 6.0±1.0 log IU/mL. Among patients who received IFN-free ALV therapy, up to half of the patients achieved undetectable HCVRNA by wk 6, with highest response in both ALV+ribavirin arms (51% with ALV600R, 48% with ALV800R and 33% with ALV1000). Both G2 and G3 patients had similar response rates to ALV IFN-free regimens. Adding PR to ALV from wk 6 to wk 8 for patients with detectable HCVRNA at wk4, markedly increased the proportion of patients with undetectable HCVRNA after only 2 wks of ALV+PR (86% ALV600R, 89% ALV800R and 85% ALV1000). Both initial IFN-containing treatment arms (ALV+P and PR) achieved high proportions of patients with undetectable HCVRNA by week 8 (92% ALV+P, 100% PR). Treatment was well tolerated, and only 2 patients discontinued treatment due to AEs. Transient hyperbilirubinemia (>5xULN) was observed in only one ALV-treated patient at wk 1 (ALV600R) associated with normalizing ALT, while on treatment. Flu-like symptoms were markedly lower in IFN-free ALV regimens. **CONCLUSIONS:** Alisporivir as IFN-free therapy achieves early on-treatment viral response in up to half of G2/3 patients by treatment wk 6, that may subsequently translate into SVR given the ALV high barrier to resistance. Switch to ALV+PR from wk 6 for patients with detectable HCVRNA at wk 4 resulted in a high proportion of patients with undetectable HCVRNA at wk 8, similar to those receiving IFN-based treatments from baseline. Alisporivir once daily shows promise to become the first IFN-free oral treatment for a substantial proportion of treatment-naive G2/3 patients.

### **A Phase 2b study of MK-7009 (vaniprevir) in patients with genotype 1 HCV infection who have failed previous pegylated interferon and ribavirin treatment** Eric Lawitz The Liver Meeting AASLD 2011 #LB-13

**BACKGROUND:** MK-7009 is an oral NS3/4A protease inhibitor being studied in combination with peginterferon alfa-2a (P) 180 µg QW and ribavirin (R) 1000-1200 mg/d for the treatment of chronic hepatitis C infection. **METHODS:** This trial evaluated the efficacy of four treatment regimens of MK-7009: 1-600mg bid plus PR for 24 weeks; 2-600mg bid plus PR for 24 weeks followed by PR for 24 weeks; 3-600mg bid plus PR for 48weeks; 4-300mg bid plus PR for 48weeks. The control regimen was PR for 48 weeks. Stratification was by prior response to PR: Null response, partial response, breakthrough and relapse. A minimum of 25% of patients were prior null responders. Patients had a minimum baseline HCV RNA of 400000 IU/mL. The primary endpoint of the study was sustained viral response (SVR24) by Roche Cobas Taqman with the lower limit of detection of 10 IU/mL. All efficacy analyses were based on the full

analysis set population. **RESULTS:** 211 non-cirrhotic patients were treated. 7% of the patients were African-Americans, and 10% were Latinos. Of the 69% of the patients who underwent a liver biopsy, 17% had Metavir F3. All MK-7009 regimens showed statistically significantly superior SVR24 rates compared to control: 71%, 85%, 67%, and 78% in the MK-7009 regimens 1 through 4 versus 19% in control. The SVR24 rates in prior null responders were 50% (6/12), 80% (8/10), 50% (5/10), 40% (4/10) in regimens 1 through 4, respectively, as compared to 0% (0/10) in control. Patients in MK-7009 regimens had higher rates of gastrointestinal (GI) adverse events (AEs) compared to control. Most GI AEs were mild to moderate. There were no significant differences in rates of anemia and rash between the MK-7009 regimens and control. Resistance associated amino acid variants were predominantly observed at positions R155, A156 and/or D168 in non-SVR patients. **CONCLUSION:** MK-7009 when combined with PR achieves significant improvement in SVR compared to PR control in this population of experienced patients and compares favorably with other first generation Protease Inhibitors. Mk-7009 is generally safe for use for up to 48 weeks of therapy.

**VX-222/telaprevir in combination with peginterferon-alfa-2a and ribavirin in treatment-naïve genotype 1 HCV patients treated for 12 Weeks: ZENITH study, SVR12 interim analysis** Dr. David R. Nelson The Liver Meeting AASLD 2011 #LB-14

**BACKGROUND:** ZENITH is assessing the safety, tolerability, and antiviral activity of VX-222 (an HCV polymerase inhibitor) with telaprevir (T, a protease inhibitor), respectively alone (DUAL), with ribavirin (Triple) or with peginterferon alfa-2a (P) and ribavirin (R) (QUAD) in chronic HCV genotype 1 treatment-naïve patients. **METHODS:** A Week 24 interim analysis of the QUAD regimen is presented. Patients in the QUAD arms received either VX-222 at 100mg (Arm C, n=29) or VX-222 at 400 mg (Arm D, n=30) plus T 1125mg bid, P 180µg/week, and R 1000-1200mg/day for 12 weeks. Patients with undetectable HCV RNA at Weeks 2 and 8 (Roche Taqman® v2 LLOQ 25 IU/mL and LOD 10-15 IU/mL) were eligible to stop **all** treatment at Week 12; those who were detectable at Week 2 and/or 8 received a total of 24 weeks of PR.

**RESULTS:** No viral breakthrough (vBT) was observed in either QUAD arm. 11/29 and 15/30 patients from arm C and D, respectively, were eligible to stop treatment at Week 12. Of those, 82% (9/11) and 93% (14/15), respectively achieved SVR12, the remaining 3 patients relapsed. 14/29 (arm C) and 13/30 (arm D) patients did not meet the short duration criteria and received 24 weeks of treatment; data was available for 26/27 patients. All 26 (100%) had undetectable HCV RNA at week 24 (EOT). 4/29 (arm C) and 2/30 (arm D) patients discontinued treatment prior to week 12; of these 2/4 (Arm C) had SVR. The most frequently reported adverse events were fatigue in 56% (33/59; mild 69%, 23/33) of patients, nausea in 49% (29/59; mild 72%, 21/29), diarrhea in 48% (28/59; mild 89%, 25/28), anemia in 37% (22/59; mild 36%, 8/22), pruritus in 34% (20/59; mild 65%, 13/20), and rash in 31% (18/59; mild 72%, 21/30). Severe events observed in at least 2 patients were: neutropenia (5.1%, 3/59), hypomagnesemia (3.4%, 2/59), and anemia (3.4%, 2/59). Three patients (10%) in each arm discontinued all study drugs due to AEs during the overall treatment phase; two patients in each arm discontinued treatment before Week 12, one patient in each arm discontinued treatment while on PR only. **CONCLUSIONS:** QUAD therapy with VX-222, telaprevir, and PR is associated with a high rate of antiviral activity in genotype 1, treatment-naïve patients and a safety profile similar to T/PR with a higher rate of mild GI events. There was no on-treatment viral breakthrough and 38-50% of patients were able to undergo only 12 weeks of therapy, resulting in 82-93% SVR12. Patients receiving 24 weeks of therapy had high EOT responses; final SVR data will be presented.

**Virologic response to an interferon-free regimen of BI201335 and BI207127, with and without ribavirin, in treatment-naïve patients with chronic genotype-1 HCV infection: Week 12 interim results of the SOUND-C2 study** Dr. Stefan Zeuzem The Liver Meeting AASLD 2011 #LB-15

**BACKGROUND:** In a previous phase Ib study (SOUND-C1) that evaluated interferon-free combination treatment of the NS3/4A protease inhibitor, BI201335, and the non-nucleoside NS5B RNA polymerase inhibitor, BI207127, along with ribavirin (RBV), in treatment-naïve patients (TN) with chronic genotype (GT)-1 hepatitis C virus (HCV) infection, rapid virological response rates were up to 100%. SOUND-C2 is a 5-arm, open-label, randomized, phase IIb study evaluating efficacy and safety of several all-oral combination regimens of these compounds for up to 40 weeks of treatment. **METHODS:** A total of 362 TN HCV GT-1 patients were treated and randomized into 5 treatment arms: (1) 120 mg QD BI201335 (1335) combined with 600 mg TID BI207127 (7127<sub>TID</sub>) and RBV for 16 weeks; (2) 1335 + 7127<sub>TID</sub> + RBV for 28 weeks; (3) 1335 + 7127<sub>TID</sub> + RBV for 40 weeks; (4) 1335 + 600 mg BID BI207127 (7127<sub>BID</sub>) + RBV for 28 weeks; (5) 1335 + 7127<sub>TID</sub> for 28 weeks. This is a planned interim analysis performed after all patients completed 12 weeks of treatment. Randomization was stratified by HCV subtype (1a vs. 1b) and IL28B GT (rs12979860 CC vs. non-CC). **RESULTS:** 52% of patients were male, 98% were white, 85% had HCV RNA  $\geq$  800,000 IU/mL at baseline, 38% were GT-1a, 10% had compensated cirrhosis and 26% were IL-28B GT CC. Intent-to-treat response rates of all treated patients are presented in the table. Asthenia, pruritus, rash, photosensitivity, jaundice, nausea, vomiting and diarrhoea were the most commonly observed (> 25%) adverse events (AEs). Discontinuation of treatment due to AEs occurred in 12%, 6% and 9% of patients in the 1335 + 7127<sub>TID</sub> + RBV arms, 1335 + 7127<sub>BID</sub> + RBV arm, and 1335 + 7127<sub>TID</sub> arm, respectively; 5%, 0% and 9% discontinued due to rash or photosensitivity, and 3%, 1% and 0% discontinued due to gastrointestinal events. **CONCLUSIONS:** Interferon-free oral combination therapy with BI201335, BI207127 and RBV provides high virologic response rates in HCV GT-1 TN patients, confirming the potent antiviral activity of this combination. The response rate in the RBV-sparing arm was substantial but lower than in other arms at Week 12. The safety and tolerability profile was comparable to other direct acting antiviral regimens and more favorable in the 1335 + 7127<sub>BID</sub> + RBV arm.

**Once Daily Narlaprevir (NVR; SCH 900518) and Ritonavir (RTV) in Combination with Peginterferon alfa-2b/Ribavirin (PR) for 12 weeks plus 12 weeks PR in Treatment-Naïve Patients with HCV Genotype 1 (G1): SVR Results from NEXT-1, a Phase 2 Study**

Dr. John M. Vierling The Liver Meeting AASLD 2011 #LB-17

**BACKGROUND:** NVR, an HCV NS3 protease inhibitor, can be dosed once daily when combined with RTV. **METHODS:** NEXT-1 is a Phase 2 randomized, dose ranging study of NVR/RTV plus P (1.5 mcg/kg/QW) and weight-based R (600-1400 mg/d). Treatment regimens included: a) once daily NVR (200 mg or 400 mg QD) with RTV (100 mg QD) and PR for 12 weeks, with or without a 4 week lead-in (LI) of PR; b) twice daily NVR (100 mg BID) with RTV (100 mg BID) and PR for 12 weeks; or c) PR alone for 48 weeks. Based on response after 4 weeks of NVR/RTV/PR, PR was continued for either an additional 12 or 36 weeks. The primary endpoint was the frequency of undetectable HCV-RNA (LLD=9.3 IU/mL) after 4 weeks of NVR/RTV/PR. Secondary endpoints were end of treatment (EOT) response and SVR24. **RESULTS:** Demographics of enrolled 111 US patients: 13% Black, 58% male, 82% viral load

>600,000 IU/mL, and 77% genotype 1a (NS5B subtyping assay). HCV RNA levels declined to SVR rates with once daily regimens of NVR/RTV with PR for 12 weeks followed by PR for another 12 weeks ranged from 68-85%; 66.7% SVR in Blacks. 55% (6/11) of patients with poor response to PR (<1 log<sub>10</sub> drop in HCV-RNA after a 4 week LI of PR) achieved SVR. Resistance variant profiles were similar to those observed with other linear protease inhibitors. AEs commonly associated with PR resulted in discontinuation in 8/91 (9%) of NVR/RTV treated patients, including GI- symptoms, homicidal ideation, tinnitus, depression, and lethargy. NVR/RTV/PR was associated with Hgb <10g/dL in 37% of patients vs. 11% with PR alone, NVR/RTV was not associated with rash. **CONCLUSIONS:** A 12 week course of once daily NVR/RTV with PR followed by PR for 12 weeks produced SVR rates up to 85% in patients with HCV genotype 1 infection and was effective in all demographic groups. NVR/RTV was safe, well tolerated, and associated only with AEs observed with PR.

**Combination Therapy of Treatment-Naïve and Nonresponder Patients with HCV Genotype 1 Infection with BMS-790052, an NS5A Replication Complex Inhibitor, in Combination with Peginterferon Alfa-2a and Ribavirin** Namiki Izumi The Liver Meeting AASLD 2011 #LB-20

**BACKGROUND:** BMS-790052 is a first-in-class NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage in vitro. Combining direct-acting antivirals with peginterferon and ribavirin (R) may improve SVR rates in patients with chronic HCV infection. This ongoing study evaluates BMS-790052 + peginterferon alfa-2a (PEG2a)/R in Japanese treatment-naïve and nonresponder patients. **METHODS:** 43 patients with genotype 1 HCV infection were enrolled: 25 naïve patients were randomized to receive PEG2a/R combined with either placebo, BMS-790052 10mg QD or 60mg QD; 17 patients with prior nonresponse to PEG/R (12 nulls and 5 partials) were randomized to receive PEG2a/R combined with either BMS-790052 10mg QD or 60mg QD; 1 patient assigned to placebo was not treated. BMS-790052 recipients who achieved a protocol-defined response (PDR; HCV RNA **RESULTS:** In naïve patients, eRVR and PDR rates were higher with BMS-790052 10mg or 60mg vs placebo. All BMS-790052 recipients with a PDR achieved SVR after only 24 weeks of treatment. One naïve patient receiving BMS-790052 10mg had viral breakthrough. In nonresponders, rates of eRVR and PDR were similar to those in naïve patients; 1 patient in each arm had viral breakthrough. Rates of adverse events (AEs) and discontinuations due to AEs were comparable across groups. The most common grade 3-4 AEs were typical of PEG/R and included leukopenia, lymphopenia and neutropenia. **CONCLUSIONS:** Similar to results in a parallel study of BMS-790052 combined with peginterferon alfa-2b, treatment with BMS-790052 + PEG2a/R therapy achieved rapid viral suppression and high SVR rates in treatment-naïve patients with early virologic response (PDR). Initial responses were similar in nonresponders but several patients relapsed post-treatment. AE profiles with PEG2a/R + BMS-790052 and PEG2a/R alone were similar.

**BMS-790052, an NS5A Replication Complex Inhibitor, in Combination with Peginterferon Alpha-2b and Ribavirin in Japanese Treatment-Naïve and Nonresponder Patients with Chronic HCV Genotype 1 Infection** Fumitaka Suzuki The Liver Meeting AASLD 2011 #LB-22

**BACKGROUND:** Improved outcomes for patients with chronic HCV infection may be achieved by combining potent antivirals with peginterferon and ribavirin (R). BMS-790052 is a

first-in-class NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage in vitro. BMS-790052 combined with peginterferon alfa-2b (PEG2b)/R is being evaluated in Japanese treatment-naïve and nonresponder patients. **METHODS:** 45 patients with HCV genotype 1 were treated: 27 treatment-naïve patients were randomized to receive PEG2b/R combined with either placebo, BMS-790052 10mg QD or 60mg QD; 18 patients with prior nonresponse to PEG/R (9 null and 9 partial responders) were randomized to receive PEG2b/R + BMS-790052 10mg QD or 60mg QD. BMS-790052 recipients who achieved a protocol-defined response (PDR; HCV RNA **RESULTS:** In naïve patients, eRVR and PDR rates were higher with both 10mg and 60mg BMS-790052 vs placebo; a high proportion of those with PDR also achieved SVR with only 24 weeks of treatment. All treatment-naïve patients receiving 60 mg BMS-790052 + PEG2b/R qualified for 24 weeks of treatment and 90% achieved SVR. Four naïve BMS-790052 recipients had viral failure or relapse, including one breakthrough in the 10mg group; all 4 were IL28B genotype CT, out of 11 CC and 7 CT overall. In nonresponders, eRVR rates were lower and 4 patients in each arm had viral breakthrough. Rates of adverse events (AEs) and discontinuations due to AEs were comparable across groups. The most common grade 3/4 AEs were anemia, lymphopenia and neutropenia, typical of PEG/R therapy. **CONCLUSIONS:** Similar to results in a parallel study of BMS-790052 combined with peginterferon alfa-2a, BMS-790052 + PEG2b/R therapy achieved rapid viral suppression and high rates of SVR in treatment-naïve early responder patients after 24 weeks of treatment. Response rates were lower in nonresponders, as expected for this difficult-to-treat population. AE profiles with PEG2b/R + BMS-790052 and PEG2b/R alone were similar.