



Caring Ambassadors Program Hepatitis C Newsletter

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August 2011

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Insulin resistance is independently associated with significant hepatic fibrosis in Asian chronic hepatitis C genotype 2 or 3 patients. Patel K, Thompson AJ, Chuang WL, et al. *J Gastroenterol Hepatol.* 2011 Jul;26(7):1182-1188. doi: 10.1111/j.1440-1746.2011.06722.x. <http://www.ncbi.nlm.nih.gov/pubmed/21410752>

BACKGROUND AND AIM: The role of insulin resistance (IR) and hepatic steatosis in fibrogenesis in chronic hepatitis C infection (CHC) has yielded conflicting data and few studies have been performed in Asian-region populations. We retrospectively investigated the relationship between host metabolic variables, including IR and hepatic steatosis, to hepatic fibrosis in Asian-region CHC genotype 2/3 patients. **METHODS:** A total of 303 treatment-naïve Asian-region patients with CHC genotype 2/3 were enrolled in a multicenter phase 3 study of albinterferon alfa-2b plus ribavirin for 24 weeks. IR was defined as Homeostasis Model for Assessment of IR (HOMA-IR) > 2. Baseline liver biopsy was evaluated by a single expert histopathologist. Post hoc subgroup logistic regression modeling selected for independent variables associated with significant fibrosis (METAVIR stage F2-F4). **RESULTS:** Insulin resistance was available in 263 non-diabetic Asian-region patients (hepatitis C virus-2 [HCV-2] = 171, HCV-3 = 92), and 433 non-Asian region patients (407 "Caucasian"); METAVIR fibrosis prevalence F0-F1 (minimal fibrosis) = 201 (77%) and F2-F4 (significant fibrosis) = 59 (23%), and steatosis prevalence of grade 0 = 169 (65%), grade 1 = 64 (25%), grade 2/3 = 27 (10%). Median HOMA-IR was 1.8 (interquartile range: 1.2-2.7); 100 (38%) patients had HOMA-IR > 2. Factors independently associated with significant fibrosis included HOMA-IR (odds ratio [OR] = 8.42), necro-inflammatory grade (OR = 3.17), age (OR = 1.07) and serum total cholesterol levels (OR = .008). This was similar to non-Asian region patients, but steatosis was not associated with significant fibrosis in either cohort. **CONCLUSIONS:** In this subgroup study of Asian-region HCV genotype 2 or 3 patients, insulin resistance, along with age, cholesterol levels and necro-inflammation, but not steatosis may be associated with significant hepatic fibrosis.

A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. Lan CL, Guillygomarc'h A, Danielou H, et al. *J Hepatol.* 2011 Jul 11. [Epub ahead of print]
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<http://www.ncbi.nlm.nih.gov/pubmed/21756854>

BACKGROUND & AIMS: Guidelines recommend 6 months of alcohol abstinence before treating hepatitis C (HCV). Abstinence is difficult for alcohol-dependent patients to achieve. This study evaluated HCV treatment in alcoholic patients with ongoing consumption or less than 6 months of abstinence. **METHODS:** A multidisciplinary management model was built by a liver unit and two centers involved in the care of addict patients. Patients were included in a prospective observational study of treatment with pegylated interferon and ribavirin if they presented alcohol dependence with ongoing intoxication or abstinence of less than 6 months. Pre-therapeutic evaluation and follow-up were multidisciplinary, and addiction care was personalized to patient condition and willingness. Alcohol abstinence or reduction was encouraged but not mandatory. The primary end point was sustained virological response (SVR). Results were compared to a control group of patients matched for genotype, viral load, fibrosis stage, sex, and age. **RESULTS:** A total of 73 patients treated between 2002 and 2008 were included in the study. Intent to treat analysis showed a SVR in 48% (35/73) of patients versus 49% (36/73) of controls. Low viral load and the length of abstinence during treatment were independently associated with SVR. During treatment, 20 (27%) patients were abstinent, 23 (32%) had controlled consumption, and 24 (33%) had excessive consumption. At the end of the follow-up, 22 (30%) patients were durably abstinent. **CONCLUSION:** A multidisciplinary approach allowed HCV treatment in alcohol-dependent patients with a satisfactory SVR rate and positive effects on addiction behavior.

Hyporesponsiveness to pegifn α 2b plus ribavirin in patients with hepatitis C-related advanced fibrosis. Prati GM, Aghemo A, Rumi MG, et al. J Hepatol. 2011 Jul 11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21756847>

BACKGROUND & AIM: The success of pegylated-interferon (PegIFN) / ribavirin (Rbv) therapy of chronic hepatitis C is compromised by liver fibrosis. Whether fibrosis equally affects the two PegIFN α -based therapies is unknown. To assess the response to the two PegIFN regimens in patients with different degree of liver fibrosis. **METHODS:** A sub-analysis of the MIST study: 431 consecutive naïve patients randomly assigned, based on HCV genotype, to receive either PegIFN α 2a 180 μ g/wk plus daily Rbv 800-1200mg (A) or PegIFN α 2b 1.5 μ g/kg/week plus daily Rbv 800-1200mg (B), were stratified according to Ishak staging (S) into mild (S0-S2) or moderate (S3,S4) fibrosis and cirrhosis (S5,S6). **RESULTS:** In A the sustained virological response (SVR) rates were not significantly influenced by fibrosis stage (71% in S0-S2, 66% in S3,S4, 53% in S5,S6, p=0.12), compared to B where the SVR rates differed according to fibrosis stage (65%, 46% and 38%, p=0.004, respectively). This was even more so in HCV-1/4 patients treated with PegIFN α 2b where the SVR rates were twice as many in S0-S2 vs S \geq 3 (44% vs 22%, p=0.02), while in A the SVR rates were similar between the two fibrosis subgroups (S0-S2: 47% vs S \geq 3: 48%, p=0.8). By logistic regression analysis genotype 1/4 and lack of rapid virological response were independent predictors of treatment failure in both treatment groups, while S \geq 3 fibrosis was associated to PegIFN α 2b treatment failure, only (OR 2.83, 95%CI 1.4 - 5.68, p=0.004). **CONCLUSION:** Liver fibrosis was an independent moderator of treatment outcome in patients receiving PegIFN α 2b, not in those receiving PegIFN α 2a.

A Randomized Controlled Trial of an Integrated Care Intervention to Increase Eligibility for Chronic Hepatitis C Treatment. Evon DM, Simpson K, Kixmiller S, et al. *Am J Gastroenterol.* 2011 Jul 19. doi: 10.1038/ajg.2011.219. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21769136>

OBJECTIVES: Mental health and substance abuse (MH/SA) comorbidities are the most oft-cited reasons for deferral from peginterferon (PegIFN) therapy for chronic hepatitis C virus (HCV). We sought to determine whether an integrated care intervention (INT) for patients deferred from PegIFN owing to MH/SA could improve subsequent treatment eligibility rates.

METHODS: In this randomized controlled trial, 101 HCV patients who were evaluated at two hepatology centers and deferred from antiviral therapy owing to MH/SA were enrolled. Participants were randomized to an INT (N=50) or standard of care (SC; N=51). The INT group received counseling and case management for up to 9 months. All participants underwent 3-, 6-, and 9-month clinical follow-up visits, where hepatologists, masked to group, re-evaluated patients for treatment eligibility. Standardized mood and alcohol use instruments were administered to all participants to aid clinicians in treatment decisions. **RESULTS:** Of 101 participants, the mean age was 48 years and 50% were men, 61% Caucasian, and 77% genotype 1. Patients were initially deferred owing to psychiatric issues (35%), alcohol abuse (31%), drug abuse (9%), or more than one of these reasons (26%). In an intent-to-treat analysis, 42% (21/50) of INT participants became eligible for therapy compared to 18% (9/51) of SC participants (P=0.009, relative risk (RR)=2.38, 95% confidence interval (CI) (1.21, 4.68)). When baseline predictors significant at P<0.10 in univariate models were entered into multivariate models adjusted for treatment group, only baseline depression remained significant (P=0.05, RR=0.98, 95% CI (0.96, 1.00)). With the exception of a model adjusted for genotype, treatment group remained significant in all models. **CONCLUSIONS:** This trial suggests that INTs can increase eligibility for HCV treatment and expand treatment to the underserved population with MH/SA comorbidities.

Improved Responses to Pegylated Interferon alfa-2b and Ribavirin by Individualizing Treatment for 24-72 Weeks. Sarrazin C, Schwendy S, Möller B, et al. *Gastroenterology.* 2011 Jul 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21784046>

BACKGROUND & AIMS: Guidelines recommend that patients with chronic hepatitis C virus (HCV) infection be treated with pegylated interferon and ribavirin for 24, 48, or 72 weeks, based on their virologic response to treatment. We investigated the effects of treating patients for individualized durations. **METHODS:** We treated 398 treatment-naïve patients who HCV genotype-1 infections with pegylated interferon alfa-2b and ribavirin for 24, 30, 36, 42, 48, 60 or 72 weeks (mean 39 weeks, termed individualized therapy); the duration of therapy was determined based on baseline viral load and the timepoint at which HCV RNA became undetectable (measured at weeks 4, 6, 8, 12, 24, and 30). Results were compared to 225 patients who received standard treatment, for 48 weeks (mean of 38 weeks). **RESULTS:** Rates of sustained virologic response (SVR) were 55% among patients that received individualized treatment and 48% among those that received standard treatment (P<.0001 for non-inferiority). SVR rates, according to the timepoint at which HCV RNA became undetectable, did not differ significantly between groups. Patients with a rapid virologic response (undetectable levels of HCV RNA at week 4) who were treated for 24-30 weeks achieved high rates of SVR (86%-88%). Rates of SVR increased among slow responders that first tested negative for HCV RNA at

week 24 and were treated for 60-72 weeks, compared with those treated for 48 weeks (60%-68% vs 43%-44%). The CC polymorphism at IL28B rs129797860 was associated with an increased rate of SVR, compared with the CT/TT polymorphism ($P < .0001$), at baseline but not among patients who had undetectable levels of HCV RNA following treatment. **CONCLUSIONS:** Individualizing treatment of patients with chronic HCV genotype 1 infections for 24-72 weeks results in high rates of SVR among rapid responders and increases SVRs among slow responders.

Association of laboratory parameters with viral factors in patients with hepatitis C. Ijaz B, Ahmad W, Javed FT, et al. *Virol J.* 2011 Jul 21;8(1):361. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21777434>

BACKGROUND AND AIMS: HCV infection may lead to hepatic fibrosis. In this study, we tried to determine whether there is any correlation of HCV genotypes and viral load to the clinical parameters such as ALT, AST, ALP, bilirubin, Hb level, patient's age and gender; and then correlated this association with disease progression in liver biopsy samples. **METHODS:** In cross-sectional and observational study, 6048 serum HCV RNA positive patients were chosen. The study consists of 53 months from March 2006 to September 2010. Patients were divided into three cohorts to validate our data. Statistical analysis and correlation of lab parameters with viral factors was determined by using SPSS version 16. **RESULTS:** The most prevalent genotype was 3 (70.9%) followed by 1 (13.3%) and 4 (7.4%), collectively. During Univariate analysis, in all cohorts; serum bilirubin, ALP, ALT and AAR showed significant correlation with genotypes, however multivariate analysis showed that all genotypes except 4a have no association with host biochemical markers. Disease progression was also independent of all genotypes. Serum ALP, ALT, bilirubin and viremia levels were significantly elevated in patients with genotype 4a. Viral load showed negative association with serum bilirubin ($r = -0.112$, $P = 0.000$) and ALP levels ($r = -0.098$, $P = 0.000$). We observed positive correlation of ALP and bilirubin levels, while negative associations of viral load with HCV liver disease progression. **CONCLUSION:** Disease progression seems independent of the genotypes. Relationship between ALP and bilirubin with viral load may be an attractive marker to guess disease progression in patients with hepatitis C.

Mallory-Denk Bodies are Associated with Outcomes and Histologic Features in Patients with Chronic Hepatitis C. Rakoski MO, Brown MB, Fontana RJ, et al. *Clin Gastroenterol Hepatol.* 2011 Jul 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21782771>

BACKGROUND & AIMS: Mallory-Denk bodies (MDBs) are inclusions found in hepatocytes of patients with chronic liver diseases. Their clinical significance and prognostic value are not understood. **METHODS:** We performed cross-sectional and longitudinal analyses of patients with chronic hepatitis C (CHC) enrolled in the HALT-C trial to identify clinical features associated with MDBs and changes in MDBs over time. Biopsies were obtained at baseline and 1.5 and 3.5 years after patients were assigned to groups for the HALT-C trial; and patients were followed to assess clinical and histologic outcomes. **RESULTS:** Of biopsy samples collected from 1050 patients, MDBs were present in 15%. They were associated with insulin resistance and laboratory and histological markers of advanced liver disease (higher levels of periportal fibrosis, pericellular fibrosis, steatosis, and inflammation). After adjusting for disease severity (the ratio of aspartate aminotransferase to alanine aminotransferase, albumin, platelets, fibrosis,

steatosis), the presence of MDBs was associated with histological progression (odds ratio [OR]=1.97; P=.04). Of the 844 patients from whom serial biopsy samples were collected, 61 (7.2%) developed MDBs (MDB gain) and 101 (12.0%) lost MDBs (MDB loss). The presence or absence of diabetes mellitus was associated with MDB gain (P=.006) or loss (P=.024), respectively. Development of MDBs was associated with decompensation (adjusted HR=2.81, P<.001) and histologic signs of progression (adjusted OR=4.02, P=.004). **CONCLUSIONS:** The presence of MDBs in liver biopsy samples from patients with CHC is independently associated with fibrosis progression. Gain of MDBs over time is associated with decompensation and progression to cirrhosis; and occurs most frequently among diabetics. MDBs might be used as prognostic factors for patients with CHC.

IL28B but not ITPA polymorphism is predictive of response to pegylated interferon, ribavirin, and telaprevir triple therapy in patients with genotype 1 hepatitis C. Chayama K, Hayes CN, Abe H, et al. J Infect Dis. 2011 Jul;204(1):84-93.

<http://www.ncbi.nlm.nih.gov/pubmed/21628662>

BACKGROUND: Pegylated interferon, ribavirin, and telaprevir triple therapy is a new strategy expected to eradicate the hepatitis C virus (HCV) even in patients infected with difficult-to-treat genotype 1 strains, although adverse effects, such as anemia and rash, are frequent. **METHODS:** We assessed efficacy and predictive factors for sustained virological response (SVR) for triple therapy in 94 Japanese patients with HCV genotype 1. We included recently identified predictive factors, such as IL28B and ITPA polymorphism, and substitutions in the HCV core and NS5A proteins. **RESULTS:** Patients treated with triple therapy achieved comparatively high SVR rates (73%), especially among treatment-naive patients (80%). Of note, however, patients who experienced relapse during prior pegylated interferon plus ribavirin combination therapy were highly likely to achieve SVR while receiving triple therapy (93%); conversely, prior nonresponders were much less likely to respond to triple therapy (32%). In addition to prior treatment response, IL28B SNP genotype and rapid viral response were significant independent predictors for SVR. Patients with the anemia-susceptible ITPA SNP rs1127354 genotype typically required ribavirin dose reduction earlier than did patients with other genotypes. **CONCLUSIONS:** Analysis of predictive factors identified IL28B SNP, rapid viral response, and transient response to previous therapy as significant independent predictors of SVR after triple therapy.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Simple assay based on restriction fragment length polymorphism associated with IL28B in chronic hepatitis C patients. Nakamoto S, Kanda T, Imazeki F, Wu S, Arai M, Fujiwara K, Yokosuka O. Scand J Gastroenterol. 2011 Jul;46(7-8):955-61.

<http://www.ncbi.nlm.nih.gov/pubmed/21529139>

OBJECTIVE: Several studies recently revealed that single nucleotide polymorphisms (SNPs) in the interleukin28B (IL28B) region are associated with the response to pegylated interferon-alfa (PEG-IFN-alfa) and ribavirin (RBV) treatment among hepatitis C virus (HCV)-infected individuals of European, African and Asian ancestry. The purpose of the study was to establish methods for determining the SNP rs8099917 associated with IL28B, which might be useful for further research of the treatment of HCV. **MATERIAL AND METHODS:** Blood samples obtained from 93 consecutive patients with chronic hepatitis C were examined. On the basis of

the sequence data, a new simple genotyping assay based on a PCR-restriction fragment length polymorphism (RFLP) with two enzymes, BsrDI and Tsp45I, was developed. **RESULTS:** The proportion of null virological responders in the combined TG/GG group was higher than that in the TT group ($p = 0.015$), suggesting that minor allele is one of the important factors playing crucial roles in IFN-resistance. Genotyping of rs8099917 by our new method showed results identical to PCR and sequence in 98.9% and 98.9% by BsrDI and Tsp45I, respectively. Using two enzymes, BsrDI and Tsp45I, it was possible to distinguish IL28B SNP rs8099917.

CONCLUSION: This simple method using RFLP will provide the framework for further studies of HCV.

Resistance mutations define specific antiviral effects for inhibitors of the hepatitis C virus p7 ion channel. Foster TL, Verow M, Wozniak AL, et al. *Hepatology*. 2011 Jul;54(1):79-90. doi: 10.1002/hep.24371.

<http://www.ncbi.nlm.nih.gov/pubmed/21520195>

The hepatitis C virus (HCV) p7 ion channel plays a critical role during infectious virus production and represents an important new therapeutic target. Its activity is blocked by structurally distinct classes of small molecules, with sensitivity varying between isolate p7 sequences. Although this is indicative of specific protein-drug interactions, a lack of high-resolution structural information has precluded the identification of inhibitor binding sites, and their modes of action remain undefined. Furthermore, a lack of clinical efficacy for existing p7 inhibitors has cast doubt over their specific antiviral effects. We identified specific resistance mutations that define the mode of action for two classes of p7 inhibitor: adamantanes and alkylated imino sugars (IS). Adamantane resistance was mediated by an L20F mutation, which has been documented in clinical trials. Molecular modeling revealed that L20 resided within a membrane-exposed binding pocket, where drug binding prevented low pH-mediated channel opening. The peripheral binding pocket was further validated by a panel of adamantane derivatives as well as a bespoke molecule designed to bind the region with high affinity. By contrast, an F25A polymorphism found in genotype 3a HCV conferred IS resistance and confirmed that these compounds intercalate between p7 protomers, preventing channel oligomerization. Neither resistance mutation significantly reduced viral fitness in culture, consistent with a low genetic barrier to resistance occurring in vivo. Furthermore, no cross-resistance was observed for the mutant phenotypes, and the two inhibitor classes showed additive effects against wild-type HCV. **Conclusion:** These observations support the notion that p7 inhibitor combinations could be a useful addition to future HCV-specific therapies.

Serum apolipoprotein C-III is independently associated with chronic hepatitis C infection and advanced fibrosis. Rowell J, Thompson AJ, Guyton JR, et al. *Hepatol Int*. 2011 Jul 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21735316>

BACKGROUND: The hepatitis C virus (HCV) is known to disrupt lipid metabolism, making serum lipoprotein levels good candidates to explore as markers of HCV disease progression. Assessment of the major apolipoproteins (Apo) and their relationship to hepatic fibrosis remain largely unexplored. **METHODS:** We compared the levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and Apo A-I, -B, -C-III, and -E between patients with cleared versus active infection ($n = 83$), and

between those chronically infected patients (n = 216) with advanced versus mild-moderate hepatic fibrosis (METAVIR stage F3-4 vs. F0-2) using multiple logistic regression. **RESULTS:** Apo C-III levels were 25% higher in subjects with cleared infection versus those with active infection (p = 0.009). Low levels of Apo C-III (p = 1.3×10^{-5}), Apo A-I (p = 2.9×10^{-5}), total cholesterol (p = 5.0×10^{-4}), LDL-C (p = 0.005), and HDL-C (p = 2.0×10^{-4}) were associated with advanced fibrosis in univariate analyses. Multivariable analysis revealed Apo C-III as the most significant factor associated with advanced fibrosis (p = 0.0004), followed by age (p = 0.013) and Apo A-I (p = 0.022). Inclusion of both Apo C-III and Apo A-I in a model to predict advanced fibrosis improved the area under the receiver operator curve only modestly. **CONCLUSIONS:** Relative to other lipoproteins, low serum Apo C-III levels are the most strongly associated with chronic versus cleared infection and decline with increasing severity of hepatic fibrosis. Apo C-III deserves further attention as a possible marker of HCV disease progression.

Mechanistic characterization of gs-9190 (tegobuvir), a novel non-nucleoside inhibitor of hepatitis c virus ns5b polymerase. Shih IH, Vliegen I, Peng B, et al. Antimicrob Agents Chemother. 2011 Jul 11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21746939>

GS-9190 (Tegobuvir) is a novel imidazopyridine inhibitor of HCV RNA replication in vitro and has demonstrated potent antiviral activity in patients chronically infected with genotype (GT) 1 HCV. GS-9190 exhibits reduced activity against a GT2a (JFH1) subgenomic replicons and GT2a (J6/JFH1) infectious virus suggesting that the compound mechanism of action involves a genotype specific viral component. To further investigate the GS-9190 mechanism of action, we utilized the susceptibility difference between GT1b and GT2a by constructing a series of replicon chimeras where combinations of 1b and 2a nonstructural proteins were encoded within the same replicon. The antiviral activity of GS-9190 against the chimeric replicons was reduced to levels comparable to that of the wild-type GT2a replicon in chimeras expressing GT2a NS5B. GT1b replicons where the β -hairpin region (a.a. 435-455) was replaced by the corresponding sequence of GT2a were markedly less susceptible to GS-9190, indicating the importance of the thumb sub-domain of the polymerase in this effect. Resistance selection in GT1b replicon cells identified several mutations in NS5B (C316Y, Y448H, Y452H and C445F) that contribute to the drug-resistant phenotype. Re-introduction of these mutations into wild-type replicons conferred resistance to GS-9190, with the number of NS5B mutations correlating with the degree of resistance. Analysis of GS-9190 cross-resistance against previously reported NS5B drug-selected mutations show that the resistance pattern of GS-9190 is different compared to other non-nucleoside inhibitors. Collectively, these data demonstrate that GS-9190 represents a novel class of non-nucleoside polymerase inhibitor that interacts with NS5B likely involving the β -hairpin in the thumb sub-domain.

Hepatitis C virus (HCV) envelope glycoproteins E1 and E2 contain reduced cysteine residues essential for virus entry. Fraser J, Boo I, Pountourios P, Drummer HE. J Biol Chem. 2011 Jul 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21768113>

The HCV envelope glycoproteins E1 and E2 contain 8 and 18 highly conserved cysteine residues, respectively. Here we examined the oxidation state of E1E2 heterodimers incorporated into retroviral pseudotyped particles (HCVpp) and investigated the significance of free

sulfhydryl groups in cell culture derived HCV (HCVcc) and HCVpp entry. Alkylation of free sulfhydryl groups on HCVcc/pp with a membrane impermeable sulfhydryl alkylating reagent 4-(N-Maleimido)benzyl- α -trimethylammonium iodide (M135) prior to virus attachment to cells abolished infectivity in a dose dependent manner. Labelling of HCVpp envelope proteins with EZ-Link Maleimide-PEG2-Biotin (maleimide-biotin) detected free thiol groups in both E1 and E2. Unlike retroviruses that employ disulfide reduction to facilitate virus entry, the infectivity of alkylated HCVcc could not be rescued by addition of exogenous reducing agents. Furthermore, the infectivity of HCVcc bound to target cells was not affected by addition of M135 indicative of a change in glycoprotein oxidation state from reduced to oxidised following virus attachment to cells. By contrast, HCVpp entry was reduced by 61% when treated with M135 immediately following attachment to cells suggesting that the two model systems might demonstrate variations in oxidation kinetics. Glycoprotein oxidation was not altered following binding of HCVpp incorporated E1E2 to soluble heparin or recombinant CD81. **These results suggest** that HCV entry is dependent on the presence of free thiol groups in E1 and E2 prior to cellular attachment and reveals a new essential component of the HCV entry process.

Activation of unfolded protein response and autophagy during HCV infection modulates innate immune response. Estrabaud E, De Muynck S, Asselah T. J Hepatol. 2011 Jul 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21723841>

Autophagy, a process for catabolizing cytoplasmic components, has been implicated in the modulation of interactions between RNA viruses and their host. However, the mechanism underlying the functional role of autophagy in the viral life cycle still remains unclear. Hepatitis C virus (HCV) is a single-stranded, positive-sense, membrane-enveloped RNA virus that can cause chronic liver disease. Here we report that HCV induces the unfolded protein response (UPR), which in turn activates the autophagic pathway to promote HCV RNA replication in human hepatoma cells. Further analysis revealed that the entire autophagic process through to complete autolysosome maturation was required to promote HCV RNA replication and that it did so by suppressing innate antiviral immunity. Gene silencing or activation of the UPR-autophagy pathway activated or repressed, respectively, IFN- β activation mediated by an HCV-derived pathogen-associated molecular pattern (PAMP). Similar results were achieved with a PAMP derived from Dengue virus (DEV), indicating that HCV and DEV may both exploit the UPR-autophagy pathway to escape the innate immune response. Taken together, these results not only define the physiological significance of HCV-induced autophagy, but also shed light on the knowledge of host cellular responses upon HCV infection as well as on exploration of therapeutic targets for controlling HCV infection.

Characterization of Serum Proteins Associated with IL28B Genotype among Patients with Chronic Hepatitis C. Cyr DD, Lucas JE, Thompson JW, et al. PLoS One. 2011;6(7):e21854. Epub 2011 Jul 5.

<http://www.ncbi.nlm.nih.gov/pubmed/21750736>

INTRODUCTION: Polymorphisms near the IL28B gene (e.g. rs12979860) encoding interferon $\lambda 3$ have recently been associated with both spontaneous clearance and treatment response to pegIFN/RBV in chronic hepatitis C (CHC) patients. The molecular consequences of this genetic variation are unknown. To gain further insight into IL28B function we assessed the association of rs12979860 with expression of protein quantitative traits (pQTL analysis) generated using

open-platform proteomics in serum from patients. **METHODS:** 41 patients with genotype 1 chronic hepatitis C infection from the Duke Liver Clinic were genotyped for rs12979860. Proteomic profiles were generated by LC-MS/MS analysis following immunodepletion of serum with MARS14 columns and trypsin-digestion. Next, a latent factor model was used to classify peptides into metaproteins based on co-expression and using only those peptides with protein identifications. Metaproteins were then analyzed for association with IL28B genotype using one-way analysis of variance. **RESULTS:** There were a total of 4,186 peptides in the data set with positive identifications. These were matched with 253 proteins of which 110 had two or more associated, identified peptides. The IL28B treatment response genotype (rs12979860_CC) was significantly associated with lower serum levels of corticosteroid binding globulin (CBG; $p=9.2 \times 10^{-6}$), a major transport protein for glucocorticoids and progestins. Moreover, the CBG metaprotein was associated with treatment response ($p=0.0148$), but this association was attenuated when both IL28B genotype and CBG were included in the model, suggesting that the CBG association may be independent of treatment response. **CONCLUSIONS:** In this cohort of chronic hepatitis C patients, IL28B polymorphism was associated with serum levels of corticosteroid binding globulin, a major transporter of cortisol, however, CBG does not appear to mediate the association of IL28B with treatment response. Further investigation of this pathway is warranted to determine if it plays a role in other comorbidities of HCV-infection.

The prognostic value of changes in serum ferritin levels during therapy for hepatitis C virus infection. Ackerman Z, Pappo O, Ben-Dov IZ. J Med Virol. 2011 Jul;83(7):1262-8. doi: 10.1002/jmv.22093.

<http://www.ncbi.nlm.nih.gov/pubmed/21567428>

An increase in serum ferritin levels during combined interferon-ribavirin treatment in chronic patients infected with hepatitis C virus (HCV) can occur. A study was conducted to determine whether observing the kinetics of serum ferritin levels during antiviral therapy, may assist in predicting the rate of sustained virological response. The kinetics of serum ferritin levels during antiviral therapy in treatment-naive, adherent patients with chronic HCV who had early virological response were characterized. Thirteen patients achieved sustained virological response (group 1) while eight patients did not (group 2). Pre-treatment serum ferritin levels were higher in group 2 patients. During antiviral therapy, serum ferritin levels increased in both groups. On treatment, the median increase (compared to baseline) and the calculated rate of the increase in serum ferritin levels was higher in group 1 patients (874% vs. 272%, $P < 0.05$, 63%/week vs. 13%/week, $P = 0.024$, respectively). Red blood cell lysis did not contribute to the increase in serum ferritin level. Post-treatment (1st month) serum ferritin levels in group 1 patients were lower than in group 2 patients. In addition, the degree of decline in the 1st month serum ferritin levels (from peak levels) in group 1 patients was higher (76% vs. 49%, $P = 0.039$). Measuring serum ferritin levels during antiviral therapy in HCV patients who had an early virological response may assist in predicting sustained virological response.

Functional impairment of dendritic cells in patients infected with hepatitis C virus genotype 1 who failed peginterferon plus ribavirin therapy. Liang CC, Liu CH, Lin YL, Liu CJ, Chiang BL, Kao JH. J Med Virol. 2011 Jul;83(7):1212-20. doi: 10.1002/jmv.22096.

<http://www.ncbi.nlm.nih.gov/pubmed/21567425>

Although chronic hepatitis C patients have a lower frequency and functions of dendritic cells (DCs) than healthy subjects, little is known about the serial changes in frequency and functions

of DCs following anti-viral treatment and the relationship with treatment outcomes. Twenty patients with hepatitis C virus genotype 1 receiving peginterferon (PEG-IFN) and ribavirin for 24 weeks were enrolled. The frequency and functions of DCs were assayed at baseline and 24 weeks post-treatment. Ten sex and age-matched healthy adults served as controls. Nineteen of the 20 chronic hepatitis C patients completed 24 weeks of combination therapy. Fifteen patients achieved rapid virologic response and 12 achieved sustained virologic response (SVR). The baseline frequency of peripheral blood myeloid DCs and plasmacytoid DCs was significantly lower in chronic hepatitis C patients than in healthy controls. In patients who achieved SVR, the frequency of DCs subsets at the end of follow-up increased to a level comparable to healthy controls. Although no functional defects of DCs was found in chronic hepatitis C patients in comparison with healthy controls, in patients without SVR had a lower CD83 expression and higher interleukin-10 production of DCs than SVR patients. The results suggest that low CD83 expression and high IL-10 production of DCs at the baseline may predict a poor virologic response to 24-week PEG-IFN plus ribavirin therapy in HCV genotype 1 patients.

High Serum Levels of CXCL11 in Mixed Cryoglobulinemia Are Associated with Increased Circulating Levels of Interferon- γ Antonelli A, Ferri C, Ferrari SM, et al. J

Rheumatol. 2011 Jul 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21724697>

OBJECTIVE: No study has evaluated circulating chemokine C-X-C motif ligand (CXCL)11 in patients with "mixed cryoglobulinemia and chronic hepatitis C infection" (MC+HCV). We measured CXCL11, and correlated this measurement to the clinical phenotype. **METHODS:** Serum CXCL11, interferon- γ (IFN- γ), and tumor necrosis factor - α (TNF- α) were assayed in 97 MC+HCV patients and in 97 sex- and age-matched controls. **RESULTS:** MC+HCV patients showed significantly higher mean CXCL11 serum levels than controls (254 ± 295 , 68 ± 16 pg/ml, respectively; $p = 0.0002$; ANOVA). CXCL11 was significantly increased in 36 cryoglobulinemic patients with compared to those without active vasculitis (303 ± 208 vs 179 ± 62 pg/ml, respectively; $p < 0.001$; ANOVA). IFN- γ levels were significantly higher in MC+HCV than in controls [6.1 (range 0.8-114.5), 1.4 (range 0.7-2.4) pg/ml, respectively; $p < 0.05$; Mann-Whitney U test]. Serum TNF- α mean levels were significantly higher in MC+HCV than in controls [13.4 (range 1.8-369), 1.1 (range 0.7-3.2) pg/ml, respectively; $p < 0.0001$; Mann-Whitney U test]. A multiple regression analysis considering CXCL11 as a dependent variable, and age, alanine aminotransferase, IFN- γ , and TNF- α as independent variables, showed in MC+HCV patients a significant association only with IFN- γ ($p < 0.0001$). **CONCLUSION:** Our study demonstrates markedly high serum levels of CXCL11 in patients with MC+HCV compared to healthy controls overall in the presence of active vasculitis. A strong relationship between circulating IFN- γ and CXCL11 was shown, strongly supporting the role of a T helper 1 immune response in the pathogenesis of MC+HCV.

Interference of replication between hepatitis B and C viruses in patients infected with HIV.

Yang RR, Gui X, Chen XY, Zhu Y. J Med Virol. 2011 Jul;83(7):1159-64. doi: 10.1002/jmv.22102.

<http://www.ncbi.nlm.nih.gov/pubmed/21567419>

The clinical and cellular interactions between hepatitis B virus (HBV) and hepatitis C virus (HCV) were investigated in patients co-infected with the human immunodeficiency virus (HIV). One hundred ninety-nine patients followed for 6 years were evaluated to compare the level of HBV DNA and HCV RNA in patients co-infected with HIV and HBV, and patients co-infected with HIV, HBV, and HCV. A full-length HBV genome and HCV JFH1 RNA were co-transfected into HuH-7.5.1 cells in vitro to examine the impact of co-infection and dependence on the HBV PreC mutant for replication interference. Before 2',3'-dideoxy-3'-thiacytidine (3TC)-based antiretroviral therapy (ART) was initiated, HBV DNA was found in 56/123 (45.4%) patients co-infected with HIV and HBV, and in 19/76 (25.0%) patients co-infected with HIV, HBV, and HCV. After 3TC-based ART was initiated, detectable HBV DNA decreased to 7/76 (9.2%) in patients co-infected with HIV, HBV, and HCV, but HCV RNA increased from 43/76 (56.6%) to 60/76 (78.9%) ($P = 0.003$). In vitro HBV and HCV co-infection led to decreased replication of both viruses. The primary factors that influenced the decreased replication were the order of the HBV and HCV infection and the HBV PreC mutation.

Treatment of acute hepatitis C infection in HIV-infected patients. Boesecke C, Rockstroh JK. Curr Opin HIV AIDS. 2011 Jul;6(4):278-84.

<http://www.ncbi.nlm.nih.gov/pubmed/21519248>

PURPOSE OF REVIEW: Clinicians started to notice the cases of an outbreak of acute hepatitis C (AHC) infections among HIV-positive MSM in Europe almost 10 years ago. Similar reports from the USA and Australia soon followed. In the absence of randomized controlled treatment trials clinicians have to rely on published data from uncontrolled clinical and cohort studies to develop treatment algorithms in these patients and give recommendations on best clinical management. **RECENT FINDINGS:** Data from recent cohort studies indicate that the early course of hepatitis C virus (HCV) RNA in the first 4 weeks after diagnosis may be a helpful predictor of spontaneous clearance of AHC in HIV-infected individuals. Additionally, single-nucleotide polymorphisms near the IL28B gene have been demonstrated to impact chances of spontaneous clearance. Pegylated interferon in combination with weight-adapted ribavirin is recommended as treatment of choice for all HCV genotypes. For patients developing a rapid virological response, defined as a negative HCV-RNA in an ultrasensitive assay, treatment duration of 24 weeks is recommended. Overall, high-sustained virological response rates of 60-80% have been observed if antiviral therapy was initiated within 24 weeks after diagnosis.

SUMMARY: The current epidemic of AHC particularly among MSM is still ongoing, and prevention and screening efforts have to be intensified to allow for control of viral dissemination. Concise recommendations for best clinical management of AHC in HIV infection have been developed on the basis of published observational data.

Influence of interferon-based therapy on liver fibrosis progression in HIV/HCV coinfecting patients: A retrospective repeated liver biopsy analysis. Ingiliz P, Valantin MA, Petrosi P, et al. J Hepatol. 2011 Jul 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21781946>

BACKGROUND: Hepatitis C virus (HCV) coinfection is one of the leading causes of mortality in human immunodeficiency virus infected patients. The current standard of care leads to cure only in a part of these patients. The course of the disease is determined by the rapidity of liver fibrosis progression (LFP). The influence of interferon on LFP in coinfecting patients has yet not been evaluated by comparative liver biopsies. **METHODS:** We extracted data of patients who had serial liver biopsies from a hospital database. Histopathological findings were compared to factors possibly linked to fibrosis progression. Furthermore, we studied the impact of response to interferon treatment on fibrosis progression. **RESULTS:** 126 patients were included, 68 had received anti-HCV treatment and 58 had not. The median time between the first and the last biopsy was 4 years. Worsened fibrosis was observed in 35 of 58 (60%) untreated patients and 22 of 50 (44%) patients in the nonresponder/relapser group and in 5 out of 18 (28%) in the SVR group. Liver fibrosis evolution was significantly better in patients achieving a SVR than in untreated and NR/R patients ($p < 0.02$, odds-ratio [95% CI] for improvement vs stability vs worsening = 3.16 [1.24-8.07]). This result persisted after adjustment for known predictors of liver fibrosis progression, HBsAg, CD4 and alcohol consumption: adjusted odds ratio = 2.89 [1.09-7.68], $p = 0.03$. **CONCLUSIONS:** HCV treatment can stop fibrosis progression and induce its regression. Nonresponders to treatment may even have a faster fibrosis progression. It remains to be clarified if the same factors that induce nonresponse to treatment may also induce faster fibrosis progression.

IL28B Polymorphism Associated with Spontaneous Clearance of Hepatitis C Infection in a Southern Brazilian HIV Type 1 Population. Lunge VR, da Rocha DB, Béria JU, Tietzmann DC, Stein AT, Simon D. AIDS Res Hum Retroviruses. 2011 Jul 26. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21790472>

About one-third of people infected with human immunodeficiency virus-1 (HIV-1) are coinfecting with hepatitis C virus (HCV) because of shared transmission routes. Studies report that HIV-1 complicates hepatitis C infection by increasing HCV viral load and reducing spontaneous clearance. Single nucleotide polymorphisms (SNPs) upstream of the IL28B gene have been associated with spontaneous and treatment-induced clearance of HCV infection. The aim of this study was to evaluate the association between the SNP rs12979860 of the IL28B gene and spontaneous clearance of HCV infection in a Brazilian HIV-1 population. The SNP was analyzed by polymerase chain reaction (PCR) followed by restriction digestion in 138 anti-HCV-positive patients. Spontaneous clearance was observed in 34 subjects (24.6%). Genotype distribution was significantly different between spontaneous clearance and HCV chronic patients. The CT/TT genotypes conferred a nearly 3-fold increased odds to chronic HCV infection relative to the CC genotype (odds ratio, 2.78; 95% confidence interval, 1.16-6.64; $p=0.011$). In conclusion, the rs12979860 polymorphism is associated with spontaneous clearance of HCV in HIV-1 Brazilian infected patients.

An overview of Triple infection with Hepatitis B, C and D viruses. Riaz M, Idrees M, Kanwal H, Kabir F. Virol J. 2011 Jul 27;8(1):368. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21791115>

Viral hepatitis is one of the major health problems worldwide, particularly in South East Asian countries including Pakistan where hepatitis C virus (HCV) and hepatitis B virus (HBV) infections are highly endemic. Hepatitis delta virus (HDV) is also not uncommon world-wide.

HCV, HBV, and HDV share parallel routes of transmission due to which dual or triple viral infection can occur in a proportion of patients at the same time. HBV and HCV are important factors in the development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). In addition to LC and HCC, chronic HDV infection also plays an important role in liver damage with oncogenic potential. The current article reviews the available literature about the epidemiology, pathogenesis, transmission, symptoms, diagnosis, replication, disease outcome, treatment and preventive measures of triple hepatitis infection by using key words; epidemiology of triple infection, risk factors, awareness status, treatment and replication cycle in PubMed, PakMediNet, Directory of Open Access Journals (DOAJ) and Google Scholar. Total data from 74 different studies published from 1983 to 2010 on triple hepatitis infections were reviewed and included in this study. The present article briefly describes triple infection with HCV, HBV and HDV.

Low-density lipoprotein receptor genotyping enhances the predictive value of IL28B genotype in HIV/hepatitis C virus-coinfected patients. Pineda JA, Caruz A, Di Lello FA, et al. AIDS. 2011 Jul 17;25(11):1415-20.

<http://www.ncbi.nlm.nih.gov/pubmed/21572301>

OBJECTIVE: The aims of this study were to appraise the predictive value of variations in a single-nucleotide polymorphism (SNP) in the low-density lipoprotein receptor (LDLR) gene for sustained virological response (SVR) to pegylated interferon (Peg-IFN) and ribavirin (RBV), as well as to analyze the relationship between LDLR genotype and other predictors of SVR, particularly IL28B genotype, in patients coinfecting with HIV and hepatitis C virus (HCV).

METHODS: One hundred and eighty-four HIV/HCV-coinfecting, treatment-naive patients with chronic HCV infection, who received Peg-IFN and RBV, were included. Variations in the SNP rs14158 and rs12979860 were tested by Taqman PCR assay. **RESULTS:** Twenty-eight (38%) patients with rs14158 TT/TC and 61 (55%) with CC (P=0.028) achieved SVR. The rates of SVR in patients with rs14158 TT/TC and with CC harboring HCV 1-4 were 20 and 41% (P=0.020), respectively, and, in those with HCV genotype 2-3, 75 and 84% (P=0.513), respectively.

Patients with rs14158 CC showed less commonly plasma HCV-RNA load at least 600000IU/ml (57 vs. 71%, P=0.047) and lower likelihood of relapse (13 vs. 30%, P=0.023). In patients with HCV genotype 1-4, the rates of SVR according to the combination of IL28B/LDLR genotypes were: CC/CC=69%; CC/non-CC: 30%; non-CC/CC: 25%; non-CC/non-CC: 14% (P<0.001).

CONCLUSION: Variations in rs14158 are associated with SVR to Peg-IFN and RBV in HIV/HCV-coinfecting patients harboring HCV genotype 1-4. LDLR and IL28B genotypes seem to have a synergistic effect on SVR. The combined use of LDLR and IL28B genotypes in routine clinical practice could enhance the predictive value of IL28B genotype alone.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Vitamin-D: An innate antiviral agent suppressing Hepatitis C virus in human hepatocytes.

Gal-Tanamy M, Bachmetov L, Ravid A, et al. Hepatology. 2011 Jul 25. doi: 10.1002/hep.24575. [Epub ahead of print]

<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 anti-viral activity which is mediated by its active metabolite. This anti-viral activity involves the induction of interferon signaling pathway resulting in expression of interferon- β 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- α synergistically inhibited viral production. **Conclusion:** This study demonstrates for the first time a direct anti-viral 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 natural anti-viral mediator. Importantly, our study implies that vitamin-D might have an interferon sparing effect thus improving antiviral treatment of HCV-infected patients.

Glycyrrhizin as antiviral agent against Hepatitis C Virus. Ashfaq UA, Masoud MS, Nawaz Z, Riazuddin S. J Transl Med. 2011 Jul 18;9(1):112. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21762538>

BACKGROUND: Hepatitis C virus is a major cause of chronic liver diseases which can lead to permanent liver damage, hepatocellular carcinoma and death. The presently available treatment with interferon plus ribavirin, has limited benefits due to adverse side effects such as anemia, depression, fatigue, and "flu-like" symptoms. Herbal plants have been used for centuries against different diseases including viral diseases and have become a major source of new compounds to treat bacterial and viral diseases. **MATERIAL:** The present study was design to study the antiviral effect of Glycyrrhizin (GL) against HCV. For this purpose, HCV infected liver cells were treated with GL at non toxic doses and HCV titer was measured by Quantitative real time RT-PCR. **RESULTS AND DISCUSSION:** Our results demonstrated that GL inhibit HCV titer in a dose dependent manner and resulted in 50% reduction of HCV at a concentration of 14+/-2 ug. Comparative studies were made with interferon alpha to investigate synergistic effects, if any, between antiviral compound and interferon alpha 2a. Our data showed that GL exhibited synergistic effect when combined with interferon. Moreover, these results were verified by transiently transfecting the liver cells with HCV 3a core plasmid. The results proved that GL dose dependently inhibit the expression of HCV 3a core gene both at mRNA and protein levels while the GAPDH remained constant. **CONCLUSION:** Our results suggest that GL inhibit HCV full length viral particles and HCV core gene expression or function in a dose dependent manner and had synergistic effect with interferon. In future, GL along with interferon will be better option to treat HCV infection.

An IL28B Genotype-Based Clinical Prediction Model for Treatment of Chronic Hepatitis

C. O'Brien TR, Everhart JE, Morgan TR, et al. PLoS One. 2011;6(7):e20904. Epub 2011 Jul 8.

<http://www.ncbi.nlm.nih.gov/pubmed/21760886>

BACKGROUND: Genetic variation in IL28B and other factors are associated with sustained virological response (SVR) after pegylated-interferon/ribavirin treatment for chronic hepatitis C (CHC). Using data from the HALT-C Trial, we developed a model to predict a patient's probability of SVR based on IL28B genotype and clinical variables. **METHODS:** HALT-C enrolled patients with advanced CHC who had failed previous interferon-based treatment. Subjects were re-treated with pegylated-interferon/ribavirin during trial lead-in. We used step-wise logistic regression to calculate adjusted odds ratios (aOR) and create the predictive model. Leave-one-out cross-validation was used to predict a priori probabilities of SVR and determine area under the receiver operator characteristics curve (AUC). **RESULTS:** Among 646 HCV genotype 1-infected European American patients, 14.2% achieved SVR. IL28B rs12979860-CC genotype was the strongest predictor of SVR (aOR, 7.56; $p < .0001$); the model also included HCV RNA (log₁₀ IU/ml), AST:ALT ratio, Ishak fibrosis score and prior ribavirin treatment. For this model AUC was 78.5%, compared to 73.0% for a model restricted to the four clinical predictors and 60.0% for a model restricted to IL28B genotype ($p < 0.001$). Subjects with a predicted probability of SVR $< 10\%$ had an observed SVR rate of 3.8%; subjects with a predicted probability $> 10\%$ (43.3% of subjects) had an SVR rate of 27.9% and accounted for 84.8% of subjects actually achieving SVR. To verify that consideration of both IL28B genotype and clinical variables is required for treatment decisions, we calculated AUC values from published data for the IDEAL Study. **CONCLUSION:** A clinical prediction model based on IL28B genotype and clinical variables can yield useful individualized predictions of the probability of treatment success that could increase SVR rates and decrease the frequency of futile treatment among patients with CHC.

Comparison of 9 blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. Zarski JP, Sturm N, Guechot J, Paris A, et al. J

Hepatol. 2011 Jul 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21781944>

BACKGROUND & AIMS: Blood tests and transient elastography (Fibroscan™) have been developed as alternatives to liver biopsy. This ANRS HCEP-23 study compared the diagnostic accuracy of 9 blood tests and transient elastography (Fibroscan™) to assess liver fibrosis, versus liver biopsy, in untreated patients with chronic hepatitis C (CHC). **METHODS:** This was a multicenter prospective independent study in 19 French University hospitals of consecutive adult patients having simultaneous liver biopsy, biochemical blood tests (performed in a centralized laboratory) and Fibroscan™. Two experienced pathologists independently reviewed the liver biopsies (mean length = 25 ± 8.4 mm). Performance was assessed using ROC curves corrected by Obuchowski's method. **RESULTS:** Fibroscan™ was not interpretable in 113 (22%) patients. In the 382 patients having both blood tests and interpretable Fibroscan™, Fibroscan™ performed similarly to the best blood tests for the diagnosis of significant fibrosis and cirrhosis. Obuchowski's measure showed Fibrometer® (0.86), Fibrotest® (0.84), Hepascore® (0.84) and interpretable Fibroscan™ (0.84) to be the most accurate tests. The combination of

Fibrotest(®), Fibrometer(®), or Hepascore(®) with Fibroscan™ or Apri increases the percentage of well classified patients from 70-73% to 80-83% for significant fibrosis, but for cirrhosis a combination offers no improvement. For the 436 patients having all the blood tests, AUROC's ranged from 0.82 (Fibrometer(®)) to 0.75 (Hyaluronate) for significant fibrosis, and from 0.89 (Fibrometer(®)) and Hepascore(®) to 0.83 (FIB-4) for cirrhosis. **CONCLUSION:** Contrarily to blood tests, performance of Fibroscan™ was reduced due uninterpretable results. Fibrotest(®), interpretable Fibroscan™, Fibrometer(®), and Hepascore(®) perform best and similarly for diagnosis of significant fibrosis and cirrhosis.

Infections and the liver. Eksteen B. Dig Dis. 2011;29(2):184-90. Epub 2011 Jul 5.

<http://www.ncbi.nlm.nih.gov/pubmed/21734383>

BACKGROUND: Hepatitis B (HBV) and hepatitis C virus (HCV) have infected nearly half a billion individuals worldwide and are major indications for liver transplantation. Key requirements to successful outcomes with modern antiviral drugs are favourable host factors.

RESULTS: Single nucleotide polymorphisms near the IL28B gene location which encode for interferon (IFN)-λ3 have a large effect in determining the likelihood of patients obtaining a cure from pegylated IFN-α and ribavirin combination therapy or spontaneous clearance of the HCV. 80% of patients who carry two copies of this advantageous variant cleared the virus during IFN therapy and remained virus-free with a sustained viral response. This mutation is more common in Caucasian and Asian populations, whereas it is only found in the 40-50% of sub-Saharan Africans who are known to be more resistant to combination therapy. Similarly, host factors control tolerance to chronic HBV infection and can fluctuate over time with increased risk of progression to cirrhosis and particularly liver cancer. Loss of viral tolerance with reactivation and hepatitis is increasingly seen with the widespread use of biological treatments for diseases such as inflammatory bowel disease or rheumatoid arthritis. Natural disasters and conflicts in some parts of the world have also seen an increase in cases of hepatitis A and E virus infection and highlighted the global public health burden from viral-induced hepatitis. **CONCLUSIONS:** Increased appreciation of the interaction between host factors and the viral life cycles is likely to significantly alter the way we target these infections in the future.

Racial differences in hepatitis C treatment eligibility. Melia MT, Muir AJ, McCone J, et al. Hepatology. 2011 Jul;54(1):70-78. doi: 10.1002/hep.24358.

<http://www.ncbi.nlm.nih.gov/pubmed/21488082>

Black Americans are disproportionately infected with hepatitis C virus (HCV) and are less likely than whites to respond to treatment with peginterferon (PEG-IFN) plus ribavirin (RBV). The impact of race on HCV treatment eligibility is unknown. We therefore performed a retrospective analysis of a phase 3B multicenter clinical trial conducted at 118 United States community and academic medical centers to evaluate the rates of and reasons for HCV treatment ineligibility according to self-reported race. In all, 4,469 patients were screened, of whom 1,038 (23.2%) were treatment ineligible. Although blacks represented 19% of treated patients, they were more likely not to be treated due to ineligibility and/or failure to complete required evaluations (40.2%) than were nonblack patients (28.5%; $P < 0.001$). After the exclusion of persons not treated due to undetectable HCV RNA or nongenotype 1 infection, blacks were 65% less likely than nonblacks to be eligible for treatment (28.1% > 17.0%; relative risk, 1.65; 95% confidence interval, 1.46-1.87; $P < 0.001$). Blacks were more likely to be ineligible due to neutropenia (14% versus 3%, $P < 0.001$), anemia (7% versus 4%, $P = 0.02$), elevated glucose (8% versus 3%, $P <$

0.001), and elevated creatinine (5% versus 1%, $P < 0.001$). **CONCLUSION:** Largely due to a higher prevalence of neutropenia and uncontrolled medical conditions, blacks were significantly less likely to be eligible for HCV treatment. Increased access to treatment may be facilitated by less conservative neutrophil requirements and more effective care for chronic diseases, namely, diabetes and renal insufficiency.

Acute hepatitis C in Korea: different modes of infection, high rate of spontaneous recovery, and low rate of seroconversion. Kim JY, Won JE, Jeong SH, et al. *J Med Virol*. 2011 Jul;83(7):1195-202. doi: 10.1002/jmv.22100.

<http://www.ncbi.nlm.nih.gov/pubmed/21567423>

The epidemiology and clinical outcomes of acute hepatitis C are different geographically. This study aimed to investigate the mode of infection, clinical characteristics, and outcomes of acute hepatitis C in Korea. Forty-seven patients with acute hepatitis C were enrolled consecutively in a study conducted in seven medical centers. The patients with the mean age of 45.8 years had mostly mild symptoms. A healthcare-related procedure was the most common exposure history (42.5%): acupuncture (17%), surgery (10.6%), needle-stick injury (8.5%), and other medical procedures (6.4%). There was no case of intravenous drug use. Twenty-one patients (44.7%) recovered spontaneously. Among the 16 patients who received antiviral therapy (34%), all of the 12 evaluable patients had a sustained virologic response, while 10 patients (21.3%) who did not receive antiviral therapy progressed to chronic infection. The overall seroconversion rate of anti-HCV antibody was 61.7%. The patients who recovered spontaneously had significantly lower rate of seroconversion compared with the patients who did not clear spontaneously the infection. In conclusion, acute hepatitis C in Korea was related to various healthcare procedures, including acupuncture, characterized by high rates of spontaneous recovery and low rates of seroconversion, which may be associated with different modes of infection and ethnic differences. The characteristics of acute hepatitis C in Asian countries warrants further study.

A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt.

Sievert W, Altraif I, Razavi HA, et al. *Liver Int*. 2011 Jul;31 Suppl 2:61-80. doi: 10.1111/j.1478-3231.2011.02540.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21651703>

BACKGROUND: The hepatitis C pandemic has been systematically studied and characterized in North America and Europe, but this important public health problem has not received equivalent attention in other regions. **AIM:** The objective of this systematic review was to characterize hepatitis C virus (HCV) epidemiology in selected countries of Asia, Australia and Egypt, i.e. in a geographical area inhabited by over 40% of the global population.

METHODOLOGY: Data references were identified through indexed journals and non-indexed sources. In this work, 7770 articles were reviewed and 690 were selected based on their relevance. **RESULTS:** We estimated that 49.3-64.0 million adults in Asia, Australia and Egypt are anti-HCV positive. China alone has more HCV infections than all of Europe or the Americas. While most countries had prevalence rates from 1 to 2% we documented several with relatively high prevalence rates, including Egypt (15%), Pakistan (4.7%) and Taiwan (4.4%). Nosocomial infection, blood transfusion (before screening) and injection drug use were identified as common risk factors in the region. Genotype 1 was common in Australia, China, Taiwan and other countries in North Asia, while genotype 6 was found in Vietnam and other Southeast Asian countries. In India and Pakistan genotype 3 was predominant, while genotype 4 was found in

Middle Eastern countries such as Egypt, Saudi Arabia and Syria. **CONCLUSION:** We recommend implementation of surveillance systems to guide effective public health policy that may lead to the eventual curtailment of the spread of this pandemic infection.

A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel.

Cornberg M, Razavi HA, Alberti A, et al. Liver Int. 2011 Jul;31 Suppl 2:30-60. doi: 10.1111/j.1478-3231.2011.02539.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21651702>

BACKGROUND AND AIM: Decisions on public health issues are dependent on reliable epidemiological data. A comprehensive review of the literature was used to gather country-specific data on risk factors, prevalence, number of diagnosed individuals and genotype distribution of the hepatitis C virus (HCV) infection in selected European countries, Canada and Israel. **METHODOLOGY:** Data references were identified through indexed journals and non-indexed sources. In this work, 13,000 articles were reviewed and 860 were selected based on their relevance. **RESULTS:** Differences in prevalence were explained by local and regional variances in transmission routes or different public health measures. The lowest HCV prevalence ($\leq 0.5\%$) estimates were from northern European countries and the highest ($\geq 3\%$) were from Romania and rural areas in Greece, Italy and Russia. The main risk for HCV transmission in countries with well-established HCV screening programmes and lower HCV prevalence was injection drug use, which was associated with younger age at the time of infection and a higher infection rate among males. In other regions, contaminated glass syringes and nosocomial infections continue to play an important role in new infections. Immigration from endemic countries was another factor impacting the total number of infections and the genotype distribution. Approximately 70% of cases in Israel, 37% in Germany and 33% in Switzerland were not born in the country. In summary, HCV epidemiology shows a high variability across Europe, Canada and Israel. **CONCLUSION:** Despite the eradication of transmission by blood products, HCV infection continues to be one of the leading blood-borne infections in the region.

Trends and projections of hepatitis C virus epidemiology in Latin America. Kershenobich

D, Razavi HA, Sánchez-Avila JF, et al. Liver Int. 2011 Jul;31 Suppl 2:18-29. doi:

10.1111/j.1478-3231.2011.02538.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21651701>

BACKGROUND AND AIM: The purpose of the present investigation is to provide an analysis of previous works on the epidemiology of the hepatitis C virus (HCV) infection from six countries throughout Latin America, to forecast the future HCV prevalence trends in Argentina, Brazil, Mexico and Puerto Rico, and to outline deficiencies in available data, highlighting the need for further research. **METHODS:** Data references were identified through indexed journals and non-indexed sources. Overall, 1080 articles were reviewed and 150 were selected based on their relevance to this work. When multiple data sources were available for a key assumption, a systematic process using multi-objective decision analysis (MODA) was used to select the most appropriate sources. When data were missing, analogues were used. Data from other countries with similar risk factors and/or population compositions were used as a proxy to help predict the future trends in prevalence. **RESULTS:** The review indicates that the dominant genotype is type 1. HCV prevalence in the analysed countries ranges from 1 to 2.3%. The Latin American countries have been very proactive in screening their blood supplies, thus minimizing the risk of transmission through transfusion. This suggests that other risk factors are set to play a major role

in continued new infections. The number of diagnosed and treated patients is low, thereby increasing the burden of complications such as liver cirrhosis or hepatocellular carcinoma. The HCV prevalence, according to our modelling is steady or increasing and the number of infected individuals will increase. **CONCLUSIONS:** The results herein reported should provide a foundation for informed planning efforts to tackle hepatitis.

A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. Hagan H, Pouget ER, Des Jarlais DC. J Infect Dis. 2011 Jul;204(1):74-83.

<http://www.ncbi.nlm.nih.gov/pubmed/21628661>

INTRODUCTION: High rates of hepatitis C virus (HCV) transmission are found in samples of people who inject drugs (PWID) throughout the world. The objective of this paper was to meta-analyze the effects of risk-reduction interventions on HCV seroconversion and identify the most effective intervention types. **METHODS:** We performed a systematic review and meta-analysis of published and unpublished studies. Eligible studies reported on the association between participation in interventions intended to reduce unsafe drug injection and HCV seroconversion in samples of PWID. **RESULTS:** The meta-analysis included 26 eligible studies of behavioral interventions, substance-use treatment, syringe access, syringe disinfection, and multicomponent interventions. Interventions using multiple combined strategies reduced risk of seroconversion by 75% (pooled relative risk, .25; 95% confidence interval, .07-.83). Effects of single-method interventions ranged from .6 to 1.6. **CONCLUSIONS:** Interventions using strategies that combined substance-use treatment and support for safe injection were most effective at reducing HCV seroconversion. Determining the effective dose and combination of interventions for specific subgroups of PWID is a research priority. However, our meta-analysis shows that HCV infection can be prevented in PWID.

Unmet needs among people reported with hepatitis C, New York City. Bornschlegel K, Crotty KJ, Sahl S, Balter S. J Public Health Manag Pract. 2011 Jul-Aug;17(4):E9-17.

<http://www.ncbi.nlm.nih.gov/pubmed/21617400>

OBJECTIVE: This project sought to describe unmet needs among patients reported with hepatitis C in New York City. **DESIGN:** From the New York City Health Department's hepatitis C surveillance database, we randomly selected patients whose positive hepatitis C test was in April or May 2005. In 2006, we interviewed patients by telephone and collected information from their clinicians or by medical record review. **SETTING:** New York City. **PARTICIPANTS:** We interviewed 180 of the 387 eligible patients and collected information from clinicians for 145 of the 180 patients. **MAIN OUTCOME MEASURES:** These included whether patients had understood their clinicians' explanation of their hepatitis C diagnosis, if they had been counseled about not drinking alcohol, information about support group attendance, vaccination against hepatitis A and B, health status, treatment, and other factors. **RESULTS:** Of the 180 patients, 7% stated that they had not understood their clinicians' explanation of their hepatitis C diagnosis, and 26% said that they had not been counseled about avoiding alcohol. Among the 90% of patients who had not attended a hepatitis support group, 31% were interested in attending. Among the 145 patients with information from clinicians, at least 28% were susceptible to hepatitis A and 18% to hepatitis B. **CONCLUSIONS:** This hepatitis C surveillance project, with information from patients and clinicians, illustrates a valuable use of a chronic hepatitis C surveillance system. The patients described here had several unmet needs,

including hepatitis A and B vaccination, basic information about the virus, support groups, and counseling about preventing further liver damage and preventing transmission to others. Relatively simple and affordable health department activities can address these needs, improving quality of life and decreasing the likelihood of liver disease progression.

The increasing mortality burden of liver disease among opioid dependent people: Cohort study. Gibson A, Randall D, Degenhardt L. *Addiction*. 2011 Jul 12. doi: 10.1111/j.1360-0443.2011.03575.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21749525>

AIMS: Hepatitis C (HCV) infection is highly prevalent among IDUs, and likely to cause significant mortality over time, but little research attention has focused upon the magnitude of this risk, particularly among ageing users. This study examined trends over time in mortality attributed to liver disease, and in particular contrasting this with other more commonly studied causes of death (AIDS, suicide and overdose) among an ageing cohort of heroin dependent people in Australia. **DESIGN:** Data linkage study of methadone treatment entrants with the National Deaths Index. **Setting:** A cohort entering methadone treatment for heroin dependence in New South Wales, Australia, 1980-1985. **PARTICIPANTS:** 2,489 people entering methadone treatment for heroin dependence and 54,847 person-years of follow-up.

Measurements: Linkage of data on all methadone entrants between 1980-1985 with data from the Australian National Deaths Index, linked using probabilistic record linkage software.

Findings: There were 8.2 deaths per 1,000 PY (95%CI 7.5-9.0), with standardised mortality ratios (SMRs) of 4.6 (95%CI 4.2-5.0). Almost one in five (17%) of deaths were from underlying liver-related causes, most commonly viral hepatitis. The overall mortality rate for any liver cause was 1.4 deaths per 1,000 PY (95%CI 1.1-1.7), 17 times higher than to the general population (95%CI 13.4-21.3), with relative elevations more marked for females (SMR 27.9; 95%CI 17.7-41.9) than males (SMR 14.5; 95%CI 10.8-19.0). Liver mortality increased over time, becoming the most common cause of death by the end of follow-up. **CONCLUSIONS:** Liver disease has become the most common cause of mortality among ageing opioid dependent people in an ageing Australian cohort. There is an imperative to reduce the long-term risks of HCV and other risks to the liver including alcohol consumption, which are typically not the major clinical focus for this group.

Gaps in the Achievement of Effectiveness of HCV Treatment in National VA Practice.

Kramer JR, Kanwal F, Richardson P, Mei M, El-Serag H, Kramerer JR. *J Hepatol*. 2011 Jul 11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21756855>

BACKGROUND & AIMS: Antiviral treatment for hepatitis C virus (HCV) has high efficacy rates for achieving sustained viral response (SVR) in randomized controlled trials (RCTs) (40% to 80%); however, it can be lower in community-based practice settings. We wanted to determine the effectiveness of HCV treatment in Veterans Administration (VA) hospitals nationwide. **METHODS:** Using the nationwide VA HCV Clinical Case Registry (CCR), we examined cohort of veterans who had HCV viremia between 2000 and 2005 and identified patients who received pegylated-interferon (PEG-INF) and ribavirin. The duration of treatment and proportion of patients completing treatment was calculated. The effectiveness of treatment was measured as the proportion of patients who achieved SVR (negative viremia at least 12 weeks after the end of treatment) in the entire cohort, and among patients who initiated and

completed treatment. **RESULTS:** We identified 99,166 patients with HCV viremia. Of those, 11.6% received PEG-INF with ribavirin and 6.4% completed treatment. Contraindications were present in 57.2% of the patients that did not receive treatment. SVR was documented in 39.9% and 58.3% of patients who completed treatment; 23.6% and 50.6% of patients who initiated treatment; and 3.9% and 11.2% of the entire HCV cohort for genotype 1 or 4 and 2 or 3, respectively. Overall, only 3.5% of the entire HCV viremic cohort had documented SVR. **CONCLUSIONS:** Treatment effectiveness for HCV is low. In addition to fixed factors, such as race and virus genotype, the drop in effectiveness is due to low rates of antiviral treatment initiation and treatment completion.

LIVER CANCER

Liver cancer and non-hodgkin lymphoma in hepatitis C virus-infected patients: results from the danvir cohort study. Omland LH, Jepsen P, Krarup H, et al. *Int J Cancer*. 2011 Jul 21. doi: 10.1002/ijc.26283. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21780099>

Hepatitis C virus (HCV)-infection can cause hepatocellular carcinoma (HCC) and most likely non-Hodgkin lymphoma (NHL). No studies have compared the risk of these cancers between patients with chronic and cleared HCV-infection. The aim of this study was to estimate the 10-year risk of HCC and NHL in HCV-infected patients and to compare the risk of these cancers between HCV-infected patients and the general population in Denmark and between patients with chronic and cleared HCV-infection. Nationwide cohorts were used: 11,975 HCV-infected patients in the DANVIR cohort and 71,850 individuals from an age- and gender-matched general population cohort. Within DANVIR, 4,158 patients with chronic HCV-infection and 2,427 patients with cleared HCV-infection were studied. The 10-year risks of HCC and NHL in HCV-infected patients were 1.0% (95% confidence interval (CI): 0.8 - 1.3%) and 0.1% (95% CI: 0.1 - 0.2%), respectively. Compared to the general population, HCV-infected patients had a 62.91 - fold increased risk of HCC (95% CI: 28.99 - 136.52), a 29.97 -fold increased risk of NHL during the first year of follow-up (95% CI: 6.08 - 147.84), and a 1.26-fold increased risk of NHL after the first year (95% CI: 0.36 - 4.41). Chronic HCV-infection was associated with a 4.71-fold increased risk of HCC (95% CI: 1.67 - 13.32) compared to cleared HCV-infection; 5 and 0 events of NHL occurred in patients with chronic and cleared HCV-infection, respectively. HCC-risk is increased substantially in HCV-infected patients compared to the general population. Chronic as opposed to cleared HCV-infection increases the risk of HCC and perhaps NHL.

Peginterferon Maintenance Therapy in Patients with Advanced Hepatitis C to Prevent Hepatocellular Carcinoma: The Plot Thickens. Aghemo A, Colombo M. *J Hepatol*. 2011 Jul 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21782763>

BACKGROUND & AIMS: Interferon reportedly decreases the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial showed that 4 years of maintenance therapy with pegylated interferon (peginterferon) does not reduce liver disease progression. We investigated whether peginterferon decreases the incidence of HCC in the HALT-C cohort over a longer posttreatment follow-up period. **METHODS:** The study included 1048 patients with chronic hepatitis C (Ishak fibrosis scores \geq 3) who did not have a sustained virologic response (SVR) to

therapy. They were randomly assigned to groups given a half-dose of peginterferon or no treatment (controls) for 3.5 years and followed up for a median of 6.1 (maximum, 8.7) years. **RESULTS:** Eighty-eight patients developed HCC (68 definite, 20 presumed): 37 of 515 who were given peginterferon (7.2%) and 51 of 533 controls (9.6%; $P = .24$). There was a significantly lower incidence of HCC among patients given peginterferon therapy who had cirrhosis, but not fibrosis, based on analysis of baseline biopsy samples. After 7 years, the cumulative incidences of HCC in treated and control patients with cirrhosis were 7.8% and 24.2%, respectively (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.24-0.83); in treated and control patients with fibrosis, incidences were 8.3% and 6.8%, respectively (HR, 1.44; 95% CI, 0.77-2.69). Treated patients with a \geq 2-point decrease in the histologic activity index, based on a follow-up biopsy, had a lower incidence of HCC than those with unchanged or increased scores (2.9% vs 9.4%; $P = .03$). **CONCLUSIONS:** Extended analysis of the HALT-C cohort showed that long-term peginterferon therapy does not reduce the incidence of HCC among patients with advanced hepatitis C who did not achieve SVRs. Patients with cirrhosis who received peginterferon treatment had a lower risk of HCC than controls.