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Hepatitis C Newsletter
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April - May 2016

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES
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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis.](#) Modi AA1, Nazario H2, Trotter JF1, et al. Liver Transpl. 2016 Mar;22(3):281-6. doi: 10.1002/lt.24324.

Combination antiviral therapy involving sofosbuvir (SOF) and simeprevir (SIM) is a treatment option in patients with genotype 1 chronic hepatitis C; however, the safety of this regimen in patients with decompensated cirrhosis is not established. Data from a combined treatment cohort of 2 large hepatology referral centers were evaluated to assess for safety and efficacy of SIM plus SOF with or without ribavirin (RBV) in patients with Child B or C cirrhosis. All (n = 42) patients included in the analysis had Child B (n = 35) or C (n = 7) cirrhosis and received 400 mg daily of SOF plus 150 mg daily of SIM, with (n = 7) or without (n = 35) RBV, for 12 weeks. Of the 42 patients in this cohort, 31 (74%) were male, 22 (52%) had failed prior treatments, and 28 (67%) were genotype 1a. Prior decompensating events included encephalopathy (57%), fluid overload (88%), or variceal hemorrhage (24%). Median Model for End-Stage Liver Disease score was 12 (range, 6-25). Treatment was well tolerated overall with more than one-half (57%) reporting no adverse events. In those reporting adverse events, the most common were fatigue (n = 6), insomnia (n = 4), headache (n = 5), nausea (n = 4), and grade 1 rash (n = 1). One patient developed chemical pancreatitis that did not require treatment discontinuation. Three of 7 patients who received RBV developed anemia, with 2 requiring blood transfusions and 1 requiring a dose reduction. No episodes of decompensation requiring hospitalization or deaths occurred on treatment. Of 42 patients, 38 (90%) patients had negative viral load at end of treatment (EOT), and 31 of 42 patients (74%) achieved sustained virological response 12 weeks after EOT; 10 of 10 patients (100%) with HCV genotype 1b achieved sustained virological response for 12 weeks (SVR12). In conclusion, SOF plus SIM was very well tolerated in patients with advanced Child B/C decompensated cirrhosis. Overall, 74% of patients achieved SVR12; 100% of patients with genotype 1b decompensated cirrhosis achieved SVR12. Liver Transpl 22:281-286, 2016. © 2015 AASLD.

[GS-9857 in patients with chronic hepatitis C virus genotype 1-4 infection: a randomized, double-blind, dose-ranging phase 1 study.](#) Rodriguez-Torres M1, Glass S2, Hill J3, et al. J Viral Hepat. 2016 Mar 9. doi: 10.1111/jvh.12527. [Epub ahead of print]

GS-9857, an inhibitor of the hepatitis C virus (HCV) nonstructural protein (NS) 3/4A, demonstrates potent activity against HCV genotypes 1-6 and improved coverage against commonly encountered NS3 resistance-associated variants (RAVs). In this study, the safety, tolerability, antiviral activity and pharmacokinetics (PK) of GS-9857 were evaluated in patients with chronic HCV genotype 1-4 infection. Patients with genotype 1-4 infection received placebo or once-daily GS-9857 at doses ranging from 50 to 300 mg for 3 days under fasting conditions. GS-9857 was well tolerated; all reported adverse events (AEs) were mild or moderate in severity. Diarrhoea and headache were the most commonly reported AEs. Grade 3 or 4 laboratory abnormalities were observed in 17% of patients receiving GS-9857; there were no Grade 3 or 4 abnormalities in alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase levels. GS-9857 demonstrated potent antiviral activity in patients with chronic HCV infection, achieving mean and median maximum reductions in HCV RNA of ≥ 3 log₁₀ IU/mL following administration of a 100-mg dose in patients with HCV genotype 1a, 1b, 2, 3 or 4 infection. The antiviral activity of GS-9857 was unaffected by the presence of pretreatment NS3 RAVs. In patients with genotype 1-4 infection, GS-9857 exhibited linear PK and was associated with a median half-life of 29-42 h, supporting once-daily dosing. Thus, the tolerability, efficacy and pharmacokinetic profile of GS-9857 support its further evaluation for treatment of patients with chronic HCV infection.

[Vaniprevir plus peginterferon alfa-2b and ribavirin in treatment-experienced Japanese patients with hepatitis C virus genotype 1 \(GT1b\) infection: phase 3 studies.](#) Kumada H1,

Mochida S2, Suzuki F1, et al. J Gastroenterol Hepatol. 2016 Mar 2. doi: 10.1111/jgh.13328.

[Epub ahead of print]

BACKGROUND AND AIM: Vaniprevir is a macrocyclic hepatitis C virus (HCV) non-structural (NS)3/4A protease inhibitor. The objective of these phase 3 multicenter, open-label trials was to evaluate the safety and efficacy of vaniprevir + peginterferon alfa-2b + ribavirin (PR) in Japanese patients with HCV genotype (GT)1 infection who had previously failed treatment with interferon-based regimens. **METHODS:** Japanese patients with chronic HCV GT1 were enrolled. In PN044, patients with previous relapse or virologic breakthrough were randomized to vaniprevir (300 mg twice daily) + PR for 12 weeks followed by PR for another 12 weeks (12-week arm) or vaniprevir + PR for 24 weeks (24-week arm). In PN045, patients with previous partial/null response received vaniprevir + PR for 24 weeks. The primary endpoint was sustained virologic response at 24 weeks after completing treatment (SVR24). **RESULTS:** In PN044 (n = 51), SVR24 was 92.0% and 96.2% in the 12- and 24-week arms, respectively. In PN045 (n = 42), SVR24 was 61.9% in all patients and 55.2% in previous null responders. In both studies, vaniprevir + PR was generally safe and well tolerated; the majority of adverse events were mild/moderate and included pyrexia, decreased hemoglobin, headache, nausea, pruritus, and decreased platelet count. Polymorphisms in the HCV NS3 gene at baseline (Y56, Q80, and V170) did not impact treatment outcome. Virologic failure was principally associated with the on-treatment emergence of R155 or D168 mutations. **CONCLUSIONS:** Vaniprevir + PR is an effective, well-tolerated treatment for Japanese patients with HCV GT1 infection who failed previous interferon-based treatment.

[Knowledge about Hepatitis C Virus Infection and Acceptability of Testing in the 1945-1965 Birth Cohort \(Baby Boomers\) Presenting to a Large Urban Emergency Department: A Pilot Study.](#) Allison WE1, Chiang W2, Rubin A2, Oshva L2, Carmody E1. J Emerg Med. 2016 Mar 4. pii: S0736-4679(16)00113-X. doi: 10.1016/j.jemermed.2016.02.001. [Epub ahead of print]

BACKGROUND: Hepatitis C virus (HCV) is responsible for the most common chronic bloodborne infection in the United States. The Centers for Disease Control (CDC) recently recommended screening all patients born between 1945-1965 (baby boomers) at least once for HCV infection. New York State has since mandated screening of baby boomers for HCV in nearly all patient care settings and encouraged it in the emergency department (ED).

OBJECTIVES: This pilot study aimed to ascertain acceptability of an HCV screening test among the 1945-1965 birth cohort presenting to the ED in advance of a study investigating the prevalence of HCV infection in this birth cohort in the ED setting. **METHODS:** We conducted a cross-sectional study of health knowledge about HCV and government recommendations regarding HCV testing using a convenience sample of baby boomers in an ED in a large public hospital in the New York metropolitan area. Surveys were administered via a series of semistructured interviews. **RESULTS:** There were 81 patient participants. Fifty-two percent of patients were born outside of the United States, 69% had a high school diploma level of education or lower, and 37% were unemployed. Patients demonstrated misconceptions about HCV transmission and curability and poor knowledge about the necessity of testing in their age cohort. Knowledge that "HCV can cause the liver to stop working" was significantly associated with acceptance of testing. **CONCLUSIONS:** Baby boomers showed limited knowledge about the necessity of HCV screening in their age group, but testing for HCV infection in the ED was acceptable for the majority.

[Dose- and Formulation-Dependent Non-Linear Pharmacokinetic Model of Paritaprevir, a Protease Inhibitor for the Treatment of Hepatitis C Virus Infection: Combined Analysis from 12 Phase I Studies.](#) Polepally AR1, Mensing S2, Khatri A3, et al. Clin Pharmacokinet. 2016 Mar 21. [Epub ahead of print]

BACKGROUND AND OBJECTIVES: Paritaprevir is a direct-acting antiviral agent that is a component of approved multidrug regimens used in the treatment of hepatitis C virus (HCV) infection. A population pharmacokinetic model for paritaprevir was developed using data from formulation, bioavailability, and drug-drug interaction studies that evaluated the pharmacokinetics of paritaprevir (coadministered with ritonavir to enhance exposure) with or without ombitasvir and/or dasabuvir at different paritaprevir dose levels. **METHODS:** A non-linear mixed-effects modeling approach was applied to data from 12 phase I, single- and multiple-dose studies that enrolled a total of 369 healthy volunteers. Age, sex, race, ethnicity, body weight, body surface area, body mass index, and baseline creatinine clearance were evaluated as covariates during model development. In addition, the influences of dose, formulation, and concomitant medications (e.g. ombitasvir and dasabuvir) on paritaprevir bioavailability were included in the model. **RESULTS:** A two-compartment model with first-order absorption and elimination optimally described paritaprevir plasma concentration-time data. Paritaprevir bioavailability was formulation- and dose-dependent, and increased supraproportionally. The accumulation of paritaprevir was 1.57-fold on repeated dosing compared with the first dose. Coadministration of dasabuvir increased paritaprevir bioavailability by 59 %; however, ombitasvir coadministration did not affect the

pharmacokinetic profile of paritaprevir. No subject-specific covariate influenced the paritaprevir pharmacokinetics. The pharmacokinetic model was robust in bootstrap evaluations and was consistent with observed data based on diagnostic goodness-of-fit plots and visual predictive checks. **CONCLUSION:** The complex pharmacokinetics of paritaprevir were well described by the model, which can be used as a basis for clinical trial dosing and further evaluations in patients with HCV.

[**A phase 3, open-label study of daclatasvir plus asunaprevir in Asian patients with chronic hepatitis C virus genotype 1b infection who are ineligible for or intolerant to interferon alfa therapies with or without ribavirin.**](#) Wei L1, Zhang M2, Xu M3, et al. J Gastroenterol Hepatol. 2016 Mar 22. doi: 10.1111/jgh.13379. [Epub ahead of print]

BACKGROUND AND AIM: Daclatasvir plus asunaprevir has demonstrated efficacy and safety in patients with chronic hepatitis C virus genotype 1b infection. This study focused on evaluating daclatasvir plus asunaprevir in interferon (\pm ribavirin)-ineligible or -intolerant Asian patients with genotype 1b infection from mainland China, Korea, and Taiwan. **METHODS:** Interferon (\pm ribavirin)-ineligible and -intolerant patients with genotype 1b infection received daclatasvir 60 mg tablets once-daily plus asunaprevir 100 mg soft capsules twice-daily for 24 weeks. The primary endpoint was sustained virologic response at post-treatment Week 24 (SVR24). **RESULTS:** Of the 159 patients treated, 89.3% were Chinese, 65.4% were female, and 73.6% were interferon-intolerant. Cirrhosis was present in 32.7% of patients and 40.3% had IL28B non-CC genotypes. SVR24 was achieved by 145/159 (91.2%) patients (100% concordance with SVR12) and was similarly high in cirrhotic patients (47/52, 90.4%). SVR24 was higher in patients without baseline NS5A (L31M or Y93H) resistance-associated variants (RAVs) (137/139, 98.6%), including those with cirrhosis (43/44, 97.7%). Prevalence of baseline NS5A RAVs was low (19/159, 11.9%), particularly in mainland China (10/127, 7.9%). One death (0.6%), five serious adverse events (3.1%), and three grade 4 laboratory abnormalities (1.9%) occurred on-treatment; none were considered related to study drugs. Two patients (1.3%) discontinued due to adverse events. Treatment was generally well-tolerated regardless of cirrhosis status. **CONCLUSIONS:** Daclatasvir plus asunaprevir achieved a SVR24 rate of 91.2%, rising to 98.6% in patients without baseline NS5A RAVs, and was generally well tolerated in interferon (\pm ribavirin)-ineligible or -intolerant patients with genotype 1b infection from mainland China, Korea, and Taiwan.

[**All-oral daclatasvir plus asunaprevir for chronic HCV genotype 1b infection: a sub-analysis in Asian patients from the HALLMARK DUAL study.**](#) Kao JH1, Lee YJ2, Heo J3, et al. Liver Int. 2016 Mar 24. doi: 10.1111/liv.13128. [Epub ahead of print]

BACKGROUND & AIMS: Daclatasvir plus asunaprevir (DCV+ASV) has demonstrated potent antiviral activity in patients with hepatitis C virus (HCV) genotype 1b (GT-1b) infection in the HALLMARK DUAL trial. This post-hoc analysis was conducted to determine the efficacy and safety of this treatment in Asian patients. **METHODS:** Treatment-naive patients were randomly assigned (2:1; double-blinded) to receive DCV (60 mg once daily) plus ASV (100 mg twice daily) or placebo for 12 weeks. Subsequently, placebo patients entered another study, and the remaining patients continued treatment for an additional 12 weeks. Non-responders to peginterferon/ribavirin and ineligible/intolerant patients received dual therapy for 24 weeks. Sustained virologic response at post-treatment Week 12 (SVR12) and safety outcomes were evaluated. **RESULTS:** This post-hoc analysis included 186 Asian patients (Korean, 78;

Taiwanese, 85; others, 23), of whom 32.3% were cirrhotic. SVR12 was observed in 92.3%, 78.6% and 80.0% of treatment-naive, ineligible/intolerant and non-responder patients, respectively, and was comparable with non-Asian patients. SVR12 by baseline factors including age, viral load, interleukin-28B genotype and cirrhosis status was similar between the Asian sub-cohorts. Among 18 Asian patients with NS5A-Y93H or NS5A-L31M/V resistance-associated variants (RAVs), seven patients achieved SVR12. Multivariate regression analysis showed a significant influence of NS5A RAVs in both Asian and non-Asian cohorts. The incidence of serious adverse events in Asian patients was low (7.2%). Two Taiwanese patients had elevated alanine aminotransferase ($\geq 5.1 \times \text{ULN}$); both achieved SVR12. **CONCLUSIONS:** All-oral dual therapy with DCV+ASV resulted in high SVR rates and was well-tolerated in Asian patients with HCV GT-1b infection.

Moderate Alcohol Use and Insulin Action in Chronic Hepatitis C Infection. Burman BE1, Bacchetti P2, Khalili M3,4. Dig Dis Sci. 2016 Mar 23. [Epub ahead of print]

BACKGROUND AND AIM: Chronic hepatitis C (HCV) is associated with metabolic abnormalities including insulin resistance (IR) and diabetes. While moderate alcohol consumption is known to have beneficial metabolic effects in the general population, such potential effects in HCV are unknown. We aimed to assess the association between graded alcohol intake and IR, insulin secretion, and metabolic syndrome in HCV. **METHODS:** Ninety-five non-diabetic HCV-infected patients underwent detailed metabolic testing. IR was directly measured via steady-state plasma glucose (SSPG) during a 240-min insulin suppression test. Total insulin secretion and insulinogenic index were determined by 75-g oral glucose tolerance test. Genotyping of CYP2E1 was performed to detect genetic polymorphisms influencing alcohol metabolism. **RESULTS:** In this cohort, 61 % were abstinent from alcohol for the past 12 months, while 22 % were moderate, and 17 % heavy drinkers. Obesity and nonwhite ethnicity were the strongest predictors of IR. Moderate alcohol intake (vs none) was significantly associated with lower SSPG only among those with normal BMI (coef -72.9, 95 % CI -128.1 to -17.6, $p = 0.01$). Alcohol use was not associated with insulin secretion parameters when controlling for IR and other factors. Heavy alcohol intake (OR 3.2, 95 % CI 0.86-12.3) and nonwhite ethnicity (OR 7.1, 95 % CI 1.5-33.3) were associated with metabolic syndrome. Among nonwhites, the odds of metabolic syndrome were fivefold higher for heavy drinkers. **CONCLUSIONS:** Moderate alcohol intake is associated with improved insulin sensitivity in HCV, although this benefit was limited to normal-weight individuals. The potential benefit of moderate alcohol on IR and its metabolic consequences in HCV warrants further longitudinal investigation.

Daclatasvir vs telaprevir plus peginterferon alfa/ribavirin for hepatitis C virus genotype 1.

Jacobson I1, Zeuzem S1, Flisiak R1, et al. World J Gastroenterol. 2016 Mar 28;22(12):3418-31. doi: 10.3748/wjg.v22.i12.3418.

AIM: To evaluate daclatasvir vs telaprevir, each combined with peginterferon alfa-2a/ribavirin (pegIFN/RBV), in treatment-naive hepatitis C virus (HCV) genotype (GT) 1-infected patients.

METHODS: In this phase 3, randomized, open-label, noninferiority study, 602 patients were randomly assigned (2:1) to daclatasvir vs telaprevir, stratified by IL28B rs12979860 host genotype (CC vs non-CC), cirrhosis status (compensated cirrhosis vs no cirrhosis), and HCV GT1 subtype (GT1a vs GT1b). Patients were selected by study inclusion criteria from a total of 793 enrolled patients. Patients received daclatasvir 60 mg once daily or telaprevir 750 mg 3

times daily plus pegIFN/RBV. Daclatasvir recipients received 24 wk of daclatasvir plus pegIFN/RBV; those without an extended rapid virologic response (eRVR; undetectable HCV-RNA at weeks 4 and 12) received an additional 24 wk of pegIFN/RBV. Telaprevir-treated patients received 12 wk of telaprevir plus pegIFN/RBV followed by 12 (with eRVR) or 36 (no eRVR) wk of pegIFN/RBV. The primary objective was to compare for noninferiority of sustained virologic response rates at posttreatment week 12 (SVR12) in GT1b-infected patients. Key secondary objectives were to demonstrate that the rates of anemia (hemoglobin < 10 g/dL) and rash-related events, through week 12, were lower with daclatasvir + pegIFN/RBV than with telaprevir + pegIFN/RBV among GT1b-infected patients. Resistance testing was performed using population-based sequencing of the NS5A region for all patients at baseline, and for patients with virologic failure or relapse and HCV-RNA \geq 1000 IU/mL, to investigate any link between NS5A polymorphisms associated with daclatasvir resistance and virologic outcome.

RESULTS: Patient demographics and disease characteristics were generally balanced across treatment arms; however, there was a higher proportion of black/African Americans in the daclatasvir groups (6.0% and 8.2% in the GT1b and GT1a groups, respectively) than in the telaprevir groups (2.2% and 3.0%). Among GT1b-infected patients, daclatasvir plus pegIFN/RBV was noninferior to telaprevir plus pegIFN/RBV for SVR12 [85% (228/268) vs 81% (109/134); difference, 4.3% (95%CI: -3.3% to 11.9%)]. Anemia (hemoglobin < 10 g/dL) was significantly less frequent with daclatasvir than with telaprevir [difference, -29.1% (95%CI: -38.8% to -19.4%)]. Rash-related events were also less common with daclatasvir than with telaprevir, but the difference was not statistically significant. In GT1a-infected patients, SVR12 was 64.9% with daclatasvir and 69.7% with telaprevir. Among both daclatasvir and telaprevir treatment groups, across GT1b- or GT1a-infected patients, lower response rates were observed in patients with IL28B non-CC and cirrhosis - factors known to affect response to pegIFN/RBV. Consistent with these observations, a multivariate logistic regression analysis in GT1b-infected patients demonstrated that SVR12 was associated with IL28B host genotype (CC vs non-CC, $P = 0.011$) and cirrhosis status (absent vs present, $P = 0.031$). NS5A polymorphisms associated with daclatasvir resistance (at L28, R30, L31, or Y93) were observed in 17.3% of GT1b-infected patients at baseline; such variants did not appear to be absolute predictors of failure since 72.1% of these patients achieved SVR12 compared with 86.9% without these polymorphisms. Among GT1b-infected patients, treatment was completed by 85.4% (229/268) in the daclatasvir group, and by 85.1% (114/134) in the telaprevir group, and among GT1a-infected patients, by 67.2% (90/134) and 69.7% (46/66), respectively. Discontinuations (of all 3 agents) due to an AE were more frequent with telaprevir than with daclatasvir, whereas discontinuations due to lack of efficacy were more frequent with daclatasvir, due, in part, to differences in futility criteria.

CONCLUSION: Daclatasvir plus pegIFN/RBV demonstrated noninferiority to telaprevir plus pegIFN/RBV for SVR12 and was well-tolerated in treatment-naïve GT1b-infected patients, supporting the use of daclatasvir with other direct-acting antivirals.

[Effects of Smoking on Pegylated Interferon alpha 2a and First Generation Protease Inhibitor-based Antiviral Therapy in Naïve Patients Infected with Hepatitis C Virus Genotype 1.](#)

Zimmermann T1, Hueppe D2, Mauss S3, et al. J Gastrointestin Liver Dis. 2016 Mar;25(1):15-24. doi: 10.15403/jgld.2014.1121.251.a2a.

BACKGROUND AND AIMS: Smoking has multiple effects on factors influencing hepatitis C and antiviral therapy, including lipid metabolism, fibrosis, platelet count and adherence aspects. The aim of this analysis was to determine the impact of smoking on hepatitis C virus antiviral

therapy. **METHODS:** Data of two cohorts of an observational multicenter study including therapy-naïve patients infected with genotype 1 hepatitis C virus (HCV) treated with dual antiviral therapy (n=7,796) with pegylated interferon alpha 2a in combination with ribavirin, or triple antiviral therapy (n=1,122) containing telaprevir or boceprevir, were analysed.

RESULTS: In the univariate matched pair analysis of dual antiviral therapy patients (n=584), smoking was significantly associated with lower sustained viral response rates (p=0.026, OR 0.69 CI: 0.50 - 0.96). The effect of smoking on sustained viral response remained significant (p=0.028, OR 0.67 CI: 0.47 - 0.96) in the multivariate analysis when adjusting for all other baseline parameters with a significant association in the univariate analysis, i.e. diabetes, fibrosis, body mass index, transaminases and baseline viral load. Under protease inhibitors the influence of smoking on virological response did not arise. **CONCLUSIONS:** Smoking has a negative impact on antiviral therapy in naïve patients infected with HCV genotype 1 independently of age, gender, history of drug use or alcoholic liver disease. The effects of smoking might be overcome by the new antiviral agents.

[An In-Depth Analysis of Patient-Reported Outcomes in Patients With Chronic Hepatitis C Treated With Different Anti-Viral Regimens.](#) Younossi ZM^{1,2}, Stepanova M³, Henry L³, Nader F³, Hunt S³. Am J Gastroenterol. 2016 Mar 29. doi: 10.1038/ajg.2016.99. [Epub ahead of print]

OBJECTIVES: Interferon- and ribavirin (RBV)-containing regimens negatively impact patients' experience. The aim of this study was to quantify the impact of different anti-viral regimens for hepatitis C on patients' work productivity, fatigue, and other patient-reported outcomes (PROs). **METHODS:** The PRO data from multicenter multinational phase 3 clinical trials of sofosbuvir with and without interferon or RBV were retrospectively used. Treatment regimens were classified as interferon+RBV-containing, interferon-free RBV-containing, and interferon-free RBV-free. Four PRO instruments (SF-36, CLDQ-HCV, FACIT-F, and WPAI:SHP) were administered to subjects at baseline, during, and up to 24 weeks after treatment. **RESULTS:** We included 3,425 subjects with chronic hepatitis C infection with PRO data. Patients were 62.8% male, 62.2% treatment naïve, 18.1% with cirrhosis, and 72.9% with HCV genotype 1. Of the study participants, 546 received interferon+RBV+sofosbuvir, 1,721 received sofosbuvir+RBV, and 1,158 received interferon- and RBV-free ledipasvir+sofosbuvir. At baseline, there were no difference in PROs between treatment groups (all P>0.01). During treatment, the decrements in PROs were up to -23.6% for the interferon+RBV group, up to -7.0% in the sofosbuvir+RBV group, whereas there was an improvement of up to +11.6% in the interferon-free RBV-free group (all P<0.0001). In multivariate analysis, the use of interferon was independently associated with up to -26.0% worsening of the PRO scores during treatment and the use of RBV with up to -9.0% worsening. After 12 weeks post-treatment, in patients with sustained virologic response-12, improvements were observed regardless of the regimen, and these improvements continued to increase by week 24 of follow-up. **CONCLUSIONS:** The use of interferon- and RBV-free regimens for HCV is associated with better patients' experience and work productivity during treatment.

Results of interferon-based treatments in Alaska Native and American Indian population with chronic hepatitis C.

Livingston SE1, Townshend-Bulson LJ1, Bruden DJ2, Homan CE1, Gove JE1, Plotnik JN1, Simons BC1, Spradling PR3, McMahon BJ1,4. Int J Circumpolar Health. 2016 Mar 29;75:30696. doi: 10.3402/ijch.v75.30696. eCollection 2016.

BACKGROUND: There have been few reports of hepatitis C virus (HCV) treatment results with interferon-based regimens in indigenous populations. **OBJECTIVE:** To determine interferon-based treatment outcome among Alaska Native and American Indian (AN/AI) population. **DESIGN:** In an outcomes study of 1,379 AN/AI persons with chronic HCV infection from 1995 through 2013, we examined treatment results of 189 persons treated with standard interferon, interferon plus ribavirin, pegylated interferon plus ribavirin and triple therapy with a protease inhibitor. For individuals treated with pegylated interferon and ribavirin, the effect of patient characteristics on response was also examined. **RESULTS:** Sustained virologic response (SVR) with standard interferon was 16.7% (3/18) and with standard interferon and ribavirin was 29.7% (11/37). Of 119 persons treated with pegylated interferon and ribavirin, 61 achieved SVR (51.3%), including 10 of 46 with genotype 1 (21.7%), 38 of 51 with genotype 2 (74.5%) and 13 of 22 with genotype 3 (59.1%). By multivariate analysis, SVR in the pegylated interferon group was associated with female sex ($p=0.002$), estimated duration of infection ($p=0.034$) and HCV genotype ($p<0.0001$). There was a high discontinuation rate due to side effects in those treated with pegylated interferon and ribavirin for genotype 1 (52.2%). Seven of 15 genotype 1 patients treated with pegylated interferon, ribavirin and telaprevir or boceprevir achieved SVR (46.7%). **CONCLUSIONS:** We had success with pegylated interferon-based treatment of AN/AI people with genotypes 2 and 3. However, there were low SVR and high discontinuation rates for those with genotype 1.

Can the Abbott RealTime hepatitis C virus assay be used to predict therapeutic outcomes in hepatitis C virus-infected patients undergoing triple therapy?

Ikeda H1, Okuse C, Watanabe T, et al. Turk J Gastroenterol. 2016 Mar;27(2):165-72. doi: 10.5152/tjg.2016.150300.

BACKGROUND/AIMS: We compared the predictive abilities of the Abbott Real Time hepatitis C virus (HCV) assay (ART) with those of standard serum HCV ribonucleic acid (RNA) detection methods in patients undergoing triple therapy, which involves treatment with a protease inhibitor combined with pegylated interferon and ribavirin. **MATERIALS AND METHODS:** In this study, 28 patients underwent triple therapy. The hepatitis C virus ribonucleic acid (HCV RNA) level of each patient was measured at weeks 0, 4, 8, and 12 after the initiation of therapy using the Roche COBAS AmpliPrep/COBAS TaqMan HCV assay version 1.0 (CAP/CTM v1.0) and ART. **RESULTS:** At week 8 after the initiation of therapy, the sustained virological response (SVR) rate among patients who tested negative and positive for HCV RNA using CAP/CTM v1.0, was 80.0% (20/25) and 33.3% (1/3), and using ART, it was 91.3% (21/23) and 0.0% (0/5), respectively. Although at week 8, the predictive capability of CAP/CTM v1.0 was 78.5%, ART was found to be a more accurate predictor of future SVR status with a rate of 92.9%. **CONCLUSION:** These results indicate that the presence or absence of serum HCV RNA, evaluated using ART at week 8 after the initiation of therapy, may be useful for predicting therapeutic outcomes in patients receiving triple therapy.

Molecular assessment of Vitamin D receptor polymorphism as a valid predictor to the response of Interferon/Ribavirin based therapy in Egyptian patients with Chronic Hepatitis C.

Abdelsalam A1, Rashed L2, Salman T3, Hammad L1, Sabry D2. J Dig Dis. 2016 Apr 29. doi: 10.1111/1751-2980.12353. [Epub ahead of print]

BACKGROUND/AIM: Egypt has the highest prevalence rate of Hepatitis C virus (HCV) infection around the globe, where, chronic hepatitis C (CHC) is considered a major health problem. The standard treatment of CHC is combination therapy of pegylated interferon and ribavirin. Successful treatment and sustained virological response (SVR) are only achieved in 30% of patients. Major adverse effects and high cost of the treatment makes predicting the treatment output is an important approach. The aim of this study to find an association between Vitamin D concentration and vitamin D receptor (VDR) polymorphisms with achieving SVR. **METHODS:** This is a case control study in which; 250 patients recruited and were divided into 3 groups (100 CHC patients who achieved SVR, 100 CHC patients who did not achieve SVR, and 50 apparently healthy individuals as control). Blood samples were collected to measure vitamin D concentration and 4 VDR polymorphisms (FokI, ApaI, TaqI, and BsmI) were detected using RFLP-PCR. **RESULTS:** Non responders were found to have significantly low vitamin D concentration compared to responders and control groups. Concerning VDR polymorphisms, both FokI and TaqI polymorphisms were associated to successful treatment. **CONCLUSION:** Vitamin D concentration, FokI, and TaqI may be considered as one of the predictors for the response of CHC patients to combination of pegylated interferon and ribvirin therapy.

Real World Effectiveness of Ledipasvir/Sofosbuvir in 4365 Treatment-Naïve Genotype 1 Hepatitis C Infected Patients. Backus LI1, Belperio PS1, Shahoumian TA1, Loomis TP1, Mole LA1. Hepatology. 2016 Apr 26. doi: 10.1002/hep.28625. [Epub ahead of print]

Real-world effectiveness data is needed to inform hepatitis C virus (HCV) treatment decisions. The uptake of ledipasvir/sofosbuvir (LDV/SOF) regimens across healthcare settings has been rapid but variations often occur in clinical practice. The aim of this study was to assess sustained virologic response (SVR) of LDV/SOF±ribavirin (RBV) in routine medical practice. This observational, intent-to-treat cohort was comprised of 4365 genotype 1 treatment-naïve HCV-infected veterans treated with LDV/SOF±RBV. SVR rates were 91.3% (3191/3495) for LDV/SOF and 92.0% (527/573) for LDV/SOF+RBV (p=0.65). African American race (OR 0.70, 95%CI 0.54-0.90, p0.004) and FIB-4 >3.25 (OR 0.56, 95%CI 0.43-0.71, p<0.001) were independently associated with decreased likelihood of SVR; age, sex, BMI, decompensated liver disease, diabetes, genotype 1 subtype and regimen did not predict SVR. In models limited to those who completed 12 weeks of treatment, African American race was no longer a significant predictor of SVR but FIB-4 >3.25 (OR 0.35, 95%CI 0.24-0.50, p<0.001) remained. Among non-cirrhotics (defined by FIB-4≤3.25) with baseline HCV RNA<6,000,000 IU/ml, SVR rates were 93.2% (1020/1094) for those who completed 8 weeks of therapy and 96.6% (875/906) for those who completed 12 weeks of therapy (p=0.001). **CONCLUSIONS:** In this real-world cohort, SVR rates with LDV/SOF±RBV nearly matched the rates reported in clinical trials and were consistently high across all subgroups. Non-cirrhotics with HCV RNA<6,000,000 IU/mL were less likely to achieve SVR with 8 weeks compared to 12 weeks of therapy although the numeric difference in SVR rates was small.

[Mean platelet volume and red cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in patients with chronic hepatitis C.](#) Karagöz E1, Tanoğlu A, Ülçay A, Erdem H, Turhan V, Kara M, Yazgan Y. Eur J Gastroenterol Hepatol. 2016 Apr 20. [Epub ahead of print]

OBJECTIVE: We designed this study to investigate the relationship between the severity of fibrosis and mean platelet volume (MPV), red cell distribution width, and red cell distribution width to platelet ratio (RPR) in patients with chronic hepatitis C (CHC). **DESIGN:** Overall, 98 biopsy-proven naïve CHC cases were enrolled in the study. Complete blood count variables, including white blood cell, hemoglobin, platelet count, MPV, red cell distribution width, platelet distribution width as well as aspartate transaminase, alanine transaminase, total bilirubin, albumin, and other routine biochemical parameters, were tested. Liver biopsy samples were assessed according to the Ishak scoring system. Data analyses were carried out using SPSS-15 software. Statistical significance was set at a P-value of less than 0.05. **RESULTS:** Of the 98 cases, 80 (81.6%) were men and 18 (18.4%) were women. Fibrosis scores of 69 cases (70.4%) (group 1) were less than 3, whereas 29 cases had fibrosis scores at least 3 (29.6%) (group 2). Significant differences in MPV and RPR were observed between these two groups (MPV: 8.19 ± 1.002 vs. 8.63 ± 0.67 fl, $P < 0.05$; RPR: 0.0526 ± 0.02 vs. 0.0726 ± 0.02 , $P = 0.001$). The areas under the curve of the RPR and MPV for predicting significant fibrosis were 0.705 and 0.670, which was superior to the aspartate transaminase-to-alanine transaminase ratio and aspartate transaminase-to-platelet ratio index scores of the study group. Cut-off values were calculated for diagnostic performance, and the cut-off values for MPV and RPR were 8.5 and 0.07 fl, respectively. **CONCLUSION:** MPV and RPR values were significantly higher in patients with CHC, associated with severity, and can be used to predict advanced histological liver damage. The use of MPV and RPR may reduce the need for liver biopsy. Further studies are required to determine the relationship between these parameters and the severity of fibrosis in hepatitis C patients.

[Frequent detection of HCV RNA and HCVcoreAg in stool of patients with chronic hepatitis C.](#) Heidrich B1, Steinmann E2, Plumeier I3, et al. J Clin Virol. 2016 Apr 14;80:1-7. doi: 10.1016/j.jcv.2016.04.006. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: HCV is transmitted mainly by parenteral routes. However, unprotected anal intercourse has also been identified as a risk factor for HCV infection. HCV RNA can be detected in blood, saliva, and bile, but the presence of HCV in stool has not been investigated yet. **STUDY DESIGN:** Therefore, stool samples of 98 patients were collected prospectively. Specific HCV primers were used to identify samples positive for HCV RNA. HCV RNA-positive samples were tested for HCVcoreAg with the Architect HCVAg assay (Abbott). Presence of occult blood was investigated by the hemoCARE guajak test. Viral stability and infectivity of recombinant HCV particles was investigated in vitro by incubation of genotype 2a chimeric virus Jc1 with bile and stool suspensions. **RESULTS:** HCV RNA could be detected in 68 out of 98 stool samples from patients with chronic hepatitis C and 16 samples also tested positive for HCVcoreAg. Presence of HCV RNA in stool was more frequent in male than in female and in patients with low platelet counts but was not associated with the detection of occult blood. Stool suspensions and to a lesser extent bile reduced the in vitro infectivity of genotype 2a chimeric Jc1 virus even though infection of Huh7 cells was not completely abrogated. **CONCLUSIONS:** In summary, this study shows for the first time that HCV can frequently be detected in stool samples of chronically infected patients irrespective of occult

bleeding. We suggest that stool can be a potential source for HCV infection and thus unprotected anal intercourse should be avoided.

Emergence of HCV resistance-associated variants in patients failing sofosbuvir-based regimens: an observational cohort.

André-Garnier E1, Ribeyrol O, et al. Antivir Ther. 2016 Apr 29. doi: 10.3851/IMP3053. [Epub ahead of print]

BACKGROUND: Real life effectiveness data of new Hepatitis C Direct-Acting Antivirals are now required. The present study aims to assess the rate of sustained viral response (SVR) and virologic failure (VF) in patients infected with chronic hepatitis C virus (HCV) treated with sofosbuvir (SOF)-based regimens in routine medical practice. **METHODS:** This observational study included a total of 106 patients infected with HCV genotypes 1 to 4, who initiated SOF-based regimens in 2014. Viral load was followed at baseline, W2, W4, W12 (or W24) and W12 post treatment. For all VF, Resistance-Associated Variants (RAVs) were determined at baseline and failure by sequencing of NS5A, NS5B and/or NS3 genes, using the Sanger method.

RESULTS: SVR rate was 85% for the whole cohort, 91% for the patients who underwent the full treatment course. The distribution of HCV genotypes was as follows: Genotype 1 n= 66 (1a=33, 1b=29) (62%) Genotype 2 n=8 (8%), Genotype 3a n=20 (19%), Genotype 4 n=12 (11%). The main regimens used were SOF+daclatasvir (37%), SOF+Ribavirin (33%), SOF+simeprevir (26%) and SOF+ledipasvir (3%). Twenty-five patients were HIV co-infected (23%) and 1 was HBV co-infected. Seventy patients (65%) had a prior treatment experience. All VF were relapses (n=9): 3 G1a, 1 G2, 4 G3a and 1 G4 and mutations conferring resistance to NS5A inhibitors were found but none for NS5B polymerase inhibitors. **CONCLUSIONS:** In a real life context, the rate of SVR in DAA treated HCV infected patients is close to clinical phase III trial results. RAVs emerged for all patients treated by the anti-NS5A daclatasvir, and persisted several weeks after the end of treatment.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Hepatitis C Virus Genotype 1-6 Protease Inhibitor Escape Variants: In Vitro Selection, Fitness and Resistance Patterns in the Context of the Infectious Viral Life Cycle.

Serre SB1, Jensen SB1, Ghanem LI, et al. Antimicrob Agents Chemother. 2016 Mar 28. pii: AAC.02929-15. [Epub ahead of print]

Hepatitis C virus (HCV) NS3 protease inhibitors (PIs) are important components of novel HCV therapy regimens. Studies of PI resistance initially focused on genotype 1. Therefore, knowledge on determinants of PI resistance for the highly prevalent genotypes 2-6 remains limited. Using Huh7.5 cell-culture infectious HCV recombinants with genotype 1-6 NS3 protease, we identified protease positions 54, 155 and 156 as hotspots for selection of resistance substitutions under treatment with the first licensed PIs telaprevir and boceprevir. Treatment of genotype 2 with newer PIs vaniprevir, faldaprevir, simeprevir, grazoprevir, paritaprevir and deltaprevir identified positions 156 and 168 as hotspots for resistance; substitution Y56H emerged for 3 newer PIs. Substitution selection also depended on the specific recombinant. Identified substitutions conferred cross-resistance to several PIs, however, most substitutions selected under telaprevir/boceprevir conferred less resistance to certain newer PIs. In a single-cycle production assay, across genotypes, PI treatment primarily decreased viral replication, which was rescued by PI resistance substitutions. Identified substitutions resulted in differential effects on viral fitness, depending on the original recombinant and the substitution. Across genotypes, fitness

impairment induced by resistance substitutions was primarily due to decreased replication. Most identified combinations of substitutions increased resistance or fitness. Combinations of resistance substitutions with fitness compensating substitutions either rescued replication or compensated for decreased replication with increased assembly. This comprehensive study provides insight into selection patterns and effects of PI resistance substitutions for HCV genotypes 1-6 in the context of the infectious viral life cycle, which is of interest for clinical and virological HCV research.

[The platelet-to-lymphocyte ratio, superior to the neutrophil-to-lymphocyte ratio, correlates with hepatitis C virus infection.](#) Meng X1, Wei G1, Chang Q1, et al. Int J Infect Dis. 2016 Mar 3;45:72-77. doi: 10.1016/j.ijid.2016.02.025. [Epub ahead of print]

OBJECTIVES: The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have been studied widely in cancer diseases. However, their correlation with hepatitis C virus (HCV) infection is unknown. The aim of this study was to investigate the correlation of PLR and NLR with disease severity in patients with HCV-related liver disease and the virological response in chronic hepatitis C (CHC) patients. **METHODS:** The clinical data of 120 HCV-infected patients and 40 healthy controls were analyzed. The clinical data of 24 CHC patients who had been followed up regularly were collected for the following time points: before treatment (week 0) and weeks 4, 48, and 72 during treatment. These data were also analyzed. All data were collected from the database of the hospital patient electronic medical record system. **RESULTS:** The HCV-related cirrhosis group and HCV-related hepatocellular carcinoma group were found to have lower PLRs (61 ± 31 and 51 ± 23) than the healthy controls (115 ± 23). The PLR of the HCV cleared group (154 ± 85) was significantly higher than that of the HCV untreated group and HCV uncleared group (90 ± 28 and 88 ± 40 , respectively). Receiver operating characteristics curve analysis for the PLR showed an area under the curve of 0.772 (95% confidence interval 0.674-0.869, $p<0.000$); for NLR, the area under the curve was 0.612 (95% confidence interval 0.495-0.730, $p=0.063$). Furthermore, an increasing PLR in CHC patients indicated a good virological response, and a stable PLR or a downward trend in PLR could predict no rapid virological response being achieved by week 4, and even no sustained virological response by week 72. **CONCLUSIONS:** The PLR is closely related to disease severity in patients with HCV-related liver disease and to the virological response in CHC patients. Dynamic continuous monitoring of the PLR will contribute to disease surveillance, with an increasing tendency predicting a good virological response.

[Hepatitis C virus NS5A protein cooperates with phosphatidylinositol 4-kinase III \$\alpha\$ to induce mitochondrial fragmentation.](#) Siu GK1, Zhou F2, Yu MK1,3, et al. Sci Rep. 2016 Mar 24;6:23464. doi: 10.1038/srep23464.

Hepatitis C virus (HCV) has long been observed to take advantage of the host mitochondria to support viral replication and assembly. The HCV core protein has been implicated to fragment host mitochondria. In this report, we have discovered that the non-structural protein 5A (NS5A) plays an instructive role in attaching ER with mitochondria, causing mitochondrial fragmentation. Dynamin-related protein 1 (Drp1), a host protein essential to mitochondrial membrane fission, does not play a role in NS5A-induced mitochondrial fragmentation. Instead, phosphatidylinositol 4-kinase III α (PI4KA), which has been demonstrated to bind to NS5A and is required to support HCV life cycle, is required for NS5A to induce mitochondrial fragmentation. Both NS5A and core are required by HCV to fragment the mitochondria, as

inhibiting either of their respective downstream proteins, PI4KA or Drp1, resulted in lengthening of mitochondria tubules in HCVcc-infected cells. By fragmenting the mitochondria, NS5A renders the cells more resistant to mitochondria mediated apoptosis. **This finding indicates** previously-ignored contribution of NS5A in HCV-induced mitochondria dysfunction.

Inhibition of hepatitis C virus in mouse models by lipidoid nanoparticle-mediated systemic delivery of siRNA against PRK2. Moon JS1, Lee SH1, Han SH1, et al. *Nanomedicine*. 2016 Mar 21. pii: S1549-9634(16)30006-5. doi: 10.1016/j.nano.2016.02.015. [Epub ahead of print] Host-targeting antivirals have an advantage over direct-acting antivirals in that they have a high genetic barrier to resistance. Here, we describe in vivo anti-hepatitis C virus (HCV) efficacy of a potent siRNA targeting the protein kinase C-related kinase 2 (PRK2), which phosphorylates HCV NS5B RNA-dependent RNA polymerase and promotes HCV replication. PRK2-silencing reduced the phosphorylated NS5B level and resulted in inhibition of NS5B RdRp activity to decrease HCV genome abundance. Systemic administration of lipidoid nanoparticle-formulated PRK2 siRNA (once every three days for a total of three injections at a dose of 3 mg kg⁻¹) resulted in a 3.72 and 1.96 log₁₀ reduction in serum HCV RNA titer, in mouse subcutaneous and orthotopic xenograft models for HCV replication, respectively. Our results verify the essential role of PRK2 in HCV replication and offer a host-targeting anti-HCV siRNA therapy that might be beneficial for non-responders to current treatment regimens.

Circulating T follicular helper cells are associated with rapid virological response in chronic hepatitis C patients undergoing peginterferon therapy. Zhang M1, Zhang L1, Li H1, et al. *Int Immunopharmacol*. 2016 May;34:235-43. doi: 10.1016/j.intimp.2016.03.005. Epub 2016 Mar 10.

BACKGROUND: Chronic hepatitis C virus (HCV) infection is associated with abnormal T cell and B cell immune responses. T follicular helper (TFH) cells are a subset of CD4(+) T-helper cells and can activate B cells. This study aimed to investigate the role of circulating CXCR5(+)CD4(+) TFH cells, CD19(+) B cells and the associated cytokines in patients with chronic HCV infection. **METHODS:** The frequencies and phenotypes of circulating TFH cells and B cell subtypes were characterized using flow cytometry in chronic hepatitis C (CHC) patients and in healthy controls (HCs). The expression of IFN- γ , IL-12p70, IL-5, IL-13, IL-17F, IL-22, IL-23, TGF- β 1, IL-10 and IL-21 associated with Th1, Th2, Th17, regulatory T cells (Treg) and TFH cells were analyzed using a Quantibody array. The patients' clinical parameters were detected, and the effect of pegylated interferon plus ribavirin treatment on these immune indicators in CHC patients was determined. **RESULTS:** The frequency of CXCR5(+)CD4(+) T cells was significantly higher in CHC patients compared to HCs. There were no significant differences in CD19(+) B cells, CD19(+)CD27(+) B cells, or CD19(+)CD38(+) B cells between CHC patients and HCs. The expressions of cytokines associated with the CD4(+) Th lineage were higher in CHC patients than in HCs, except for IL-21. Patients with rapid virological response (RVR) showed an increased CXCR5(+)CD4(+) T cell count and decreased PD-1(+) CXCR5(+)CD4(+) T cell count compared to non-RVR patients after PEG-IFN/ribavirin treatment. **CONCLUSIONS:** These data demonstrate that circulating TFH cells and CD4(+) Th lineage-associated cytokines may play a role in HCV-related immune responses.

LPS AND TNF- α INHIBIT INTERFERON-SIGNALING IN HEPATOCYTES BY INCREASING USP18 EXPRESSION. MacParland SA1, Ma XZ1, Chen L2, et al. *J Virol.* 2016 Mar 23. pii: JVI.02557-15. [Epub ahead of print]

BACKGROUND: Inflammation may be maladaptive to the control of viral infection when it impairs interferon (IFN) responses, enhancing viral replication and spread. Dysregulated immunity as a result of inappropriate innate inflammatory responses is a hallmark of chronic viral infections such as, hepatitis B virus (HBV) and hepatitis C virus (HCV). Previous studies from our laboratory have shown that expression of an IFN-stimulated gene (ISG), ubiquitin-like protease (USP)18 is upregulated in chronic HCV infection, leading to impaired hepatocyte responses to IFN- α . **METHODS:** We examined the ability of inflammatory stimuli including tumour necrosis factor (TNF)- α , lipopolysaccharide (LPS), interleukin (IL)-6 and IL-10 to upregulate hepatocyte USP18 expression and blunt the IFN- α response. Human hepatoma cells and primary murine hepatocytes were treated with TNF- α /LPS/IL-6/IL-10 and USP18, phosphorylated (p)-STAT1 and myxovirus (influenza virus) resistance 1 (Mx1) expression was determined. **RESULTS:** Treatment of Huh7.5 cells and primary murine hepatocytes with LPS and TNF- α , but not IL-6 or IL-10, led to upregulated USP18 expression and induced an IFN- α refractory state, which was reversed by USP18 knockdown. Liver inflammation was induced in vivo using a murine model of hepatic ischemia/reperfusion injury. Hepatic ischemia/reperfusion injury led to an induction of USP18 expression in liver tissue and promotion of lymphocytic choriomeningitis (LCMV) replication. **CONCLUSIONS:** These data demonstrate that certain inflammatory stimuli (TNF- α , LPS) but not others (IL-6, IL-10) target USP18 expression and thus inhibit IFN-signaling. These findings represent a new paradigm for how inflammation alters hepatic innate immune responses, with USP18 representing a potential target for intervention in various inflammatory states. **IMPORTANCE:** Inflammation may prevent the control of viral infection when it impairs the innate immune response, enhancing viral replication and spread. Blunted immunity as a result of inappropriate innate inflammatory responses is a common characteristic of chronic viral infections. Previous studies have shown that expression of certain interferon-stimulated genes is upregulated in chronic HCV infection, leading to impaired hepatocyte responses. In this study, we show that multiple inflammatory stimuli can modulate interferon stimulated gene expression and thus inhibit hepatocyte interferon signaling via USP18 induction. These findings represent a new paradigm for how inflammation alters hepatic innate immune responses, with the induction of USP18 representing a potential target for intervention in various inflammatory states.

Evaluation of antiviral drug synergy in an infectious HCV system. Lin B1, He S, Yim HJ, Liang TJ, Hu Z. *Antivir Ther.* 2016 Apr 1. doi: 10.3851/IMP3044. [Epub ahead of print]

BACKGROUND: Direct-acting antivirals (DAAs) have greatly improved the treatment of hepatitis C virus (HCV) infection. To improve response and prevent resistance, combination regimens have been the focus of clinical development. Regimens are often first assessed in vitro, with most combination studies to date using subgenomic replicon systems, which do not replicate the complete HCV life cycle and preclude study of entry and assembly inhibitors. Infectious full-length HCV systems have been developed and are being used to test drug efficacy. **METHODS:** Using cell-based HCV Con1b replicon and an infectious full-length HCV (HCVcc-Luc) infection systems, we systematically tested the synergy, additivity or antagonism of combinations between protease, NS5A, and nucleotide NS5B inhibitor classes as well as the combination of these DAAs with host-targeting agent cyclosporin A or non-antibody entry

inhibitor (S)-chlorcyclizine. Two computational software packages, MacSynergyII and CalcuSyn, were used for data analysis. **RESULTS:** Combinations between different classes showed good consistency across the two viral assay systems and two software platforms. Combinations between NS5A and nucleotide NS5B inhibitors were synergistic, while combinations of protease inhibitors with the other two classes were additive to slightly antagonistic. As expected, combinations of antivirals of the same class were additive. Combination studies between these DAA classes and cyclosporin A or (S)-chlorcyclizine demonstrated additive to synergistic effects and highly synergistic effects, respectively. Combinations of these drugs did not show any added or unexpected cytotoxicity.

CONCLUSIONS: Our results show that in vitro combination studies of anti-HCV DAAs in the HCVcc system may provide useful guidance for drug combination designs in clinical studies. We also demonstrate that these DAAs in combination with HTAs or entry inhibitors may improve HCV treatment response.

[Clinical value of on-treatment HCV RNA levels during different approved sofosbuvir-based antiviral regimens.](#)

Maasoumy B1, Vermehren J2, Welker MW2, et al. J Hepatol. 2016 Apr 13. pii: S0168-8278(16)30108-8. doi: 10.1016/j.jhep.2016.04.006. [Epub ahead of print]

BACKGROUND & AIMS: EASL guidelines recommend HCV-RNA measurements at specific time-points during sofosbuvir(SOF)-therapy. However, it remains unclear, how these results should be interpreted. We aimed to analyse whether on-treatment HCV-RNA levels predict relapse comparing the CobasAmpliPrep/CobasTaqMan v2.0 (CAP/CTM) and Abbott RealTime HCV (ART) assays. **METHODS:** Samples were collected from 298 patients(HCV-genotypes; GT1-5) at weeks(w) 0, 1, 2, 4, 8, 12, 16, 20 and 24 during SOF-based therapy at two University clinics and tested for HCV-RNA level by CAP/CTM and ART. Patients were treated with SOF/ribavirin(RBV) 12/24w (n=99), pegylated-interferon-alfa(Peg-IFN)/SOF/RBV 12w (n=51), SOF/simeprevir(SMV)±RBV 12w (n=69) or SOF/daclatasvir±RBV 12/24w (n=79).

RESULTS: HCV-RNA levels during the first 4 weeks of SOF/RBV-therapy were significantly lower in GT3-patients who achieved SVR compared with those who relapsed. All GT3-patients with a week 2 result <45IU/ml by CAP/CTM achieved SVR but only 33% of those with ≥45IU/ml(p=0.0003). Similar results were documented with ART and 60IU/ml as cut-off (SVR:100% vs. 29%;p=0.0002). In contrast, HCV-RNA levels during early treatment phases were not significantly related to relapse in patients treated with other SOF-based regimens. Residual HCV-RNA was frequently detected by ART at later stages of therapy. However, SVR-rates remained high in these patients. At the end of SOF/SMV±RBV-therapy HCV-RNA was detectable with ART in 20% of patients, of whom 92% achieved SVR. **CONCLUSIONS:** HCV-RNA levels assessed at week 2 of SOF/RBV-therapy can predict relapse in GT3-patients. Detectable HCV-RNA results at later stages during SOF-based therapy may occur frequently with the more sensitive ART. However, this should not lead to treatment extension.

[Alirocumab, a Therapeutic Human Antibody to PCSK9, Does Not Affect CD81 Levels or Hepatitis C Virus Entry and Replication into Hepatocytes.](#)

Ramanathan A1, Gusarova V1, Stahl N1, Gurnett-Bander A1, Kyratsous CA1. PLoS One. 2016 Apr 26;11(4):e0154498. doi: 10.1371/journal.pone.0154498. eCollection 2016.

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PSCK9) is secreted mainly from the liver and binds to the low-density lipoprotein receptor (LDLR), reducing LDLR availability and thus resulting in an increase in LDL-cholesterol. While the LDLR has been

implicated in the cell entry process of the hepatitis C virus (HCV), overexpression of an artificial non-secreted, cell membrane-bound form of PCSK9 has also been shown to reduce surface expression of CD81, a major component of the HCV entry complex, leading to concerns that pharmacological inhibition of PCSK9 may increase susceptibility to HCV infection by increasing either CD81 or LDLR availability. Here, we evaluated effects of PCSK9 and PCSK9 blockade on CD81 levels and HCV entry with a physiologically relevant model using native secreted PCSK9 and a monoclonal antibody to PCSK9, alirocumab. **METHODS AND RESULTS:** Flow cytometry and Western blotting of human hepatocyte Huh-7 cells showed that, although LDLR levels were reduced when cells were exposed to increasing PCSK9 concentrations, there was no correlation between total or surface CD81 levels and the presence and amount of soluble PCSK9. Moreover, inhibiting PCSK9 with the monoclonal antibody alirocumab did not affect expression levels of CD81. In an in vitro model of HCV entry, addition of soluble PCSK9 or treatment with alirocumab had no effect on the ability of either lentiviral particles bearing the HCV glycoproteins or JFH-1 based cell culture virus to enter hepatocytes. Consistent with these in vitro findings, no differences were observed in hepatic CD81 levels using in vivo mouse models, including *Pcsk9*^{-/-} mice compared with wild-type controls and hyperlipidemic mice homozygous for human *Pcsk9* and heterozygous for *Ldlr* deletion, treated with either alirocumab or isotype control antibody. **CONCLUSION:** These results suggest that inhibition of PCSK9 with alirocumab has no effect on CD81 and does not result in increased susceptibility to HCV entry.

Free Article

[PD-1/PD-L1 signal pathway participates in HCV F protein-induced T cell dysfunction in chronic HCV infection.](#) Xiao W1, Jiang LF2, Deng XZ3,4, et al. Immunol Res. 2016

Apr;64(2):412-23. doi: 10.1007/s12026-015-8680-y.

Programmed cell death-1/programmed cell death-1 ligand 1 (PD-1/PD-L1) inhibitory signal pathway has been verified to be involved in the establishment of persistent viral infections. Blockade of PD-1/PD-L1 engagement to reinvigorate T cell activity is supposed to be a potential therapeutic scheme. Studies have verified the participation of PD-1/PD-L1 in hepatitis C virus (HCV) core protein-regulated immune response. To determine the roles of PD-1/PD-L1 signal pathway in HCV F protein-induced immunoreaction in chronic HCV infection, variations in T cells were examined. The results showed that PD-1 expression on CD8(+) and CD4(+) T cells was increased with HCV F stimulation in both chronic HCV patients and healthy controls, and could be reduced partly by PD-1/PD-L1 blocking. Additionally, by PD-1/PD-L1 blocking, HCV F-induced inhibition of T cell proliferation and promotion of cellular apoptosis were partly or even totally recovered. Furthermore, levels of both Th1 and Th2 cytokines were elevated in the presence of anti-PD-L1 antibody. All these results indicated that PD-1/PD-L1 signal pathway also participates in HCV F protein-induced immunoregulation. PD-1/PD-L1 blocking plays important roles in the restoration of effective functionality of the impaired T cells in chronic HCV patients.

[A Complex Network of Interactions between S282 and G283 of Hepatitis C Virus Nonstructural Protein 5B and the Template Strand Affects Susceptibility to Sofosbuvir and Ribavirin.](#)

Kulkarni AS1, Damha MJ2, Schinazi RF3, Mo H4, Doehle B4, Sagan SM1, Götte M5. Antimicrob Agents Chemother. 2016 Mar 25;60(4):2018-27. doi: 10.1128/AAC.02436-15. Print 2016 Apr.

The hepatitis C virus (HCV) RNA-dependent RNA-polymerase NS5B is essentially required for viral replication and serves as a prominent drug target. Sofosbuvir is a prodrug of a nucleotide analog that interacts selectively with NS5B and has been approved for HCV treatment in combination with ribavirin. Although the emergence of resistance to sofosbuvir is rarely seen in the clinic, the S282T mutation was shown to decrease susceptibility to this drug. S282T was also shown to confer hypersusceptibility to ribavirin, which is of potential clinical benefit. Here we devised a biochemical approach to elucidate the underlying mechanisms. Recent crystallographic data revealed a hydrogen bond between S282 and the 2'-hydroxyl of the bound nucleotide, while the adjacent G283 forms a hydrogen bond with the 2'-hydroxyl of the residue of the template that base pairs with the nucleotide substrate. We show that DNA-like modifications of the template that disrupt hydrogen bonding with G283 cause enzyme pausing with natural nucleotides. However, the specifically introduced DNA residue of the template reestablishes binding and incorporation of sofosbuvir in the context of S282T. Moreover, the DNA-like modifications of the template prevent the incorporation of ribavirin in the context of the wild-type enzyme, whereas the S282T mutant enables the binding and incorporation of ribavirin under the same conditions. **Together, these findings provide strong evidence** to show that susceptibility to sofosbuvir and ribavirin depends crucially on a network of interdependent hydrogen bonds that involve the adjacent residues S282 and G283 and their interactions with the incoming nucleotide and complementary template residue, respectively.

[**The Role of MicroRNA in Pathogenesis and as Markers of HCV Chronic Infection.**](#) Lee CH, Kim JH, Lee SW1. Curr Drug Targets. 2016 Apr 1. [Epub ahead of print]

Hepatitis C virus (HCV) is a worldwide major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Accumulating evidence indicates that a number of microRNAs (miRNAs), which are able to exert an effect on liver biology and pathology, can regulate or be regulated by HCV infection. Many studies demonstrate that HCV utilizes host miRNAs and modulates expression of miRNAs in infected hepatocytes for its infection and propagation. In turn, host miRNAs can directly regulate HCV replication through interaction with the HCV RNA genome or by indirectly controlling the host pathways associated with the virus replication, which eventually induce HCV-related liver diseases such as liver fibrosis, hepatic cirrhosis, or HCC. Recently, extracellular miRNAs (circulating miRNAs) detected in human serum and plasma are proposed as biomarker candidates for pathological conditions due to their remarkably stable nature and the non-invasiveness of their detection. Since these circulating miRNAs exhibit consistent levels between healthy individuals but significantly changed profiles in disease conditions, considerable effort has been employed to investigate the alteration in the circulating miRNA pattern that is related with HCV infection and associated liver diseases. In this review, we summarize the features of miRNAs critical for HCV-associated liver disease initiation and progress, and discuss growing evidence that distinctive circulating miRNA patterns are related with HCV infection and associated liver diseases. These will shed light on the development of miRNA-based therapeutic modalities and non-invasive biomarkers for the diagnosis and prognosis of HCV infection and associated diseases.

Ion Channel Function and Cross-Species Determinants in Viral Assembly of Nonprimate Hepacivirus p7. Walter S1, Bollenbach A1, Doerrbecker J1, et al. J Virol. 2016 Apr 29;90(10):5075-89. doi: 10.1128/JVI.00132-16. Print 2016 May 15.

Nonprimate hepacivirus (NPHV), the closest homolog of hepatitis C virus (HCV) described to date, has recently been discovered in horses. Even though the two viruses share a similar genomic organization, conservation of the encoded hepaciviral proteins remains undetermined. The HCV p7 protein is localized within endoplasmic reticulum (ER) membranes and is important for the production of infectious particles. In this study, we analyzed the structural and functional features of NPHV p7 in addition to its role during virus assembly. Three-dimensional homology models for NPHV p7 using various nuclear magnetic resonance spectroscopy (NMR) structures were generated, highlighting the conserved residues important for ion channel function. By applying a liposome permeability assay, we observed that NPHV p7 exhibited liposome permeability features similar to those of HCV p7, indicative of similar ion channel activity. Next, we characterized the viral protein using a p7-based trans-complementation approach. A similar subcellular localization pattern at the ER membrane was observed, although production of infectious particles was likely hindered by genetic incompatibilities with HCV proteins. To further characterize these cross-species constraints, chimeric viruses were constructed by substituting different regions of HCV p7 with NPHV p7. The N terminus and transmembrane domains were nonexchangeable and therefore constitute a cross-species barrier in hepaciviral assembly. In contrast, the basic loop and the C terminus of NPHV p7 were readily exchangeable, allowing production of infectious trans-complemented viral particles. In conclusion, comparison of NPHV and HCV p7 revealed structural and functional homology of these proteins, including liposome permeability, and broadly acting determinants that modulate hepaciviral virion assembly and contribute to the host-species barrier were identified.

IMPORTANCE: The recent discovery of new relatives of hepatitis C virus (HCV) enables for the first time the study of cross-species determinants shaping hepaciviral pathogenesis. Nonprimate hepacivirus (NPHV) was described to infect horses and represents so far the closest homolog of HCV. Both viruses encode the same viral proteins; however, NPHV protein functions remain poorly understood. In this study, we aimed to dissect NPHV p7 on a structural and functional level. By using various NMR structures of HCV p7 as templates, three-dimensional homology models for NPHV p7 were generated, highlighting conserved residues that are important for ion channel function. A p7-based trans-complementation approach and the construction of NPHV/HCV p7 chimeric viruses showed that the N terminus and transmembrane domains were nonexchangeable. In contrast, the basic loop and the C terminus of NPHV p7 were readily exchangeable, allowing production of infectious viral particles. These results identify species-specific constraints as well as exchangeable determinants in hepaciviral assembly.

The Combination of Grazoprevir, a Hepatitis C Virus (HCV) NS3/4A Protease Inhibitor, and Elbasvir, an HCV NS5A Inhibitor, Demonstrates a High Genetic Barrier to Resistance in HCV Genotype 1a Replicons. Lahser FC1, Bystol K2, Curry S2, et al. Antimicrob Agents Chemother. 2016 Apr 22;60(5):2954-64. doi: 10.1128/AAC.00051-16. Print 2016 May.

The selection of resistance-associated variants (RAVs) against single agents administered to patients chronically infected with hepatitis C virus (HCV) necessitates that direct-acting antiviral agents (DAAs) targeting multiple viral proteins be developed to overcome failure resulting from emergence of resistance. The combination of grazoprevir (formerly MK-5172), an NS3/4A protease inhibitor, and elbasvir (formerly MK-8742), an NS5A inhibitor, was therefore studied in

genotype 1a (GT1a) replicon cells. Both compounds were independently highly potent in GT1a wild-type replicon cells, with 90% effective concentration (EC90) values of 0.9 nM and 0.006 nM for grazoprevir and elbasvir, respectively. No cross-resistance was observed when clinically relevant NS5A and NS3 RAVs were profiled against grazoprevir and elbasvir, respectively. Kinetic analyses of HCV RNA reduction over 14 days showed that grazoprevir and elbasvir inhibited prototypic NS5A Y93H and NS3 R155K RAVs, respectively, with kinetics comparable to those for the wild-type GT1a replicon. In combination, grazoprevir and elbasvir interacted additively in GT1a replicon cells. Colony formation assays with a 10-fold multiple of the EC90 values of the grazoprevir-elbasvir inhibitor combination suppressed emergence of resistant colonies, compared to a 100-fold multiple for the independent agents. The selected resistant colonies with the combination harbored RAVs that required two or more nucleotide changes in the codons. Mutations in the cognate gene caused greater potency losses for elbasvir than for grazoprevir. Replicons bearing RAVs identified from resistant colonies showed reduced fitness for several cell lines and may contribute to the activity of the combination. These studies demonstrate that the combination of grazoprevir and elbasvir exerts a potent effect on HCV RNA replication and presents a high genetic barrier to resistance. The combination of grazoprevir and elbasvir is currently approved for chronic HCV infection.

Broad Anti-Hepatitis C Virus (HCV) Antibody Responses Are Associated with Improved Clinical Disease Parameters in Chronic HCV Infection. Swann RE1, Cowton VM1, Robinson MW2, et al. J Virol. 2016 Apr 14;90(9):4530-43. doi: 10.1128/JVI.02669-15. Print 2016 May 1. During hepatitis C virus (HCV) infection, broadly neutralizing antibody (bNAb) responses targeting E1E2 envelope glycoproteins are generated in many individuals. It is unclear if these antibodies play a protective or a pathogenic role during chronic infection. In this study, we investigated whether bNAb responses in individuals with chronic infection were associated with differences in clinical presentation. Patient-derived purified serum IgG was used to assess the breadth of HCV E1E2 binding and the neutralization activity of HCV pseudoparticles. The binding and neutralization activity results for two panels bearing viral envelope proteins representing either an intergenotype or an intragenotype 1 group were compared. We found that the HCV load was negatively associated with strong cross-genotypic E1E2 binding (P= 0.03). Overall, we observed only a modest correlation between total E1E2 binding and neutralization ability. The breadth of intergenotype neutralization did not correlate with any clinical parameters; however, analysis of individuals with genotype 1 (gt1) HCV infection (n= 20), using an intragenotype pseudoparticle panel, found a strong association between neutralization breadth and reduced liver fibrosis (P= 0.006). A broad bNAb response in our cohort with chronic infection was associated with a single nucleotide polymorphism (SNP) in the HLA-DQB1 gene (P= 0.038), as previously reported in a cohort with acute disease. Furthermore, the bNAbs in these individuals targeted more than one region of E2-neutralizing epitopes, as assessed through cross-competition of patient bNAbs with well-characterized E2 antibodies. We conclude that the bNAb responses in patients with chronic gt1 infection are associated with lower rates of fibrosis and host genetics may play a role in the ability to raise such responses.

IMPORTANCE: Globally, there are 130 million to 150 million people with chronic HCV infection. Typically, the disease is progressive and is a major cause of severe liver cirrhosis and hepatocellular carcinoma. While it is known that neutralizing antibodies have a role in spontaneous clearance during acute infection, little is known about their role in chronic infection. In the present work, we investigated the antibody response in a cohort of chronically infected

individuals and found that a broadly neutralizing antibody response is protective and is associated with reduced levels of liver fibrosis and cirrhosis. We also found an association between SNPs in class II HLA genes and the presence of a broadly neutralizing response, indicating that antigen presentation may be important for the production of HCV-neutralizing antibodies.

[Protective T Cell and Antibody Immune Responses against Hepatitis C Virus Achieved Using a Biopolyester-Bead-Based Vaccine Delivery System.](#) Martínez-Donato G1, Piniella B2, Aguilar D2, et al. Clin Vaccine Immunol. 2016 Apr 4;23(4):370-8. doi: 10.1128/CVI.00687-15. Print 2016 Apr.

Hepatitis C virus (HCV) infection is a major worldwide problem. Chronic hepatitis C is recognized as one of the major causes of cirrhosis, hepatocellular carcinoma, and liver failure. Although new, directly acting antiviral therapies are suggested to overcome the low efficacy and adverse effects observed for the current standard of treatment, an effective vaccine would be the only way to certainly eradicate HCV infection. Recently, polyhydroxybutyrate beads produced by engineered *Escherichia coli* showed efficacy as a vaccine delivery system. Here, an endotoxin-free *E. coli* strain (ClearColi) was engineered to produce polyhydroxybutyrate beads displaying the core antigen on their surface (Beads-Core) and their immunogenicity was evaluated in BALB/c mice. Immunization with Beads-Core induced gamma interferon (IFN- γ) secretion and a functional T cell immune response against the HCV Core protein. With the aim to target broad T and B cell determinants described for HCV, Beads-Core mixed with HCV E1, E2, and NS3 recombinant proteins was also evaluated in BALB/c mice. Remarkably, only three immunization with Beads-Core+CoE1E2NS3/Alum (a mixture of 0.1 μ g Co.120, 16.7 μ g E1.340, 16.7 μ g E2.680, and 10 μ g NS3 adjuvanted in aluminum hydroxide [Alum]) induced a potent antibody response against E1 and E2 and a broad IFN- γ secretion and T cell response against Core and all coadministered antigens. This immunological response mediated protective immunity to viremia as assessed in a viral surrogate challenge model. Overall, it was shown that engineered biopolyester beads displaying foreign antigens are immunogenic and might present a particulate delivery system suitable for vaccination against HCV.

[Hepatitis C Virus-Induced Degradation of Cell Death-Inducing DFFA-Like Effector B Leads to Hepatic Lipid Dysregulation.](#) Lee EM1, Alsagheir A2, Wu X1, et al. J Virol. 2016 Mar 28;90(8):4174-85. doi: 10.1128/JVI.02891-15. Print 2016 Apr 15.

Individuals chronically infected with hepatitis C virus (HCV) commonly exhibit hepatic intracellular lipid accumulation, termed steatosis. HCV infection perturbs host lipid metabolism through both cellular and virus-induced mechanisms, with the viral core protein playing an important role in steatosis development. We have recently identified a liver protein, the cell death-inducing DFFA-like effector B (CIDEB), as an HCV entry host dependence factor that is downregulated by HCV infection in a cell culture model. In this study, we investigated the biological significance and molecular mechanism of this downregulation. HCV infection in a mouse model downregulated CIDEB in the liver tissue, and knockout of the CIDEB gene in a hepatoma cell line results in multiple aspects of lipid dysregulation that can contribute to hepatic steatosis, including reduced triglyceride secretion, lower lipidation of very-low-density lipoproteins, and increased lipid droplet (LD) stability. The potential link between CIDEB downregulation and steatosis is further supported by the requirement of the HCV core and its LD

localization for CIDEB downregulation, which utilize a proteolytic cleavage event that is independent of the cellular proteasomal degradation of CIDEB.

[Enhancement of the Replication of Hepatitis C Virus Replicons of Genotypes 1 to 4 by Manipulation of CpG and UpA Dinucleotide Frequencies and Use of Cell Lines Expressing SECL14L2 for Antiviral Resistance Testing.](#) Witteveldt J1, Martin-Gans M1, Simmonds P2. Antimicrob Agents Chemother. 2016 Apr 22;60(5):2981-92. doi: 10.1128/AAC.02932-15. Print 2016 May.

Treatment for hepatitis C virus (HCV) has improved greatly through the use of direct-acting antivirals (DAAs). However, their effectiveness and potential for drug resistance development in non-genotype 1 variants of HCV remain relatively unexplored, as in vitro assays to assess drug susceptibility are poorly developed and unsuited for a transient-transfection format. In the current study, we have evaluated the effects of dinucleotide frequency changes in the replicon and the use of a SECL14L2-expressing cell line on the replication of HCVs of different genotypes and evaluated the resulting assay formats for measurements of susceptibility to the DAA sofosbuvir. Removal of CpG and UpA dinucleotides from the luciferase gene used in HCV replicons of genotype 1b (Con1) and genotype 2a (JFH-1) achieved between 10- and 100-fold enhancement of replication over that of the wild type posttransfection. Removal of CpG and UpA dinucleotides in the neomycin gene or deletion of the whole gene in replicons of genotype 3a (S52) and genotype 4a (ED43) enhanced replication, but phenotypic effects on altering luciferase gene composition were minimal. A further 10-fold replication enhancement of replicons from all four genotypes was achieved by using a transgenic Huh7.5 cell line expressing SECL14L2, whose expression showed a dose-dependent effect on HCV replication that was reversible by small interfering RNA (siRNA) knockdown of gene expression. By combining these strategies, the 100- to 1,000-fold enhancement of replication allowed the susceptibility of all four genotypes to the RNA polymerase inhibitor sofosbuvir to be robustly determined in a transient-transfection assay format. These methods of replication enhancement provide new tools for monitoring the susceptibility and resistance of a wide range of HCV genotypes to DAAs.

HIV/HCV COINFECTION

[12 Weeks of Daclatasvir in Combination with Sofosbuvir for HIV-HCV Coinfection \(ALLY-2 study\): Efficacy and Safety by HIV Combination Antiretroviral Regimens.](#)

Luetkemeyer AF1, McDonald C2, Ramgopal M3, Noviello S4, Bhore R5, Ackerman P6. Clin Infect Dis. 2016 Mar 29. pii: ciw163. [Epub ahead of print]

BACKGROUND: Highly-effective hepatitis C virus (HCV) direct-acting antiviral therapies are needed that do not require modification of human immunodeficiency virus (HIV) antiretroviral regimens. This analysis evaluates the efficacy and safety of the combination of daclatasvir+sofosbuvir (DCV+SOF) for 12 weeks by antiretroviral regimen in HIV-HCV coinfecting patients. **METHODS:** In the randomized, open-label ALLY-2 study (NCT02032888), HIV-HCV coinfecting patients received 8 or 12 weeks of once-daily (QD) DCV 60mg+SOF 400mg. Results were stratified by antiretroviral class for the 151 patients who received 12 weeks of DCV+SOF. **RESULTS:** Fifty-one patients were HCV treatment-experienced, 100 were treatment-naïve, 89% were male, 33% were black. HCV genotypes were GT1a (69%), GT1b (15%), GT2 (8%), GT3 (6%), GT4 (2%). Sustained virologic response 12 weeks post-treatment (SVR12) was 97% and was similar across antiretroviral regimens

($p=0.774$): protease inhibitor-based, 97% (95% CI: 90%-99.7%); non-nucleoside reverse transcriptase inhibitor-based, 100% (95% CI: 91%-100%); and integrase inhibitor-based, 95% [95% CI: 83%-99.4%]). SVR12 by NRTI backbone containing either tenofovir disoproxil fumarate or abacavir was 98% [95% CI: 93%-99.5%] and 100% [95% CI: 85%-100%], respectively. Age, gender, race, cirrhosis, HCV treatment history, HCV genotype, baseline HCV viral load and CD4 cell count did not affect SVR12. HIV virologic control was not compromised. There were no treatment-related serious adverse events (SAEs) or AEs leading to discontinuation : **CONCLUSION:** DCV+SOF QD for 12 weeks led to high SVR rates (97%) across a broad range of antiretroviral regimens and was safe and well tolerated. DCV+SOF is a highly efficacious, all-oral, pangenotypic HCV treatment for HIV-HCV coinfection.

Molecular alterations in hepatocellular carcinoma associated with hepatitis B and hepatitis C infections. Tornesello ML1, Buonaguro L1, Izzo F2, Buonaguro FM1. *Oncotarget*. 2016 Mar 2. doi: 10.18632/oncotarget.7837. [Epub ahead of print]

Chronic infections with hepatitis B (HBV) and hepatitis C viruses (HCV) are the leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. Both viruses encode multifunctional regulatory proteins activating several oncogenic pathways, which induce accumulation of multiple genetic alterations in the infected hepatocytes. Gene mutations in HBV- and HCV-induced HCCs frequently impair the TP53, Wnt/b-catenin, RAS/RAF/MAPK kinase and AKT/mTOR pathways, which represent important anti-cancer targets. In this review, we highlight the molecular mechanisms underlying the pathogenesis of primary liver cancer, with particular emphasis on the host genetic variations identified by high-throughput technologies. In addition, we discuss the importance of genetic alterations, such as mutations in the telomerase reverse transcriptase (TERT) promoter, for the diagnosis, prognosis, and tumor stratification for development of more effective treatment approaches.

Hyperbilirubinaemia in HIV-HCV co-infected patients on antiretroviral therapy: drug effect or liver disease severity? Kaspar MB1, Sterling RK2. *BMJ Open Gastroenterol*. 2016 Mar 2;3(1):e000072. doi: 10.1136/bmjgast-2015-000072. eCollection 2016.

OBJECTIVE: Hyperbilirubinaemia (HB) is common in HIV and hepatitis C virus (HIV-HCV) co-infected patients and poses a unique challenge in management as it may be due to medications such as the protease inhibitors (PIs) or to hepatic dysfunction. There are no data on the relationship of HB to liver histology and PI use in this population. Clinicians caring for these patients are faced with the difficult task of determining whether increasing serum bilirubin is due to drug effects or progression of liver disease. **METHODS:** To address this gap in knowledge, we performed a retrospective analysis of 344 consecutive HIV-HCV co-infected patients undergoing liver biopsy to identify factors associated with HB. Demographic, clinical, laboratory data were collected. Advanced fibrosis was defined as bridging fibrosis or cirrhosis. Those with hepatitis B virus, hepatic decompensation or hepatocellular carcinoma were excluded.

RESULTS: The prevalence of HB (range 1.3-9.4) was 33% and more common in those on a PI (46%) than those who were not (10%; $p\leq 0.001$) and mostly in those on indinavir (40%) or atazanavir (46%). Of the patients on these PIs, HB was not associated with fibrosis grade, demographics, or other clinical variables. Conversely, in those not on a PI, HB was associated with fibrosis grade ($p\leq 0.0001$) after adjusting for other clinical and demographic variables.

CONCLUSIONS: In the setting of indinavir or atazanavir use, HB is common and unrelated to underlying disease severity and the medications can be continued safely. Conversely, HB in

HIV-HCV co-infected patients not on a PI is due to their underlying liver disease and suggests these patients require closer monitoring.

Real-world Sustained Virologic Response Rates of Sofosbuvir-containing Regimens in Patients Coinfected with Hepatitis C and HIV. Del Bello D1, Cha A2, Sorbera M2, et al. Clin Infect Dis. 2016 Mar 1. pii: ciw119. [Epub ahead of print]

BACKGROUND: Patients with hepatitis C virus (HCV) monoinfection achieve high sustained virological response (SVR) rates on sofosbuvir (SOF)-containing regimens. Real world data on patients coinfecting with HCV and the human immunodeficiency virus (HIV) treated with SOF-based regimens are lacking. **METHODS:** This observational cohort study included HIV/HCV coinfecting adults with genotype 1 HCV initiating treatment with a SOF-containing regimen between April, 2014, and December, 2014, (n= 89) at the Mount Sinai Hospital or the Brooklyn Hospital Center. The primary outcome was sustained virological response (SVR) at 12 weeks after the end of treatment. The secondary outcomes were risk factors for treatment failure, serious adverse events and side effects. A post-hoc per protocol analysis of SVR was performed on patients who completed treatment and follow-up. **RESULTS:** In an intention-to-treat analysis, SVR rates were 76% (31/41) for simeprevir (SMV)/SOF, 94% (16/17) for SMV/SOF/ribavirin (RBV), and 52% (16/31) for SOF/RBV. The SVR rates of SMV/SOF/RBV and SMV/SOF did not differ significantly in this small study (p=0.15); however the SVR rate of SMV/SOF/RBV was higher than that of SOF/RBV (p<0.01). In a per-protocol analysis, SMV/SOF/RBV had a higher SVR rate than SOF/RBV: 100% (16/16) versus 57% (16/28) (p <0.01). The most commonly reported adverse effects were rash, pruritus, fatigue and insomnia. One patient, who had decompensated cirrhosis prior to treatment initiation, died while receiving SMV/SOF. **CONCLUSIONS:** SMV/SOF±RBV is an effective and safe option with minimal adverse effects for most HIV positive patients with genotype 1 HCV. SMV should be avoided in patients with decompensated cirrhosis

The CD4/CD8 ratio is inversely associated with cIMT progression in HIV infected patients on antiretroviral treatment. Bernal Morell E1, Serrano Cabeza J2, Muñoz A3, et al. AIDS Res Hum Retroviruses. 2016 Mar 22. [Epub ahead of print]

Inversion of the CD4/CD8 ratio (< 1) has been identified as a surrogate marker of immunosenescence, and an independent predictor of AIDS events in HIV infected patients and mortality in the general population. We aimed to assess the association between the CD4/CD8 ratio and carotid intima-media thickness (cIMT) progression in treated HIV-infected patients as a marker of coronary heart disease. A longitudinal study was conducted during three years in 96 virally suppressed HIV infected patients receiving antiretroviral treatment (ART). We analyzed the associations between the CD4/CD8 ratio, cardiovascular risk factors and antiretroviral treatment (ARV), and progression of subclinical atherosclerosis assessed using carotid cIMT at baseline and after three years. Finally, ninety-six patients completed the study. Seventy six (79.1%) patients were male, aged 44±10 years, 39 (40.6%) were on treatment with protease inhibitors; 49 (51.04%) with non-nucleoside reverse transcriptase inhibitors (NNRTI), 6 (6.25%) with integrase inhibitors, 3 (3.12%) with maraviroc and 2 (2.08%) just with nucleoside reverse transcriptase inhibitors (NRTI). The mean of ARV exposition was 6.9±5.9 years. Twenty six (27%) patients had family history of ischemic heart disease, 51(53.12%) were smokers, 12 (12.5%) were hypertensive, 4 (4.16%) had type 2 diabetes, 23 (23.9%) had dyslipidemia and 31 (32.3%) were infected with hepatitis C virus. Baseline cIMT was significantly associated with age (rho =

0.497; $p < 0.001$), basal glucemia ($\rho=0.323$; $p = 0.001$), tryglicerides ($\rho=0.232$; $p=0.023$), Framingham risk score ($\rho=0.324$; $p=0.001$), CD4/CD8 ratio ($\rho = -0.176$; $p=0.05$) and dyslipidemia (0.72 ± 0.16 mm vs 0.63 ± 0.11 mm; $p=0.029$). In multivariable analysis where cardiovascular risk factor and ARV were included, cIMT progression was inversely associated with CD4/CD8 ratio (OR = 0.283; IC95% 0.099-0.809; $p=0.019$). In conclusion, the inversion of CD4/CD8 ratio in treated HIV-infected patients is independently associated with cIMT progression, a marker of coronary heart disease. Therefore, it might be clinically useful as predictor of cardiovascular events.

[Impact of Safety-Related Dose Reductions or Discontinuations on Sustained Virologic Response in HCV-Infected Patients: Results from the GUARD-C Cohort.](#) Foster GR1,

Coppola C2, Derbala M3, et al. PLoS One. 2016 Mar 28;11(3):e0151703. doi: 10.1371/journal.pone.0151703. eCollection 2016.

BACKGROUND: Despite the introduction of direct-acting antiviral agents for chronic hepatitis C virus (HCV) infection, peginterferon alfa/ribavirin remains relevant in many resource-constrained settings. The non-randomized GUARD-C cohort investigated baseline predictors of safety-related dose reductions or discontinuations (sr-RD) and their impact on sustained virologic response (SVR) in patients receiving peginterferon alfa/ribavirin in routine practice.

METHODS: A total of 3181 HCV-mono-infected treatment-naïve patients were assigned to 24 or 48 weeks of peginterferon alfa/ribavirin by their physician. Patients were categorized by time-to-first sr-RD (Week 4/12). Detailed analyses of the impact of sr-RD on SVR24 (HCV RNA <50 IU/mL) were conducted in 951 Caucasian, noncirrhotic genotype (G)1 patients assigned to peginterferon alfa-2a/ribavirin for 48 weeks. The probability of SVR24 was identified by a baseline scoring system (range: 0-9 points) on which scores of 5 to 9 and <5 represent high and low probability of SVR24, respectively. **RESULTS:** SVR24 rates were 46.1% (754/1634), 77.1% (279/362), 68.0% (514/756), and 51.3% (203/396), respectively, in G1, 2, 3, and 4 patients. Overall, 16.9% and 21.8% patients experienced ≥ 1 sr-RD for peginterferon alfa and ribavirin, respectively. Among Caucasian noncirrhotic G1 patients: female sex, lower body mass index, pre-existing cardiovascular/pulmonary disease, and low hematological indices were prognostic factors of sr-RD; SVR24 was lower in patients with ≥ 1 vs. no sr-RD by Week 4 (37.9% vs. 54.4%; $P = 0.0046$) and Week 12 (41.7% vs. 55.3%; $P = 0.0016$); sr-RD by Week 4/12 significantly reduced SVR24 in patients with scores <5 but not ≥ 5 . **CONCLUSIONS:** In conclusion, sr-RD to peginterferon alfa-2a/ribavirin significantly impacts on SVR24 rates in treatment-naïve G1 noncirrhotic Caucasian patients. Baseline characteristics can help select patients with a high probability of SVR24 and a low probability of sr-RD with peginterferon alfa-2a/ribavirin.

[Resistance-associated mutations to HCV protease inhibitors naturally pre-existed in HIV/HCV coinfecting, treatment-naïve patients.](#) Cao Y1, Bao Y2, Xia W3, Wu H3, Wei F3, Zhang Y1, Zhang R1, Xu X4. Clin Res Hepatol Gastroenterol. 2016 Mar 23. pii: S2210-7401(16)30030-4. doi: 10.1016/j.clinre.2016.02.004. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: Presently, it has been approved to treat hepatitis C virus (HCV) infection with protease inhibitors (PIs). In the present study, we aimed to illustrate the natural prevalence of HCV NS3/4A PI resistance mutations in HIV/HCV coinfecting, treatment-naïve patients. **METHODS:** Population sequence analysis of the NS3/4A protease was conducted in 96 HIV/HCV coinfecting, treatment-naïve patients. **RESULTS:** Complete HCV

NS3/4A sequence information was obtained from 70 (72.92%) samples, including 68 patients (97.14%) with genotype 1b and 2 patients (2.86%) with genotype 2a. A total of 21 patients (30.88%) of the 68 patients with HCV genotype 1b showed amino acid substitutions associated with HCV PI resistance. Mutation F43S was observed in 1.47% of patients with genotype 1b. The mutations of T54S, Q80K/R, R155K, A156G and D168A/E/G were found in 4.41%, 1.47%/1.47%, 2.94%, 23.53% and 1.47%/1.47%/1.47% of patients with genotype 1b, respectively. In addition, 4.41% of patients with genotype 1b showed double mutations in the NS3 region. The multiple mutations of Q80R+R155K+D168G and Q80K+R155K+A156G+D168A were detected in 1.47% and 1.47% of patients with HCV genotype 1b, respectively. **CONCLUSIONS:** The most predominant HCV genotype was 1b in patients with HIV/HCV coinfection. Naturally occurring mutations resistant to HCV PIs (simeprevir, vaniprevir, boceprevir, telaprevir, asunaprevir and paritaprevir) pre-existed in patients with HIV/HCV genotype 1b coinfection. The effects of baseline PI resistance on treatment outcome should be further analyzed.

[Responder Interferon Lambda genotypes are associated with higher risk of liver fibrosis in HIV-Hepatitis C Virus Co-infection.](#)

Moqueet N1, Cooper C2, Gill J3, Hull M4, Platt RW1, Klein MB5; Canadian Co-infection Cohort. *J Infect Dis.* 2016 Mar 16. pii: jiw088. [Epub ahead of print]

BACKGROUND: Liver fibrosis progresses faster in HIV-HCV co-infected individuals. Interferon Lambda 3 (IFNL3) protein has both antiviral and pro-inflammatory properties. Genotypes at IFNL SNPs (rs12979860CC, rs8099917TT) are linked to higher HCV clearance, potentially via rs8103142. We examined the relationship between IFNL genotypes and significant liver fibrosis in HIV-HCV co-infection. **METHODS:** From the prospective Canadian Co-infection Cohort (n=1423), HCV RNA-positive participants with IFNL genotypes, free of fibrosis, end-stage liver disease and chronic Hepatitis B at baseline (n=485) were included. Time to significant fibrosis (AST-to-platelet ratio index (APRI) ≥ 1.5) by IFNL genotypes was analyzed using Cox proportional hazards, adjusting for age, sex, ethnicity, alcohol use, CD4 count, HCV genotype, GGT and baseline APRI. Haplotype analysis was performed, adjusting for ethnicity. **RESULTS:** 125 participants developed fibrosis over 1595 person-years (7.84/100 person-years, 95% CI: 6.58, 9.34). Each genotype increased fibrosis risk (aHR [95% CI]): rs12979860CC, 1.37 [0.94, 2.02]; rs8103142TT, 1.34 [0.91, 1.97]; rs8099917TT, 1.79 [1.24, 2.57]. Haplotype TCT was also linked with higher risk, 1.14 [0.73, 1.77]. **CONCLUSIONS:** IFNL SNPs rs12979860, rs8099917 and rs8103142 were individually linked to higher rate of fibrosis in HIV-HCV co-infection. IFNL genotypes may be useful to target HCV treatments to those who are at higher risk of liver disease.

[Non-initiation of hepatitis C virus antiviral therapy in patients with human immunodeficiency virus/hepatitis C virus co-infection.](#)

Oramasionwu CU1, Kashuba AD1, Napravnik S1, Wohl DA1, Mao L1, Adimora AA1. *World J Hepatol.* 2016 Mar 8;8(7):368-75. doi: 10.4254/wjh.v8.i7.368.

AIM: To assess whether reasons for hepatitis C virus (HCV) therapy non-initiation differentially affect racial and ethnic minorities with human immunodeficiency virus (HIV)/HCV co-infection. **METHODS:** Analysis included co-infected HCV treatment-naïve patients in the University of North Carolina CFAR HIV Clinical Cohort (January 1, 2004 and December 31, 2011). Medical records were abstracted to document non-modifiable medical (e.g., hepatic decompensation,

advanced immunosuppression), potentially modifiable medical (e.g., substance abuse, severe depression, psychiatric illness), and non-medical (e.g., personal, social, and economic factors) reasons for non-initiation. Statistical differences in the prevalence of reasons for non-treatment between racial/ethnic groups were assessed using the two-tailed Fisher's exact test. Three separate regression models were fit for each reason category. Odds ratios and their 95% CIs (Wald's) were computed. **RESULTS:** One hundred and seventy-one patients with HIV/HCV co-infection within the cohort met study inclusion. The study sample was racially and ethnically diverse; most patients were African-American (74%), followed by Caucasian (19%), and Hispanic/other (7%). The median age was 46 years (interquartile range = 39-50) and most patients were male (74%). Among the 171 patients, reasons for non-treatment were common among all patients, regardless of race/ethnicity (50% with ≥ 1 non-modifiable medical reason, 66% with ≥ 1 potentially modifiable medical reason, and 66% with ≥ 1 non-medical reason). There were no significant differences by race/ethnicity. Compared to Caucasians, African-Americans did not have increased odds of non-modifiable [adjusted odds ratio (aOR) = 1.47, 95% CI: 0.57-3.80], potentially modifiable (aOR = 0.72, 95% CI: 0.25-2.09) or non-medical (aOR = 0.90, 95% CI: 0.32-2.52) reasons for non-initiation. **CONCLUSION:** Race/ethnicity alone is not predictive of reasons for HCV therapy non-initiation. Targeted interventions are needed to improve access to therapy for all co-infected patients, including minorities.

[Interferon Stimulated Gene Expression in HIV/HCV Coinfected Patients Treated with Nitazoxanide/Peginterferon-Alfa-2a and Ribavirin.](#) Petersen T1, Lee YJ1, Osinusi A1,2,3, et al. *AIDS Res Hum Retroviruses*. 2016 Mar 14. [Epub ahead of print]

A combination of nitazoxanide (NTZ), peginterferon (PegIFN), and ribavirin (RBV) may result in higher sustained virologic response (SVR) rates in hepatitis C virus (HCV) mono-infected patients. This study evaluated the effect of NTZ on interferon-stimulated gene (ISG) expression in vitro and in vivo among HIV/HCV genotype-1 (GT-1) treatment-naive patients. The ability of NTZ to enhance host response to interferon (IFN) signaling using the HCV cell culture system was initially evaluated. Second, ISG expression in 53 patients with treatment outcomes [21 SVR and 32 nonresponders (NR)] in the ACTG A5269 trial, a phase-II study (4-week lead in of NTZ 500 mg daily followed by 48 weeks of NTZ, PegIFN, and weight-based RBV), was assessed. The relative expression of 48 ISGs in peripheral blood mononuclear cells (PBMCs) was measured at baseline, week 4, and week 8 of treatment in a blinded manner. In vitro NTZ produced a direct and additive antiviral effect with IFN- α , with pretreatment of NTZ resulting in maximal HCV suppression. NTZ augmented IFN-mediated ISG induction in PBMCs from relapsers and SVRs ($p < 0.05$), but not NR. In ACTG A5269, baseline expression of most ISGs was similar between NR and SVR. NTZ minimally induced 17 genes in NR and 13 genes in SVR after 4 weeks of therapy. However, after initiation of PegIFN and RBV, ISG induction was predominantly observed in the SVR group and not NR group. NTZ treatment facilitates IFN-induced suppression of HCV replication. Inability to achieve SVR with IFN-based therapy in this clinical trial is associated with diminished ISG response to therapy that is refractory to NTZ.

[Clinical Significance of Myeloid-Derived Suppressor Cells in HIV-1/HCV Coinfected Patients.](#) Lei A1, Yang Q1, Cai W2, Liu Y1, Lan Y2, Qin A1, Hu F2, Zhou J1,3. *Scand J Immunol*. 2016 Mar 12. doi: 10.1111/sji.12429. [Epub ahead of print]

Myeloid-derived suppressor cells (MDSCs) are known to accumulate during chronic viral infection, including human immunodeficiency virus-1 (HIV-1) and hepatitis C virus (HCV)

infection, and play a critical role in suppressing immune responses. However, the role of MDSCs in HIV/HCV coinfection is unclear. Here, we observed a dramatic increase in monocytic MDSCs (M-MDSCs) level in the peripheral blood of HIV/HCV-coinfected patients compared to that of healthy controls; the level of M-MDSCs proportion in coinfection was not higher than that in HIV or HCV mono-infection. Interestingly, we found the M-MDSCs level in coinfecting patients correlated well with CD4+ T cell loss ($r = -0.5680$; $P = 0.0058$), HIV-1 load ($r = 0.6011$; $P = 0.0031$), HCV load ($r = 0.6288$; $P = 0.0017$) and activated CD38+ T cells ($r = 0.5139$; $P = 0.0144$). Initiation of highly active antiretroviral therapy (HAART) considerably reduced both M-MDSCs and CD8+ CD38+ -activated T-cell proportion in coinfecting patients, and they showed a parallel course of decline. Thus, our results suggest that HIV-1 infection and high chronic immune activation may contribute to the expansion of M-MDSCs and accelerate the disease progression in HIV/HCV-coinfecting patients.

Differential predictors of ART adherence among HIV-mono-infected versus HIV/HCV-coinfecting individuals. Shuper PA1,2, Joharchi N1, Irving H3, et al. AIDS Care. 2016 Mar 14:1-9. [Epub ahead of print]

Although adherence is an important key to the efficacy of antiretroviral therapy (ART), many people living with HIV (PLWH) fail to maintain optimal levels of ART adherence over time. PLWH with the added burden of Hepatitis C virus (HCV) coinfection possess unique challenges that potentially impact their motivation and ability to adhere to ART. The present investigation sought to (1) compare ART adherence levels among a sample of HIV/HCV-coinfecting versus HIV-mono-infected patients, and (2) identify whether ART-related clinical and psychosocial correlates differ by HCV status. PLWH receiving ART ($N = 215$: 105 HIV/HCV-coinfecting, 110 HIV-mono-infected) completed a comprehensive survey assessing ART adherence and its potential correlates. Medical chart extraction identified clinical factors, including liver enzymes. Results demonstrated that ART adherence did not differ by HCV status, with 83.7% of coinfecting patients and 82.4% of mono-infected patients reporting optimal (i.e., $\geq 95\%$) adherence during a four-day recall period ($p = .809$). Multivariable logistic regression demonstrated that regardless of HCV status, optimal ART adherence was associated with experiencing fewer adherence-related behavioral skills barriers (AOR = 0.56; 95%CI = 0.43-0.73), lower likelihood of problematic drinking (AOR = 0.15; 95%CI = 0.04-0.67), and lower likelihood of methamphetamine use (AOR = 0.14; 95%CI = 0.03-0.69). However, among HIV/HCV-coinfecting patients, optimal adherence was additionally associated with experiencing fewer ART adherence-related motivational barriers (AOR = 0.23; 95%CI = 0.08-0.62) and lower likelihood of depression (AOR = 0.06; 95%CI = 0.00-0.84). Findings suggest that although HIV/HCV-coinfecting patients may face additional, distinct barriers to ART adherence, levels of adherence commensurate with those demonstrated by HIV-mono-infected patients might be achievable if these barriers are addressed.

Enhanced liver fibrosis marker as a noninvasive predictor of mortality in HIV/hepatitis C virus-coinfecting women from a multicenter study of women with or at risk for HIV.

Peters MG1, Bacchetti P, Boylan R, et al. AIDS. 2016 Mar 13;30(5):723-9. doi: 10.1097/QAD.0000000000000975.

OBJECTIVE: Coinfection with hepatitis C virus (HCV) is a major cause of morbidity and mortality among individuals with HIV. Our objective was to assess the prognostic performance of noninvasive measures of liver fibrosis in predicting all-cause mortality in women with

HIV/HCV coinfection. **DESIGN:** We studied HCV/HIV coinfecting women enrolled in the prospective, multicenter Women's Interagency HIV Study. Aspartate aminotransferase to platelet ratio and FIB-4 were used to identify women without fibrosis at all visits and women who progressed to severe fibrosis. **METHODS:** Enhanced liver fibrosis (ELF), which utilizes direct measures of fibrosis, hyaluronic acid, procollagen III aminoterminal peptide and tissue inhibitor of matrix metalloproteinase was performed. **RESULTS:** Included were 381 women with 2296 ELF measurements, with mean follow-up 8.3 ± 3.3 years. There were 134 deaths (60% with severe liver fibrosis). Receiver operator characteristic curves at fixed time windows prior to death or at end of follow-up showed that ELF was best at predicting mortality when tested within a year of death (area under the curve for ELF 0.85 vs. APRI 0.69, $P < 0.0001$ and vs. FIB-4 0.75, $P = 0.0036$); and 1-3 years prior (ELF 0.71 vs. APRI 0.61, $P = 0.005$ and vs. FIB-4 0.65, $P = 0.06$). Use of all three measures did not improve on ELF alone. In multivariate logistic regression models controlling for CD4 cell count, HIV viral load, antiretroviral use and age, ELF continued to perform better than APRI and FIB-4. **CONCLUSION:** ELF predicted all-cause mortality and was superior to APRI and FIB-4 in HIV/HCV coinfecting women.

[Optimal vitamin D plasma levels are associated with lower bacterial DNA translocation in HIV/hepatitis c virus coinfecting patients.](#)

García-Álvarez M1, Berenguer J, Jiménez-Sousa MÁ, et al. AIDS. 2016 Apr 24;30(7):1069-74. doi: 10.1097/QAD.0000000000001007.

OBJECTIVE: Vitamin D has been linked to the immune response modulation and the integrity of the intestinal mucosal barrier. Therefore, vitamin D might be involved in bacterial translocation related to HIV infection. Our major aim was to analyze the association between plasma levels of 25-hydroxy-vitamin D [25(OH)D] and bacterial 16S ribosomal DNA (bactDNA) in 120 HIV/hepatitis c virus (HCV) coinfecting patients. **DESIGN:** Cross-sectional study. **METHODS:** Plasma 25(OH)D levels were quantified by enzyme immunoassay. The vitamin D status was defined as deficient (< 25 nmol/l), insufficient (25-74 nmol/l), and optimal (≥ 75 nmol/l) plasma levels. Plasma bactDNA levels were measured by quantitative real-time PCR. For bactDNA levels the cutoffs used were as follows: low [$< p25$ th (46 copies/ μ l)], moderate [$p25$ th to $p50$ th (78 copies/ μ l)], high [$p50$ th to $p75$ th (159 copies/ μ l)], and very high ($> p75$ th). **RESULTS:** Eighteen (15%) patients had 25(OH)D deficiency, 93 (77.5%) had insufficiency and nine (7.5%) had 25(OH)D optimal values. The bactDNA levels were lower in patients with 25(OH)D at least 75 nmol/l [37 copies/ μ l] than in patients with 25(OH)D insufficiency [84.2 copies/ μ l; $P = 0.042$]. Conversely, low bactDNA levels ($< p25$ th) were found in 66.7% of patients with 25(OH)D optimal levels, whereas bactDNA levels above $p25$ th were found only in 11.1% of them ($P = 0.029$). The plasma 25(OH)D not less than 75 nmol/l was associated with low bactDNA levels ($< p25$ th) [adjusted OR=8.13 (95% confidence interval=1.82; 36.67); $P = 0.006$]. The patients with optimal vitamin D status [25(OH)D ≥ 75 nmol/l] had lower plasma levels of CCL7 ($P = 0.047$) and basic fibroblast growth factor ($P = 0.042$). **CONCLUSION:** The optimal vitamin D status was associated with low bacterial translocation and inflammation in HIV/HCV coinfecting patients.

[Long-term efficacy of Peg-Interferon/Ribavirin with and without Lamivudine therapy for HBeAg-positive hepatitis B and C dual infection.](#)

Yeh ML1,2,3, Hsieh MY1, Huang CI4, et al. J Gastroenterol Hepatol. 2016 Apr;31(4):835-41. doi: 10.1111/jgh.13203.

BACKGROUND: The optimal therapeutic strategy for hepatitis B virus (HBV) e antigen (HBeAg)-seropositive and hepatitis C virus (HCV) dually infected patients remains unknown.

We aimed to elucidate the effectiveness of peginterferon (Peg-IFN)/ribavirin (RBV) with and without lamivudine (LAM) combination therapy in the clinical settings. **PATIENTS AND METHODS:** Nine patients seropositive for HBV surface antigen, HBeAg, antibodies to HCV and HCV RNA for >6 months were treated with Peg-IFN/RBV with (n = 5) and without (n = 4) a 12-month LAM add-on therapy at treatment week 12. The treatment duration of Peg-IFN/RBV was 24 weeks (HCV genotype 1 [HCV-1] with rapid virological response [RVR] or HCV-2) or 48 weeks (HCV-1 without RVR). Primary endpoints included HBeAg loss and HCV-sustained virological response (SVR). **RESULTS:** All of the nine patients had undetectable HCV RNA at treatment weeks 4 and 12 and end-of-Peg-IFN/RBV therapy. However, SVR was achieved in 100% of patients treated with triple therapy, compared with only 50% in those with Peg-IFN/RBV therapy (P = 0.167). The 3-year durability of HCV SVR was 100%. HBeAg loss and HBV DNA <2000 IU/mL at 6 months post-LAM treatment were found in 100% and 40% of patients treated with triple therapy, compared with none of the four patients with Peg-IFN/RBV therapy achieved any HBV responses. Of the five patients with triple therapy, four had persistent HBeAg loss during 3-year follow-up period; one developed HBeAg seroreversion 15 months after treatment. **CONCLUSION:** For HBeAg-positive HBV/HCV dually infected patients, Peg-IFN/RBV was effective for HCV eradication. Add-on LAM might promote HBeAg loss in the clinical setting.

[Interferon-free treatment with sofosbuvir/daclatasvir achieves sustained virologic response in 100% of HIV/hepatitis C virus-coinfected patients with advanced liver disease.](#)

Mandorfer M1, Schwabl P, Steiner S, et al. AIDS. 2016 Apr 24;30(7):1039-47. doi: 10.1097/QAD.0000000000001020.

AIM: We aimed to investigate the safety and efficacy of interferon (IFN) and ribavirin (RBV)-free therapy with sofosbuvir along with daclatasvir (SOF/DCV) in HIV/hepatitis C virus (HCV)-coinfected patients (HIV/HCV), who have an urgent need for effective antiviral therapy. We also assessed its impact on liver stiffness and liver enzymes. **DESIGN:** Thirty-one patients thoroughly documented HIV/HCV with advanced liver disease (advanced liver fibrosis and/or portal hypertension) who were treated with SOF/DCV were retrospectively studied.

METHODS: The following treatment durations were applied: HCV-genotype (HCV-GT)1/4 without cirrhosis: 12 weeks; HCV-GT1/4 with cirrhosis: 24 weeks; HCV-GT3: 24 weeks; if HCV-RNA was detectable 4 weeks before the end of treatment, treatment was extended by 4 weeks at a time. **RESULTS:** Fifty-two percent of patients were treatment-experienced. The majority of patients had HCV-GT1 (68%), whereas HCV-GT3 and HCV-GT4 were observed in 23 and 10% of patients, respectively. Ninety-four percent had liver stiffness greater than 9.5kPa or METAVIR fibrosis stage higher than F2 and 45% had liver stiffness above 12.5kPa or METAVIR F4. Portal hypertension (HVPG \geq 6mmHg) and clinically significant portal hypertension (HVPG \geq 10mmHg) were observed in 67% (18/27) and 26% (7/27) of patients, respectively. Sustained virologic response 12 weeks after the end of treatment (SVR12) was achieved in 100% (31/31). Treatment with SOF/DCV was generally well tolerated and there were no treatment discontinuations. HCV eradication improved liver stiffness from 11.8 [interquartile range (IQR): 11.5kPa] to 6.9 (IQR: 8.2)kPa [median change: -3.6 (IQR:5.2)kPa; P<0.001] and decreased liver enzymes. The mean time period between treatment initiation and follow-up liver stiffness measurement was 32.7 \pm 1.2 weeks. **CONCLUSION:** IFN- and RBV-free treatment with SOF/DCV was well tolerated and achieved SVR12 in all HIV/HCV with

advanced liver disease. It also significantly improved liver stiffness, suggesting anti-fibrotic and anti-portal hypertensive effects.

[Evaluation of Drug-Drug Interactions between Direct-Acting Anti-Hepatitis C Virus Combination Regimens and the HIV-1 Antiretroviral Agents Raltegravir, Tenofovir, Emtricitabine, Efavirenz, and Rilpivirine.](#)

Khatri A1, Dutta S2, Dunbar M2, Podsadecki T2, Trinh R2, Awni W2, Menon R2. Antimicrob Agents Chemother. 2016 Apr 22;60(5):2965-71. doi: 10.1128/AAC.02605-15. Print 2016 May.

The three direct-acting antiviral agent (3D) regimen is a novel combination of direct-acting antiviral agents (DAAs) that has proven effective for the treatment of hepatitis C virus (HCV) infection. Given the potential for coadministration in patients with human immunodeficiency virus infection, possible drug interactions with antiretroviral drugs must be carefully considered. Four phase 1, multiple-dose pharmacokinetic studies were conducted in healthy volunteers (n = 66). The 3D regimen of 150/100 mg daily paritaprevir/ritonavir, 25 mg daily ombitasvir, and 400 mg twice-daily dasabuvir was administered alone or in combination with 200 mg daily of emtricitabine and 300 mg daily of tenofovir disoproxil fumarate (tenofovir DF), 25 mg daily of rilpivirine, or 400 mg of raltegravir twice daily. A 2-DAA regimen of 150/100 mg daily paritaprevir/ritonavir and 400 mg of dasabuvir twice daily was also studied in combination with efavirenz/emtricitabine/tenofovir DF at 600/200/300 mg daily, respectively (Atripla; Bristol-Myers Squibb). Pharmacokinetic parameters were determined from plasma drug concentrations. No clinically significant drug interactions were observed ($\leq 32\%$ change in exposure) between the 3D regimen and that of emtricitabine plus tenofovir DF. Raltegravir exposure was increased up to 134% when the drug was coadministered with the 3D regimen. Although coadministration with rilpivirine was well tolerated in healthy volunteers, observed elevations in rilpivirine exposures may increase the potential for adverse drug reactions. Concomitant use of the 2-DAA regimen and efavirenz/emtricitabine/tenofovir DF was discontinued owing to poor tolerability and adverse events. No dose adjustment is required during coadministration of raltegravir, tenofovir DF, or emtricitabine with the 3D regimen. Rilpivirine is not recommended and efavirenz is contraindicated for coadministration with the 3D regimen.

[HIV and Hepatitis C-Coinfected Patients Have Lower Low-Density Lipoprotein Cholesterol Despite Higher Proprotein Convertase Subtilisin Kexin 9 \(PCSK9\): An Apparent "PCSK9-Lipid Paradox".](#)

Kohli P1, Ganz P2, Ma Y3, et al. J Am Heart Assoc. 2016 Apr 29;5(5). pii: e002683. doi: 10.1161/JAHA.115.002683.

BACKGROUND: Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors reduce low-density lipoprotein cholesterol (LDL-C) and improve outcomes in the general population. HIV-infected individuals are at increased risk for cardiovascular events and have high rates of dyslipidemia and hepatitis C virus (HCV) coinfection, making PCSK9 inhibition a potentially attractive therapy. **METHODS AND RESULTS:** We studied 567 participants from a clinic-based cohort to compare PCSK9 levels in patients with HIV/HCV coinfection (n=110) with those with HIV infection alone (n=385) and with uninfected controls (n=72). The mean age was 49 years, and the median LDL-C level was 100 mg/dL (IQR 77-124 mg/dL); 21% were taking statins. The 3 groups had similar rates of traditional risk factors. Total cholesterol, LDL-C, and high-density lipoprotein cholesterol levels were lower in coinfecting patients compared with controls (P<0.001). PCSK9 was 21% higher in HIV/HCV-coinfecting patients versus controls (95% CI 9-34%, P<0.001) and 11% higher in coinfecting individuals versus those with HIV

infection alone (95% CI 3-20%, P=0.008). After adjustment for cardiovascular risk factors, HIV/HCV coinfection remained significantly associated with 20% higher PCSK9 levels versus controls (95% CI 8-33%, P=0.001). Interleukin-6 levels increased in a stepwise fashion from controls (lowest) to HIV-infected to HIV/HCV-coinfected individuals (highest) and correlated with PCSK9 (r=0.11, P=0.018). **CONCLUSIONS:** Despite having lower LDL-C, circulating PCSK9 levels were increased in patients coinfecting with HIV and HCV in parallel with elevations in the inflammatory, proatherogenic cytokine interleukin-6. Clinical trials should be conducted to determine the efficacy of targeted PCSK9 inhibition in the setting of HIV/HCV coinfection.

Directly acting antivirals for hepatitis C virus arrive in HIV/hepatitis C virus co-infected patients: from 'mind the gap' to 'where's the gap?'

Childs K1, Taylor C, Dieterich D, Agarwal K. AIDS. 2016 Apr 24;30(7):975-89. doi: 10.1097/QAD.0000000000001042.

In patients living with HIV infection with hepatitis C (HCV) is common. HIV/HCV co-infection results in more rapid liver fibrosis progression than HCV alone and end-stage liver disease is a major cause of morbidity and mortality in co-infected patients. Historically, treatment outcomes with interferon based therapy in this group have been poor but with the advent of directly acting antiviral (DAA) drugs for HCV, rates of cure have improved dramatically. This article reviews recent evidence on the treatment of HCV in co-infected patients including the efficacy of new regimens and information on drug-drug interactions between DAAs and antiretroviral therapy. We also discuss the relationship between the pathogenesis of HIV and HCV infections, the treatment of acute hepatitis C and the current debate regarding the cost-effectiveness and affordability of DAAs.

Safe Reduction in CD4 Cell Count Monitoring in Stable, Virologically Suppressed Patients With HIV Infection or HIV/Hepatitis C Virus Coinfection.

Nicolás D1, Esteve A2, Cuadros A3, et al. Clin Infect Dis. 2016 Apr 28. pii: ciw157. [Epub ahead of print]

BACKGROUND: It has been suggested that routine CD4 cell count monitoring in human immunodeficiency virus (HIV)-monoinfected patients with suppressed viral loads and CD4 cell counts >300 cells/ μ L could be reduced to annual. HIV/hepatitis C virus (HCV) coinfection is frequent, but evidence supporting similar reductions in CD4 cell count monitoring is lacking for this population. We determined whether CD4 cell count monitoring could be reduced in monoinfected and coinfecting patients by estimating the probability of maintaining CD4 cell counts \geq 200 cells/ μ L during continuous HIV suppression. **METHODS:** The PISCIS Cohort study included data from 14 539 patients aged \geq 16 years from 10 hospitals in Catalonia and 2 in the Balearic Islands (Spain) since January 1998. All patients who had at least one period of 6 months of continuous HIV suppression were included in this analysis. Cumulative probabilities with 95% confidence intervals were calculated using the Kaplan-Meier estimator stratified by the initial CD4 cell count at the period of continuous suppression initiation.

RESULTS: A total of 8695 patients were included. CD4 cell counts fell to <200 cells/ μ L in 7.4% patients, and the proportion was lower in patients with an initial count >350 cells/ μ L (1.8%) and higher in those with an initial count of 200-249 cells/ μ L (23.1%). CD4 cell counts fell to <200 cells/ μ L in 5.7% of monoinfected and 11.1% of coinfecting patients. Of monoinfected patients with an initial CD4 cell count of 300-349 cells/ μ L, 95.6% maintained counts \geq 200 cells/ μ L. In the coinfecting group with the same initial count, this rate was lower, but 97.6% of coinfecting patients with initial counts >350 cells/ μ L maintained counts \geq 200 cells/ μ L.

CONCLUSIONS: From our data, it can be inferred that CD4 cell count monitoring can be safely performed annually in HIV-monoinfected patients with CD4 cell counts >300 cells/ μ L and HIV/HCV-coinfected patients with counts >350 cells/ μ L.

[HCV Specific IL-21 Producing T Cells but Not IL-17A Producing T Cells Are Associated with HCV Viral Control in HIV/HCV Coinfection.](#) MacParland SA1, Fadel SM1, Mihajlovic V1, et al. PLoS One. 2016 Apr 28;11(4):e0154433. doi: 10.1371/journal.pone.0154433. eCollection 2016.

BACKGROUND: Decreased hepatitis C virus (HCV) clearance, faster cirrhosis progression and higher HCV RNA levels are associated with Human Immunodeficiency virus (HIV) coinfection. The CD4+ T helper cytokines interleukin (IL)-21 and IL-17A are associated with virus control and inflammation, respectively, both important in HCV and HIV disease progression. Here, we examined how antigen-specific production of these cytokines during HCV mono and HIV/HCV coinfection was associated with HCV virus control. **METHODS:** We measured HCV-specific IL-21 and IL-17A production by transwell cytokine secretion assay in PBMCs from monoinfected and coinfecting individuals. Viral control was determined by plasma HCV RNA levels. **RESULTS:** In acutely infected individuals, those able to establish transient/complete HCV viral control tended to have stronger HCV-specific IL-21-production than non-controllers. HCV-specific IL-21 production also correlated with HCV viral decline in acute infection. Significantly stronger HCV-specific IL-21 production was detected in HAART-treated coinfecting individuals. HCV-specific IL-17A production was not associated with lower plasma HCV RNA levels in acute or chronic HCV infection and responses were stronger in HIV coinfection. HCV-specific IL-21/ IL-17A responses did not correlate with microbial translocation or fibrosis. Exogenous IL-21 treatment of HCV-specific CD8+ T cells from monoinfected individuals enhanced their function although CD8+ T cells from coinfecting individuals were somewhat refractory to the effects of IL-21. **CONCLUSIONS:** These data show that HCV-specific IL-21 and IL-17A-producing T cells are induced in HIV/HCV coinfection. In early HIV/HCV coinfection, IL-21 may contribute to viral control, and may represent a novel tool to enhance acute HCV clearance in HIV/HCV coinfecting individuals.

[No significant effect of cannabis use on the count and percentage of circulating CD4 T-cells in HIV-HCV co-infected patients \(ANRS CO13-HEPAVIH French cohort\).](#) Marcellin F1,2,3, Lions C1,2,3, Rosenthal E4,5, et al. Drug Alcohol Rev. 2016 Apr 13. doi: 10.1111/dar.12398. [Epub ahead of print]

INTRODUCTION AND AIMS: Despite cannabis use being very common in patients co-infected with HIV and hepatitis C virus (HCV), its effect on these patients' immune systems remains undocumented. Documenting the potential effect of cannabis use on HIV immunological markers would help caregivers make more targeted health recommendations to co-infected patients. We performed a longitudinal analysis of the relationship between cannabis use and peripheral blood CD4 T-cell measures in co-infected patients receiving antiretroviral therapy. **DESIGN AND METHODS:** Cannabis use was assessed using annual self-administered questionnaires in 955 patients (2386 visits) enrolled in the ANRS CO13-HEPAVIH cohort. The effect of cannabis use on circulating CD4 T-cell count and percentage was estimated using multivariate linear regression models with generalised estimating equations. Sensitivity analyses were conducted after excluding visits where (i) tobacco use and (ii) smoking \geq 10 tobacco cigarettes/day were reported. **RESULTS:** At the first visit, 48% of patients reported cannabis use

during the previous four weeks, and 58% of these patients also smoked ≥ 10 tobacco cigarettes/day. After multiple adjustment, cannabis use was not significantly associated with either circulating CD4 T-cell count [model coefficient (95% confidence interval): 0.27 (-0.07; 0.62), $P = 0.12$] or percentage [-0.04 (-0.45; 0.36), $P = 0.83$]. Sensitivity analyses confirmed these results. **DISCUSSION AND CONCLUSIONS:** Findings show no evidence for a negative effect of cannabis use on circulating CD4 T-cell counts/percentages in HIV-HCV co-infected patients. In-depth immunological studies are needed to document whether cannabis has a harmful effect on CD4 levels in lungs and on cells' functional properties. [Marcellin F, Lions C, Rosenthal E, Roux P, Sogni P, Wittkop L, Protopopescu C, Spire B, Salmon-Ceron D, Dabis F, Carrieri MP, HEPAVIH ANRS CO13 Study Group. No significant effect of cannabis use on the count and percentage of circulating CD4 T-cells in HIV-HCV co-infected patients (ANRSCO13-HEPAVIH French cohort). *Drug Alcohol Rev* 2016;xxx-xxx].

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Jill, Nothing for two months.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[Hepatitis C Disease Burden in the United States in the Era of Oral Direct-Acting Antivirals.](#) Chhatwal J1,2,3, Wang X4,5, Ayer T4, et al. *Hepatology*. 2016 Mar 25. doi: 10.1002/hep.28571. [Epub ahead of print]

Oral direct-acting antivirals (DAAs) represent a major advance in hepatitis C virus (HCV) treatment. Along with recent updates in HCV screening policy and expansions in insurance coverage, the treatment demand in the United States is changing rapidly. Our objective was to project the characteristics and number of people needing antiviral treatment, and HCV-associated disease burden in the era of oral DAAs. We used a previously developed and validated Hepatitis C Disease Burden Simulation model (HEP-SIM). HEP-SIM simulated the actual clinical management of HCV from 2001 onwards, which included antiviral treatment with peginterferon-based therapies as well as the recent oral DAAs, risk-based and birth-cohort HCV screening, and the impact of the Affordable Care Act. We also simulated two hypothetical scenarios-no treatment and treatment with peginterferon-based therapies only. We estimated that in 2010, 2.5 (95% CI: 1.9-3.1) million non-institutionalized people were viremic, which dropped to 1.9 (95% CI: 1.4-2.6) million in 2015, and projected to drop below 1 million by 2020. A total of 1.8 million HCV patients will receive HCV treatment from the launch of oral DAAs in 2014 until 2030. Based on current HCV management practices, it will take 4-6 years to treat the majority of patients aware of their disease. However, 560,000 patients would still remain unaware by 2020. Even in the oral DAA era, 320,000 patients will die, 157,000 will develop hepatocellular carcinoma, and 203,000 will develop decompensated cirrhosis in the next 35 years.

[Evaluation of Fucosylated Haptoglobin and Mac-2 Binding Protein as Serum Biomarkers to Estimate Liver Fibrosis in Patients with Chronic Hepatitis C.](#) Tawara S1, Tatsumi T1, Iio S2, et al. *PLoS One*. 2016 Mar 22;11(3):e0151828. doi: 10.1371/journal.pone.0151828. eCollection 2016.

Fucosylated haptoglobin (Fuc-Hpt) and Mac-2 binding protein (Mac-2 bp) are identified as cancer biomarkers, based on the results from a glyco-proteomic analysis. Recently, we reported

that these glyco-biomarkers were associated with liver fibrosis and/or ballooning hepatocytes in patients with nonalcoholic fatty liver disease (NAFLD). We evaluated the ability of these glycoproteins to estimate liver fibrosis in 317 patients with chronic hepatitis C. We measured the serum Fuc-Hpt and Mac-2 bp levels using a lectin-antibody ELISA and ELISA, respectively. The serum levels of both Fuc-Hpt and Mac-2 bp increased with the progression of liver fibrosis. The multivariate analysis revealed that Mac-2 bp was an independent factor associated with moderate liver fibrosis ($F \geq 2$). In contrast, Fuc-Hpt was an independent factor associated with advanced liver fibrosis ($F \geq 3$). In terms of evaluating liver fibrosis, the serum levels of these glycomarkers were correlated with well-known liver fibrosis indexes, such as the aspartate aminotransferase to platelet ratio index (APRI) and Fibrosis-4 (FIB4) index. An assay that combined the APRI or FIB4 index and the Fuc-Hpt or Mac-2 bp levels increased the AUC value for diagnosing hepatic fibrosis. Interestingly, the cumulative incidence of hepatocellular carcinoma (HCC) was significantly higher in the patients with elevated serum levels of Fuc-Hpt and Mac-2 bp. In conclusion, both Fuc-Hpt and Mac-2 bp could be useful glyco-biomarkers of liver fibrosis and predictors of HCC in patients with chronic hepatitis C.

Identification and Fibrosis Staging of Hepatitis C Patients Using the Electronic Medical Record System. Anand V1, Hyun C, Khan QM, Hall C, Hessefort N, Sonnenberg A, Fimmel CJ. *J Clin Gastroenterol.* 2016 Mar 11. [Epub ahead of print]

BACKGROUND AND AIMS: The aim of this study was to noninvasively assess the severity of chronic hepatitis C virus (HCV) in large patient populations. It would be helpful if fibrosis scores could be calculated solely on the basis of data contained in the patients' electronic medical records (EMR). We performed a pilot study to identify all HCV-infected patients in a large health care system, and predict their fibrosis stage on the basis of demographic and laboratory data using common data from their EMR. **MATERIALS AND METHODS:** HCV-infected patients were identified using the EMR. The liver biopsies of 191 HCV patients were graded using the Ishak and Metavir scoring systems. Demographic and laboratory data were extracted from the EMR and used to calculate the aminotransferase to platelet ratio index, Fib-4, Fibrosis Index, Forns, Göteborg University Cirrhosis Index, Lok Index, and Vira-HepC. **RESULTS:** In total, 869 HCV-infected patients were identified from a population of over 1 million. In the subgroup of patients with liver biopsies, all 7 algorithms were significantly correlated with the fibrosis stage. The degree of correlation was moderate, with correlation coefficients ranging from 0.22 to 0.60. For the detection of advanced fibrosis (Metavir 3 or 4), the areas under the receiver operating characteristic curve ranged from 0.71 to 0.84, with no significant differences between the individual scores. Sensitivities, specificities, and positive and negative predictive values were within the previously reported range. All scores tended to perform better for higher fibrosis stages. **CONCLUSIONS:** Our study demonstrates that HCV-infected patients can be identified and their fibrosis staged using commonly available EMR-based algorithms.

Health-related quality of life in thrombocytopenic patients with chronic hepatitis C with or without cirrhosis in the ENABLE-1 and ENABLE-2 studies. Grotzinger KM1, Younossi ZM2, Giannini EG3, et al. *Health Qual Life Outcomes.* 2016 Mar 22;14(1):49. doi: 10.1186/s12955-016-0447-1.

BACKGROUND: Despite changes in the treatment paradigm towards non-interferon-based therapies, interferon-based treatments are still used in some geographical regions for treating patients with hepatitis C virus (HCV) infection. Use of eltrombopag with interferon-based

treatment for patients with thrombocytopenia and HCV was assessed in two similarly designed phase 3 trials (Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects With Hepatitis C-Related Liver Disease [ENABLE-1 and ENABLE-2]). These trials also aimed to determine whether response to antiviral therapy (e.g., sustained virologic response [SVR]) is associated with changes in health-related quality of life (HRQoL). This pooled, post-hoc analysis aimed to (1) determine whether or not specific aspects of clinical response to treatment (i.e., achieving SVR) are associated with a significant change in HRQoL, and (2) to determine the magnitude and direction of the association between important changes in HRQoL, clinical response to interferon-based therapy (e.g., SVR) and treatment (eltrombopag or placebo), and patient and disease attributes. **METHODS:** The Short-Form 36 Health Survey version 2 and Chronic Liver Disease Questionnaire-Hepatitis C Virus version were administered at various time points during the studies. Results from both trials were pooled for the analyses. Logistic regression analysis was used to assess the influence of 5 clinical factors (SVR, early virologic response [EVR], genotype [2/3 vs. non-2/3], treatment [eltrombopag or placebo], and cumulative interferon dose), plus other factors including ethnicity, model of end-stage liver disease score, and platelets as predictors of meaningful changes in HRQoL. **RESULTS:** Between antiviral therapy baseline and the end of the 24-week post-treatment follow-up, declines in HRQoL were smaller in eltrombopag-treated patients than in placebo-treated patients, but the differences were not statistically significant. Mean changes among patients achieving SVR and EVR were small in comparison to thresholds of minimally important changes. Logistic models did not confirm the strength of the 5 clinical factors as predictors of meaningful changes in HRQoL during antiviral therapy, with the exception of the interaction between SVR and EVR ($P = 0.0009$). Asian ethnicity had a consistent effect on HRQoL, with East Asian patients being more likely to experience deterioration in HRQoL compared with white and/or other non-East Asian patients. **CONCLUSIONS:** While on active antiviral therapy, declines in HRQoL were not statistically different for eltrombopag-treated patients versus placebo-treated patients, suggesting that eltrombopag neither worsened HRQoL nor mitigated the effects of antiviral therapy on HRQoL.

[Impact of depressive symptoms and hepatic encephalopathy on health-related quality of life in cirrhotic hepatitis C patients.](#) Barboza KC1, Salinas LM2, Sahebjam F2, Jesudian AB3, Weisberg IL4, Sigal SH2. *Metab Brain Dis.* 2016 Mar 31. [Epub ahead of print]

Depression, common in chronic medical conditions, and hepatic encephalopathy (HE), a reversible neuropsychiatric syndrome due to liver dysfunction, are associated with impaired health-related quality of life (HRQOL) in cirrhosis and hepatitis C (HCV). This study investigated the impact of depression and HE on HRQOL in cirrhotic patients with HCV. A convenience sample of 43 ambulatory patients, with varying degrees of cirrhosis secondary to HCV, was prospectively enrolled in this study. Participants were assessed for any current depressive, fatigue, and daytime sleepiness symptoms and underwent a psychometric evaluation to determine the presence of HE symptoms. Participants reported current HRQOL on general health and liver disease-specific questionnaires. Diagnosis and current health status were confirmed via medical records. The associations between disease severity, depressive symptoms, HE, fatigue, and daytime sleepiness were measured. Predictors of HRQOL in this sample were determined. Depressive symptoms (70 %) and HE (77 %) were highly prevalent in this sample, with 58 % actively experiencing both conditions at the time of study participation. A significant positive association was found between depressive symptoms and HE severity ($P = .05$). Depressive symptoms were significantly associated with fatigue ($P < .001$), daytime sleepiness

($P < .001$), general HRQOL ($P < .001$), and disease-specific HRQOL ($P < .001$). HE was significantly associated with fatigue ($P = .02$), general HRQOL ($P < .001$), and disease-specific HRQOL ($P < .001$). Depressive symptoms and HE were significant predictors of reduced HRQOL ($P < .001$), with depressive symptoms alone accounting for 58.8 % of the variance. Depressive symptoms and HE accounted for 68.0 % of the variance. Findings suggest a possible pathophysiological link between depression and HE in cirrhosis, and potentially a wider-reaching benefit of treating minimal and overt HE than previously appreciated.

[Treatment of chronic hepatitis C in patients with cirrhosis.](#) Chen T1, Terrault N. *Curr Opin Gastroenterol.* 2016 Mar 28. [Epub ahead of print]

PURPOSE OF REVIEW: This article reviews treatment options of the approved and soon-to-be approved direct-acting antivirals (DAA)-based therapies in individuals with hepatitis C virus (HCV) cirrhosis. **RECENT FINDINGS:** DAA-based therapies have been shown to be well tolerated and effective in achieving viral cure in individuals with compensated and decompensated cirrhosis. Preliminary studies suggest that viral eradication arrests fibrosis progression and could lead to fibrosis regression. Long-term benefits of successful HCV treatment in this population translate into less frequent hepatic decompensation and hepatocellular carcinoma development, improvements in liver disease severity, reduction of liver-related mortality, and potential obviation of the need for transplantation. The optimization of viral eradication rates requires longer duration therapy and/or more complex combinations of drugs, including ribavirin. Treatment decisions are guided by HCV genotype, renal function, drug-drug interactions, and the severity of cirrhosis. Safety concerns are paramount in individuals with advanced liver disease and continued vigilance for hepatotoxicity and other complications is warranted, especially in those with decompensated cirrhosis. **SUMMARY:** The availability of high potency DAA-based therapies with excellent safety profiles has transformed the HCV-infected cirrhotic population into a group that is no longer 'difficult-to-treat'. Understanding the pretreatment factors that predict clinical benefits vs. harm remains key in treating this population.

[Presence of hepatitis C \(HCV\) infection in Baby Boomers with Medicare is independently associated with mortality and resource utilisation.](#) Sayiner M1, Wymer M1, Golabi P1, Ford J2, Srishord I1, Younossi ZM1,2. *Aliment Pharmacol Ther.* 2016 Mar 15. doi: 10.1111/apt.13592. [Epub ahead of print]

BACKGROUND: Hepatitis C virus is common among Baby Boomers (BB). As this cohort ages, they will increasingly become Medicare eligible. **AIM:** To evaluate resource utilisation and mortality of BB-Medicare recipients with HCV. **METHODS:** We used in-patient and out-patient Medicare databases (2005-2010). HCV was identified using ICD-9 codes. Outcomes included resource utilisation [payment/case and in-patient length of stay (LOS)] and short-term mortality. **RESULTS:** Of 1 153 862 BB Medicare recipients (2005-2010), 3.2% ($N = 37\ 365$) had HCV. During this period, in-patient Medicare-BB (39 793-55 235) and their claims (78 924-106 232) increased. Furthermore, their overall mortality increased from 8.94% to 10.25% ($P < 0.0001$). In multivariate analysis, HCV [OR = 1.23 (1.16-1.29)], older age [OR = 1.98 (1.82-2.14)], male gender [OR = 1.25 (1.22-1.29)], ESRD [OR = 1.31 (1.26-1.36)], Charlson score [OR = 1.41 (1.40-1.42)] and LOS [OR = 1.02 (1.02-1.02)] predicted mortality. LOS decreased from 12.98 to 11.74 days ($P < 0.0001$), whereas total payments increased from \$22 157 to \$23 185 ($P < .0001$). During the study, the number of out-patient Medicare BB patients (123 097-192 110) and claims

(863 978-1 340 260) also increased. Furthermore, overall mortality increased from 3.15% to 3.31% (P = 0.0131). Again, HCV [OR = 1.23 (1.16-1.30)], older age [OR = 2.03 (1.89-2.17)], ESRD [OR = 3.40 (3.28-3.51)], disabled status [OR = 1.49 (1.40-1.58)] and Charlson score [OR = 1.39 (1.38-1.40)] predicted mortality. Annual total out-patient payments increased from \$3781 to \$4001 (P < 0.0001). HCV [36.04% [34.28-37.82%]], 45-49 age [4.21% (3.14-5.28%)], ESRD [966.31% (954.86-977.88%)], disabled status [43.22% (41.67-44.80%)], Charlson score [46.78% (46.31-47.26%)] and study year [2.72% (2.58-2.85%)] independently predicted increases in payments. **CONCLUSIONS:** In BB Medicare recipients, diagnosis of HCV is independently associated with higher mortality and resource utilisation.

[Access to Subspecialty Care And Survival Among Patients With Liver Disease.](#)

Mellinger JL1, Moser S2,3, Welsh DE2,3, et al. Am J Gastroenterol. 2016 Mar 29. doi: 10.1038/ajg.2016.96. [Epub ahead of print]

OBJECTIVES: Access to subspecialty care may be difficult for patients with liver disease, but it is unknown whether access influences outcomes among this population. Our objectives were to determine rates and predictors of access to ambulatory gastrointestinal (GI) subspecialty care for patients with liver disease and to determine whether access to subspecialty GI care is associated with better survival. **METHODS:** We studied 28,861 patients within the Veterans Administration VISN 11 Liver Disease cohort who had an ICD-9-CM diagnosis code for liver disease from 1 January 2000 through 30 May 2011. Access was defined as a completed outpatient clinic visit with a gastroenterologist or hepatologist at any time after diagnosis. Multivariable logistic regression was used to determine predictors of access to a GI subspecialist. Survival curves were compared between those who did and those who did not see a specialist, with propensity score adjustment to account for other covariates that may affect access. **RESULTS:** Overall, 10,710 patients (37%) had a completed GI visit. On multivariable regression, older patients (odds ratio (OR) 0.98, P<0.001), those with more comorbidities (OR 0.98, P=0.01), and those living farther from a tertiary-care center (OR 0.998/mi, P<0.001) were less likely to be seen in clinic. Patients who were more likely to be seen included those who had hepatitis C (OR 1.5, P<0.001) or cirrhosis (OR 3.5, P<0.001) diagnoses prior to their initial visit. Patients with an ambulatory GI visit at any time after diagnosis were less likely to die at 5 years when compared with propensity-score-matched controls (hazard ratio 0.81, P<0.001). **CONCLUSIONS:** Access to ambulatory GI care was associated with improved 5-year survival for patients with liver disease. Innovative care coordination techniques may prove beneficial in extending access to care to liver disease patients.

[Primary Care Physician Perspectives on Hepatitis C Management in the Era of Direct-Acting Antiviral Therapy.](#)

Thomson M1, Konerman MA2, Choxi H3, Lok AS4. Dig Dis Sci. 2016 Mar 8. [Epub ahead of print]

BACKGROUND: Primary care physicians (PCPs) play a critical role in the care cascade for patients with chronic hepatitis C (CHC). **AIM:** To assess PCP knowledge and perspectives on CHC screening, diagnosis, referral, and treatment. **METHODS:** An anonymous survey was distributed to PCPs who participated in routine outpatient care at our hospital. **RESULTS:** Eighty (36 %) eligible PCPs completed the survey. More than half were females (60 %) aged 36-50 (55 %) from family (44 %) or internal (49 %) medicine. Overall, PCPs correctly identified high-risk populations for screening, though 19 % failed to identify baby boomers and 45 % failed to identify hemodialysis patients as populations to screen. Approximately half reported they were

able to screen at risk patients <50 % of the time secondary to time constraints and difficulty assessing if patients had already been screened. 71 % of PCPs reported they refer all newly diagnosed patients to specialty care. 70 % of PCPs did not feel up to date with current treatment. The majority grossly underestimated efficacy, tolerability and ease of administration, and overestimated treatment duration. Only 9 % felt comfortable treating CHC, even those without cirrhosis. Practice patterns were influenced by specialty and Veterans Affairs Hospital affiliation. **CONCLUSIONS:** Although the majority of PCPs are up to date with CHC screening recommendations, few are able to routinely screen in practice. Most PCPs are not up to date with treatment and do not feel comfortable treating CHC. Interventions to overcome screening barriers and expand treatment into primary care settings are needed to maximize access to and use of curative therapies.

Chronic Hepatitis C: Treatment, Complications, and Long-term Outcomes in a Population of Latino Veterans. Santiago-Rolón A1, Purcell D1, Grigg N1, Toro DH1. P R Health Sci J. 2016 Mar;35(1):30-4.

OBJECTIVE: Chronic hepatitis C (CHC) is a major public health problem in Puerto Rico. It is the most common cause of chronic liver disease and the most frequent indication for liver transplantation in the United States. Our main objectives were to estimate the seroprevalence of CHC infection, to describe the demographic and histological parameters of the infection in our sample population, and to evaluate the treatment outcomes in Puerto Rican veterans.

METHODS: To determine overall seroprevalence, we reviewed all the hepatitis C cases (encompassing from January 1, 2002, to December 31, 2009) of the VA Caribbean Healthcare System, Department of Veterans Affairs. The records of only those individuals who received treatment with pegylated interferon and ribavirin were reviewed to determine risks factors for infection, response rates, adverse events, and outcomes. **RESULTS:** During the study period, there were a total of 1,496 patients identified as being infected with HCV, for an estimated seroprevalence of 2.3%. Of these, approximately 10% (137) were treated with combination therapy and were included in this study. The mean age was 58 (± 6.4); 96.4% were men. The most common genotype was type 1. The responses to treatment were generally poor, with only 48.4% of the patients achieving sustained virological response. **DISCUSSION:** Though the seroprevalence of chronic hepatitis C in the Latino veteran population of Puerto Rico is high, relatively few patients have received treatment, most probably because of the contraindications of the medications used. Combination therapy with pegylated interferon plus weight-based ribavirin was inefficient and plagued with side effects; as a whole, this therapy was not found to be overly beneficial to our patients. New emerging and approved therapies will change this paradigm, allowing the treatment of a larger population without the side effects of the studied therapy.

Hepatitis C and sex. Page EE1, Nelson M2. Clin Med (Lond). 2016 Apr;16(2):189-92. doi: 10.7861/clinmedicine.16-2-189.

An outbreak of acute hepatitis C among HIV-positive men who have sex with men (MSM) in the last decade has been shown to be sexually transmitted. Initially recreational drug use, in particular drug injection, was not prevalent among those becoming infected with hepatitis C. However more recently chemsex (the use of drugs to enhance sexual experience) and its associated drugs, which are not uncommonly injected, have become more frequently reported among those diagnosed with hepatitis C. It is hoped that the widespread -introduction of direct-

acting antivirals and upscaling of numbers treated may have a positive impact on this epidemic. However their introduction may negatively impact on the perceived risk of acquiring hepatitis C and in conjunction with the introduction of HIV transmission prevention strategies may result in increased transmissions and spread to the HIV-negative MSM population.

Long-term Follow-up of Children Treated With Peginterferon and Ribavirin for Hepatitis C Virus Infection. Haber B1, Alonso E, Pedreira A, et al. J Pediatr Gastroenterol Nutr. 2016 Apr 21. [Epub ahead of print]

OBJECTIVES: To describe the 5-year follow-up of children who received peginterferon and ribavirin in a global, open-label study. **METHODS:** A 5-year follow-up study of 107 children and adolescents aged 3-17 years with chronic hepatitis C virus infection who received peginterferon and ribavirin for 24 or 48 weeks. No drugs were administered during follow-up. **RESULTS:** Ninety-four patients were enrolled in the long-term follow-up portion of the study; the median duration of follow-up was 287 weeks (range, 73-339). Of 63 patients with sustained virologic response who were enrolled, 54 completed 5 years of follow-up; none had relapse in the 5-year follow-up period. Significant decreases in height z scores were observed during treatment. The impact of treatment on height z score was larger in patients treated for 48 weeks compared with those treated for 24 weeks (mean change from baseline to the end of treatment was -0.13 (p<.001) and -0.44 (p<.001) in the 24-week and 48-week treatment groups, respectively). Among patients treated for 24 weeks, full recovery of height z scores to baseline was observed by year 1 of follow-up, whereas only partial recovery was observed during 5 years of follow up in patients treated for 48 weeks (mean change from baseline to the final follow-up visit was -0.16 (p=NS) and -0.32 (p<.05) in the 24-week and 48-week treatment groups, respectively). Similar patterns were observed for weight and body mass index z scores. **CONCLUSIONS:** Impairment of growth should be considered when assessing the risk-benefit profile of peginterferon/ribavirin therapy in children with hepatitis C virus infection. In deciding to treat children with chronic hepatitis C virus, considerations should include both deferring treatment in patients during optimal growth periods, and the possibility that interferon-free regimens may be available to children in the next 5-10 years.

Prevention knowledge, risk behaviours and seroprevalence among nonurban injectors of southwest Connecticut. Grau LE1, Zhan W1,2, Heimer R1. Drug Alcohol Rev. 2016 Apr 13. doi: 10.1111/dar.12396. [Epub ahead of print]

INTRODUCTION AND AIMS: Little is known about injection-associated risk behaviours, knowledge and seroprevalence of viral infections among people who inject drugs (PWID) in nonurban locales in the US. Harm reduction services are more available in urban locales. The present study examined a cohort of active PWID residing in non urban areas of Connecticut to investigate how primarily injecting in urban or non urban areas was associated with injection-associated risk behaviours, knowledge and prevalence of blood-borne viruses. **DESIGN AND METHODS:** We described the sample and performed bivariate and multivariable analyses on injection-associated risk behaviours, HIV/hepatitis/overdose knowledge and baseline serological data to identify differences between individuals who injected primarily in nonurban locales and those who did not. **RESULTS:** Harm reduction knowledge and use of harm reduction services were poor in both groups. Those injecting most often in urban settings were 1.88 (1.19, 2.98 95% confidence interval) times more likely to engage in at least one injection-associated risk

behaviour than their nonurban counterpart. Seroprevalence rates (23.6% for hepatitis B virus, 39.2% for hepatitis C virus, and 1.1% for HIV) were no different between the two groups.

DISCUSSION AND CONCLUSIONS: The data provided little evidence that the benefits of urban harm reduction programs, such as syringe exchange, risk reduction interventions and education programs have penetrated into this nonurban population, even among those who injected in urban locales where such programs exist. Harm reduction interventions for nonurban communities of PWID are needed to reduce HIV and hepatitis B and C transmission. [Grau LB, Zhan W, Heimer R. Prevention knowledge, risk behaviours and seroprevalence among nonurban injectors of southwest Connecticut. *Drug Alcohol Rev* 2016;00:000-000].

[Hepatitis C Virus Infection Is Positively Associated with Gallstones in Liver Cirrhosis.](#)

Zhang FM1, Chen LH, Chen HT, et al. *Digestion*. 2016 Apr 19;93(3):221-228. [Epub ahead of print]

AIM: To elucidate the prevalence and risk factors of gallstone disease (GD) among patients with liver disease and explore their association with the aetiology and severity of hepatic injury.

METHODS: We analysed 4,832 subjects of hepatic injury induced by one of the following aetiologies: hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, excessive alcohol consumption. The risk factors significantly associated with GD were analysed using stepwise logistic regression analysis, the influence of aetiology and severity of liver disease on the prevalence of GD were assessed by multiple logistic regression analysis adjusting for confounding factors. **RESULTS:** Three thousand forty eight patients were of positive HBV surface antigen alone with a prevalence of GD of 18.6%, 526 were tested as positive Anti-HCV alone with a prevalence of GD of 22.4%, and 1,258 were identified with excessive alcohol consumption patterns with a prevalence of GD of 13.5%. In each aetiological category, the prevalence of GD increased by age. Stepwise logistic regression analysis showed that age, female, low-density lipoprotein-cholesterol (LDL-Cho), family history of GD, HBV infection, HCV infection, chronic hepatitis and cirrhosis were independent associated with HCV-related cirrhosis in both genders, HBV-related cirrhosis in males and alcohol-related cirrhosis in females compared with patients with less severe liver disease. After adjusting for gender, age, LDL-Cho and family history of GD, patients with HCV-related cirrhosis (OR 2.66, 95% CI 1.49-3.84) but not HBV-related cirrhosis (OR 1.52, 95% CI 0.73-1.82) were more likely to have GD compared with alcohol-related cirrhosis. **CONCLUSION:** HCV infection is positively associated with gallstone formation especially in those with cirrhosis patients.

[No Differences in Achieving Hepatitis C Virus Care Milestones Between Patients Identified by Birth Cohort vs Risk-based Screening.](#)

Norton B1, Southern WN2, Steinman M3, et al. *Clin Gastroenterol Hepatol*. 2016 Apr 19. pii: S1542-3565(16)30078-7. doi: 10.1016/j.cgh.2016.04.017. [Epub ahead of print]

National hepatitis C virus (HCV) screening guidelines recommended 1-time testing of persons born between 1945 and 1965. We performed a retrospective study to compare care milestones achieved by HCV-infected patients identified by birth cohort vs risk-based screens. We determined the proportions of patients newly identified with HCV infection who met care milestones (viral load, referral to and evaluation by a specialist, offer of treatment, initiation of treatment, and sustained viral response) and the time it took to reach them. We found no differences in HCV care milestones for patients identified via birth cohort testing vs risk-based screening. Overall, only 43% of HCV antibody-positive patients were referred to care, and less

than 4% started treatment. The time to each care milestone was lengthy and varied greatly; treatment was initiated in a median of 308 days. Although birth cohort testing will likely increase identification of patients with HCV infection, it does not appear to increase the number of patients that meet management milestones. New methods are needed to increase access to care and establish efficient models of health care delivery.

[Extension for Community Health Outcomes-hepatitis C: Small steps carve big footprints in the allocation of scarce resources for hepatitis C virus treatment to remote developing areas.](#) Tahan V1, Almashhrawi A1, Kahveci AM1, Mutrux R1, Ibdah JA1. World J Hepatol. 2016 Apr 18;8(11):509-12. doi: 10.4254/wjh.v8.i11.509.

Hepatitis C virus (HCV) infection is still a major health problem throughout the world. HCV patients living in rural areas are less fortunate than their counterparts residing in populous urbanized regions. The lack of medical resources and properly trained medical personnel in rural regions make it especially burdensome for HCV patients seeking treatment. Dr. Sanjeev Arora at the University of New Mexico Health Sciences Center took initiative to resolve the issue at hand by developing a model named Project Extension for Community Health Outcomes (ECHO). ECHO connects primary care providers (PCPs), usually family medicine physicians, in local communities with specialists. ECHO providers test the efficacy of treatment given using the ECHO model vs that at academic medical centers. The ECHO model has produced promising results such that the sustained virologic response rates for both types of sites were near-equivalent. Show Me ECHO was adapted from Project ECHO to train PCPs in Missouri and equip them with the tools and skills to properly treat and diagnose HCV in a timely manner. This healthcare model can be implemented for treating other common infections and chronic diseases. Telemedicine is the direction healthcare is headed for the next several decades. It has potential to be applied in developing countries to alleviate agony and despair resulting from limited resources and lack of access to expert medical care.

[Emerging Biological Agents For Hepatitis C.](#) Zuccaro V1, Columpsi P1, Apollinari A1, et al. Expert Opin Emerg Drugs. 2016 Apr 28. [Epub ahead of print]

INTRODUCTION:

New direct-acting antiviral agents have changed the landscape of treatment of chronic HCV infection. Despite current treatments are well tolerated with a high rate of sustained virological response (SVR), some medical needs remain. Nowadays there are a large number of approved medications for the treatment of HCV infection; nevertheless, new studies are conducted to find new agents and new combinations. Areas covered: A literature research of new antiviral compounds indicated for the treatment of HCV infection was achieved by an online search of medication undergoing development on Pubmed and clinicalTrials.gov clinical trials registry. We considered phase I/II studies and some randomized Phase III trials. Expert opinion: More knowledge about impact of HCV eradication on disease progression and more confidence regarding drug-drug interaction are needed. Furthermore, each treatment should be individualized targeting the patients needs with the aim not only to obtain viral suppression but also to stop progression of liver disease and HCV related conditions, and to improve patient health status.

Early detection of hepatocellular carcinoma co-occurring with hepatitis C virus infection: A mathematical model. Zekri AR1, Youssef AS1, Bakr YM1, et al. World J Gastroenterol. 2016 Apr 28;22(16):4168-82. doi: 10.3748/wjg.v22.i16.4168.

AIM: To develop a mathematical model for the early detection of hepatocellular carcinoma (HCC) with a panel of serum proteins in combination with α -fetoprotein (AFP). **METHODS:** Serum levels of interleukin (IL)-8, soluble intercellular adhesion molecule-1 (sICAM-1), soluble tumor necrosis factor receptor II (sTNF-RII), proteasome, and β -catenin were measured in 479 subjects categorized into four groups: (1) HCC concurrent with hepatitis C virus (HCV) infection (n = 192); (2) HCV related liver cirrhosis (LC) (n = 96); (3) Chronic hepatitis C (CHC) (n = 96); and (4) Healthy controls (n = 95). The R package and different modules for binary and multi-class classifiers based on generalized linear models were used to model the data. Predictive power was used to evaluate the performance of the model. Receiver operating characteristic curve analysis over pairs of groups was used to identify the best cutoffs differentiating the different groups. **RESULTS:** We revealed mathematical models, based on a binary classifier, made up of a unique panel of serum proteins that improved the individual performance of AFP in discriminating HCC patients from patients with chronic liver disease either with or without cirrhosis. We discriminated the HCC group from the cirrhotic liver group using a mathematical model $(-11.3 + 7.38 \times \text{Prot} + 0.00108 \times \text{sICAM} + 0.2574 \times \beta\text{-catenin} + 0.01597 \times \text{AFP})$ with a cutoff of 0.6552, which achieved 98.8% specificity and 89.1% sensitivity. For the discrimination of the HCC group from the CHC group, we used a mathematical model $[-10.40 + 1.416 \times \text{proteasome} + 0.002024 \times \text{IL} + 0.004096 \times \text{sICAM-1} + (4.251 \times 10^{-4}) \times \text{sTNF} + 0.02567 \times \beta\text{-catenin} + 0.02442 \times \text{AFP}]$ with a cutoff 0.744 and achieved 96.8% specificity and 89.7% sensitivity. Additionally, we derived an algorithm, based on a binary classifier, for resolving the multi-class classification problem by using three successive mathematical model predictions of liver disease status. **CONCLUSION:** Our proposed mathematical model may be a useful method for the early detection of different statuses of liver disease co-occurring with HCV infection.

Disparities in Hepatitis C Testing in U.S. Veterans Born 1945-1965. Sarkar S1, Esserman DA2, Skanderson M3, Levin FL4, Justice AC5, Lim JK6. J Hepatol. 2016 Apr 26. pii: S0168-8278(16)30144-1. doi: 10.1016/j.jhep.2016.04.012. [Epub ahead of print]

BACKGROUND/AIMS: Universal one-time antibody testing for hepatitis C virus (HCV) infection has been recommended by the Centers for Disease Control (CDC) and the United States Preventive Services Task Force (USPSTF) for Americans born 1945-1965 (birth cohort). Limited data exists addressing national HCV testing practices. We studied patterns and predictors of HCV testing across the U.S. within the birth cohort utilizing data from the national corporate data warehouse (CDW) of the U.S. Veterans Administration (VA) health system.

METHOD: Testing was defined as any HCV test including antibody, RNA or genotype performed during 2000-2013. **RESULT:** Of 6,669,388 birth cohort veterans, 4,221,135 (63%) received care within the VA from 2000-2013 with two or more visits. Of this group, 2,139,935 (51%) had HCV testing with 8.1% HCV antibody and 5.4% RNA positive. Significant variation in testing was observed across centers (Range: 7-83%). Older, male, African-Americans, with established risk factors and receiving care from urban centers of excellence were more likely to be tested. Among veterans free of other established risk factors (HIV negative, HBV negative, $\text{ALT} \leq 40 \text{ U/L}$, $\text{FIB-4} \leq 1.45$, or $\text{APRI} < 0.5$), HCV antibody and RNA were positive in 2.8% and 0.9%, respectively, comparable to established national average. At least 2.4-4.4% of veterans had

scores suggesting advanced fibrosis (APRI \geq 1.5 or FIB-4 $>$ 3.25) with >30-43% having positive HCV RNA but >16-20% yet to undergo testing for HCV. **CONCLUSION:** Significant disparities are observed in HCV testing within the U.S. VA health system. Examination of the predictors of testing and HCV positivity may help inform national screening policies. **LAY SUMMARY:** Analysis of United States Veterans Administration data show significant disparities in Hepatitis C Virus (HCV) testing of veterans born 1945-1965 (birth cohort). A fifth of those not tested had evidence of advanced liver fibrosis. Our data suggests some predictors for this disparity and will potentially help inform future policy measures in the era of universal birth cohort testing for HCV.

Barriers to access to hepatitis C treatment. Yilmaz H1, Yilmaz EM, Leblebicioglu H. J Infect Dev Ctries. 2016 Apr 28;10(4):308-16. doi: 10.3855/jidc.7849.

Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. Only 1%-30% of patients in need of treatment may get it. In recent years, the availability of direct-acting antiviral agents (DAA) has been an important advancement in treating HCV infection. However, due to cost, it is not possible to receive these drugs in many countries where infection is endemic. In these low- and middle-income countries, the main barriers to controlling HCV infection are lack of knowledge about the infection, constraints on diagnostic testing and treatment, and lack of experts. Both national and international support are essential to overcoming these barriers. In low- and middle-income countries, interferon and ribavirin-based therapies still are the first choices due to their availability and to government payment support. In addition, in developed countries, efforts to provide lower-cost DAA drugs continue. Pharmaceutical companies continue to research manufacture of bio-equivalent drugs to reduce treatment costs. Considering the fake drug market, all developments need to be monitored closely by the institutions involved. This review focuses on barriers to hepatitis C treatment and ways to overcome those barriers.

Hepatitis C testing in substance use disorder treatment: the role of program managers in adoption of testing services. Frimpong JA1, D'Aunno T2. Subst Abuse Treat Prev Policy. 2016 Apr 1;11:13. doi: 10.1186/s13011-016-0057-2.

BACKGROUND: Health care organizations do not adopt best practices as often or quickly as they merit. This gap in the integration of best practices into routine practice remains a significant public health concern. The role of program managers in the adoption of best practices has seldom been investigated. **METHODS:** We investigated the association between characteristics of program managers and the adoption of hepatitis C virus (HCV) testing services in opioid treatment programs (OTPs). Data came from the 2005 (n = 187) and 2011 (n = 196) National Drug Abuse Treatment System Survey (NDATSS). We used multivariate regression models to examine correlates of the adoption of HCV testing. We included covariates describing program manager characteristics, such as their race/ethnicity, education, and their sources of information about developments in the field of substance use disorder treatment. We also controlled for characteristics of OTPs and the client populations they serve. **RESULTS:** Program managers were predominantly white and female. A large proportion of program managers had post-graduate education. Program managers expressed strong support for preventive services, but they reported making limited use of available sources of information about developments in the field of substance use disorder (SUD) treatment. The provision of any HCV testing (either on-site or off-site) in OTPs was positively associated with the extent to which a program manager was supportive of preventive services. Among OTPs offering any HCV testing to their clients, on-site

HCV testing was more common among programs with an African American manager. It was also more common when program managers relied on a variety of information sources about developments in SUD treatment. **CONCLUSIONS:** Various characteristics of program managers are associated with the adoption of HCV testing in OTPs. Promoting diversity among program managers, and increasing managers' access to information about developments in SUD treatment, may help foster the adoption of best practices.

[A Follow-Up Study of 50 Chronic Hepatitis C Patients: Adiponectin as a Resilience Biomarker for Major Depression.](#) Fábregas BC1, Vieira ÉL, Moura AS, et al.

Neuroimmunomodulation. 2016 Apr 2. [Epub ahead of print]

OBJECTIVE: Major depression (MD) is a condition associated with both hepatitis C virus (HCV) infection and pegylated interferon (IFN)- α treatment. IFN induces a depressive syndrome that is associated with an inflammatory profile. We aimed to investigate whether there is any specific alteration in plasma biomarkers associated with MD. **METHODS:** HCV-monoinfected patients, with and without IFN treatment, were followed up for 18 months and went through structured psychiatric evaluation. We assessed plasma levels of brain-derived neurotrophic factor, tumor necrosis factor (TNF) and its soluble type 1 and type 2 receptors (sTNFR1 and sTNFR2, respectively), and adipokines (adiponectin, leptin and resistin) using ELISA.

RESULTS: Among the 50 patients included in the study, 14 were treated with IFN during the follow-up. Being older, not married, presenting higher body mass index, higher liver inflammatory activity, lower baseline adiponectin levels and use of IFN were associated with MD development. Higher levels of sTNFR1 during IFN treatment were associated with sustained virological response. The lack of a control group without HCV infection did not allow any assumption of a biomarker change exclusively due to the infection itself. **CONCLUSION:** Adiponectin may be a resilience biomarker for MD in HCV-infected patients.

[Genotype 1 hepatitis C virus and the pharmacist's role in treatment.](#) Sebhatu P1, Martin MT2. Am J Health Syst Pharm. 2016 Apr 28. pii: ajhp150704. [Epub ahead of print]

PURPOSE: The treatment of hepatitis C virus (HCV) genotype 1 has changed rapidly with recently approved direct-acting antiviral (DAA) regimens. The role of the pharmacist in the management of HCV therapy has increased. **SUMMARY:** Chronic HCV infection is the main cause of end-stage liver disease and the primary reason for liver transplantation, liver-related death, and hepatocellular carcinoma in the United States. The recent approval of several DAAs has led to improved tolerability, sustained virological response (SVR) rates, and shorter treatment durations compared with treatment with pegylated interferon and ribavirin. Most HCV cases can be treated with the currently available regimens, and expected SVR rates exceed 90%. Several fixed-dose and pangenotypic antiviral regimens are currently in various phases of clinical trials. Pharmacists are well equipped to assist the medical team and patients with comprehensive management of HCV treatment. Pharmacists in various settings can play an instrumental role in access to HCV medications, selection of HCV treatment, detection of drug-drug interactions, and education of patients about potential adverse effects and the importance of adherence and laboratory test monitoring during HCV treatment. However, the high cost of HCV treatment poses challenges for ubiquitous treatment. **CONCLUSION:** Available DAA regimens have improved HCV treatment outcomes and are selected based on efficacy, potential drug interactions, and the patient's ability to obtain medication coverage. Each of these factors provides an opportunity for pharmacist involvement in HCV management.

[Chronic Hepatitis B Is Associated with Higher Inpatient Resource Utilization and Mortality Versus Chronic Hepatitis C.](#)

Cholankeril G1, Perumpail RB2, Hu M3, Skowron G4, Younossi ZM5,6, Ahmed A7. *Dig Dis Sci.* 2016 Apr 15. [Epub ahead of print]

BACKGROUND: Chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections remain one of the leading causes of chronic liver disease and hepatocellular carcinoma. Healthcare initiatives for chronic viral hepatitis to facilitate early diagnosis and linkage to care in an effort to reduce inpatient resource utilization associated with late diagnosis and end-stage liver disease have been partially successful. **AIMS:** Our objective was to determine the impact of liver-related complications from chronic HBV and HCV infections on inpatient cost of care, length of stay, and mortality. **METHODS:** Using the Healthcare Cost and Utilization Project, National Inpatient Sample (HCUP-NIS), we studied the impact of chronic HBV and HCV infections on inpatient healthcare system following hospitalizations from 2003 to 2012. **RESULTS:** Of the 79,185,729 million hospitalizations among adult patients in the USA from 2003 to 2012, 143,896 (0.18 %) hospitalizations were HBV related and 1,073,269 (1.36 %) hospitalizations HCV related. HBV hospitalizations had a higher inpatient mortality (OR 1.34; 95 % CI 1.30, 1.38), median cost of care per hospitalization (+\$2100.33; 95 % CI 1982.53, 2217.53), and increased length of hospitalization stay (+0.64 days; 95 % CI 0.60, 0.68; $p < 0.01$) compared to HCV. **CONCLUSIONS:** Despite higher per case resource utilization following hospitalization, HBV-infected patients demonstrate a lower inpatient survival in comparison with chronic HCV infection. These disparate observations underscore the need for early diagnosis of chronic HBV infection in at-risk population and prompt linkage to care.

[The Hepatitis Viral Status in Patients With Hepatocellular Carcinoma: a Study of 3843 Patients From Taiwan Liver Cancer Network.](#)

Chang IC1, Huang SF, Chen PJ, et al. *Medicine (Baltimore).* 2016 Apr;95(15):e3284. doi: 10.1097/MD.00000000000003284.

Hepatocellular carcinoma (HCC) is the leading cancer death in Taiwan. Chronic viral hepatitis infections have long been considered as the most important risk factors for HCC in Taiwan. The previously published reports were either carried out by individual investigators with small patient numbers or by large endemic studies with limited viral marker data. Through collaboration with 5 medical centers across Taiwan, Taiwan liver cancer network (TLCN) was established in 2005. All participating centers followed a standard protocol to recruit liver cancer patients along with their biosamples and clinical data. In addition, detailed viral marker analysis for hepatitis B virus (HBV) and hepatitis C virus (HCV) were also performed. This study included 3843 HCC patients with available blood samples in TLCN (recruited from November 2005 to April 2011). There were 2153 (56.02%) patients associated with HBV (HBV group); 969 (25.21%) with HCV (HCV group); 310 (8.07%) with both HBV and HCV (HBV+HCV group); and 411 (10.69%) were negative for both HBV and HCV (non-B non-C group). Two hundred two of the 2463 HBV patients (8.20%) were HBsAg(-), but HBV DNA (+). The age, gender, cirrhosis, viral titers, and viral genotypes were all significantly different between the above 4 groups of patients. The median age of the HBV group was the youngest, and the cirrhotic rate was lowest in the non-B non-C group (only 25%). This is the largest detailed viral hepatitis marker study for HCC patients in the English literatures. Our study provided novel data on the interaction of HBV and HCV in the HCC patients and also confirmed that the HCC database of TLCN is highly representative for Taiwan and an important resource for HCC research.

Improved Survival Among all Interferon- α -Treated Patients in HCV-002, a Veterans Affairs Hepatitis C Cohort of 2211 Patients, Despite Increased Cirrhosis Among Nonresponders.

Cozen ML1, Ryan JC1, Shen H1, et al. Dig Dis Sci. 2016 Apr 8. [Epub ahead of print]

BACKGROUND: As the era of interferon-alpha (IFN)-based therapy for hepatitis C ends, long-term treatment outcomes are now being evaluated. **AIM:** To more fully understand the natural history of hepatitis C infection by following a multisite cohort of patients. **METHODS:** Patients with chronic HCV were prospectively enrolled in 1999-2000 from 11 VA medical centers and followed through retrospective medical record review. **RESULTS:** A total of 2211 patients were followed for an average of 8.5 years after enrollment. Thirty-one percent of patients received HCV antiviral therapy, 15 % with standard IFN/ribavirin only, 16 % with pegylated IFN/ribavirin, and 26.7 % of treated patients achieved sustained virologic response (SVR). Cirrhosis developed in 25.8 % of patients. Treatment nonresponders had a greater than twofold increase in the hazard of cirrhosis and hepatocellular carcinoma, compared to untreated patients, whereas SVR patients were only marginally protected from cirrhosis. Nearly 6 % developed hepatocellular carcinoma, and 27.1 % died during the follow-up period. Treated patients, regardless of response, had a significant survival benefit compared to untreated patients (HR 0.58, CI 0.46-0.72). Improved survival was also associated with college education, younger age, lower levels of alcohol consumption, and longer duration of medical service follow-up-factors typically associated with treatment eligibility. **CONCLUSIONS:** As more hepatitis C patients are now being assessed for all-oral combination therapy, these results highlight that patient compliance and limiting harmful behaviors contribute a significant proportion of the survival benefit in treated patients and that the long-term clinical benefits of SVR may be less profound than previously reported.

Implementation of baby boomer hepatitis C screening and linking to care in gastroenterology practices: a multi-center pilot study. Younossi ZM1,2,3, LaLuna LL4, Santoro JJ5, et al. BMC Gastroenterol. 2016 Apr 4;16(1):45. doi: 10.1186/s12876-016-0438-z.

BACKGROUND: Estimates suggest that only 20 % of HCV-infected patients have been identified and <10 % treated. However, baby boomers (1945-1965) are identified as having a higher prevalence of HCV which has led the Centers for Disease Control and Prevention to make screening recommendations. The aim of this study was to implement the CDC's screening recommendations in the unique setting of gastroenterology practices in patients previously unscreened for HCV. **METHODS:** After obtaining patient informed consent, demographics, clinical and health-related quality of life (HRQOL) data were collected. A blood sample was screened for HCV antibody (HCV AB) using the OraQuick HCV Rapid Antibody Test. HCV AB-positive patients were tested for presence of HCV RNA and, if HCV RNA positive, patients underwent treatment discussions. **RESULTS:** We screened 2,000 individuals in 5 gastroenterology centers located close to large metropolitan areas on the East Coast (3 Northeast, 1 Mid-Atlantic and 1 Southeast). Of the screened population, 10 individuals (0.5 %) were HCV AB-positive. HCV RNA testing was performed in 90 % (9/10) of HCV AB-positive individuals. Of those, 44.4 % (4/9) were HCV RNA-positive, and all 4 (100 %) were linked to caregiver. Compared to HCV AB negative subjects, HCV AB-positive individuals tended to be black (20.0 vs. 5.2 %, $p = 0.09$) and reported significantly higher rates of depression: 60.0 vs. 21.5 %, $p = 0.009$. These individuals also reported a significantly lower HRQOL citing having more fatigue, poorer concentration, and a decreased level of energy ($p < 0.05$).

DISCUSSION: Although the prevalence of HCV AB-positive was low in previously unscreened subjects screened in the gastroenterology centers, the linkage to care was very high. The sample of patients used in this study may be biased, so further studies are needed to assess the effectiveness of the CDC screening recommendations.

[Epidemiology and outcomes of hepatitis C infection in elderly US Veterans.](#) El-Serag HB1,2, Kramer J1,3, Duan Z3, Kanwal F1,2. J Viral Hepat. 2016 Apr 3. doi: 10.1111/jvh.12533. [Epub ahead of print]

The chronic hepatitis C (CHC) cohort in the United States is getting older. Elderly patients with CHC may be at a high risk of cirrhosis and hepatocellular carcinoma (HCC), but also other nonhepatic comorbidities that negatively impact their likelihood of receiving or responding to antiviral treatment. There is little information on the clinical epidemiology or outcomes of CHC and its treatment in the elderly. We conducted a retrospective cohort study of 1 61 744 patients with a positive Hepatitis C virus RNA in the Veterans Health Administration Hepatitis C Clinical Case Registry to examine the association between age subgroups (20-49, 50-64, 65-85 years) and risk of cirrhosis, HCC or death using Cox proportional hazards models. We also examined the effect of treatment with a sustained viral response (SVR) on these outcomes in each age subgroup. The age distribution was 36.8% 20- to 49-year-olds, 57.6% 50- to 64-year-olds and 5.6% 65- to 85-year-olds (i.e. elderly). Risk of cirrhosis, HCC and death was significantly elevated in elderly patients [HR cirrhosis = 1.14 (1.00-1.29), HR HCC = 2.44 (1.99-2.99); HR death 2.09 (1.98-2.22)] compared with younger patients. The incidence of HCC was than 8.4 per 1000 PY in the elderly compared with 2.6 per 1000 PY and 5.7 per 1000 PY, among the 20-49 and 50-64 age groups, respectively. Elderly patients were significantly less likely to receive antiviral treatment (3.8% vs 14.8% and 19.1%, $P < 0.0001$), but among those who received treatment SVR was not different among the age groups (33.5% vs 33.2% and 32.1%). In an analysis limited to those who received treatment, SVR compared to treatment receipt with no SVR was associated with a reduction in risk of developing cirrhosis (HR = 0.34; 0.18-0.66) and HCC (HR = 0.60; 0.22-1.61) and all-cause mortality risk (HR = 0.52, 0.33-0.82). Elderly patients with CHC are more likely to develop HCC than younger patients but have traditionally received less antiviral treatment than younger patients. However, receipt of curative treatment is associated with a benefit in reducing cirrhosis, HCC and overall mortality, irrespective of age.

LIVER CANCER

[Hepatocellular Carcinoma Surveillance Among Cirrhotic Patients With Commercial Health Insurance.](#) Goldberg DS1, Valderrama A, Kamalakar R, Sansgiry SS, Babajanyan S, Lewis JD. J Clin Gastroenterol. 2016 Mar;50(3):258-65. doi: 10.1097/MCG.0000000000000411.

GOALS: To evaluate hepatocellular carcinoma (HCC) surveillance rates among commercially insured patients, and evaluate factors associated with compliance with surveillance recommendations. **BACKGROUND:** Most HCC occurs in patients with cirrhosis. American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines each recommend biannual HCC surveillance for cirrhotic patients to diagnose HCC at an early, curable stage. However, compliance with these guidelines in commercially insured patients is unknown. **STUDY:** We used the Truven Health Analytics databases from 2006 to 2010, using January 1, 2006 as the anchor date for evaluating outcomes. The primary outcome was continuous surveillance measure, defined as the proportion of time "up-to-date" with

surveillance (PTUDS), with the 6-month interval immediately following each ultrasound categorized as "up-to-date." **RESULTS:** During a median follow-up of 22.9 (interquartile range, 16.3 to 33.9) months among 8916 cirrhotic patients, the mean PTUDS was 0.34 (SD, 0.29), and the median was 0.31 (interquartile range, 0.03 to 0.52). These values increased only modestly with inclusion of serum alpha-fetoprotein testing, contrast-enhanced abdominal computed tomographic scans or magnetic resonance imagings, and/or extension of up-to-date time to 12 months. Being diagnosed by a nongastroenterology provider and increasing age were significantly associated with decreased HCC surveillance ($P<0.05$), whereas a history of a hepatic decompensation event, presence of any component of the metabolic syndrome, and diagnosis of hepatitis B or hepatitis C were significantly associated with increased surveillance ($P<0.05$). However, even among patients with the most favorable characteristics, surveillance rates remained low. **CONCLUSIONS:** HCC surveillance rates in commercially insured at-risk patients remain poor despite formalized guidelines, highlighting the need to develop interventions to improve surveillance rates.

[Interferon lambda and hepatitis C virus core protein polymorphisms associated with liver cancer.](#) Moreira JP1, Malta FM2, Diniz MA3, et al. *Virology*. 2016 Mar 29;493:136-141. doi: 10.1016/j.virol.2016.03.008. [Epub ahead of print]

BACKGROUND: Hepatitis C virus (HCV) infection is often persistent and gradually advances from chronic hepatitis to liver cirrhosis and hepatocellular carcinoma (HCC). Worldwide, hepatocellular carcinoma is the fifth most common neoplasm. **METHOD OF STUDY:** the Interferon lambda (IFNL) polymorphisms genotypes (rs8099917, rs12979860 and rs12980275) and the presence of mutations in HCV core protein were analyzed in 59 patients with HCC, and also in 50 cirrhotic patients (without HCC). **RESULTS:** the rs12980275-AG genotype was associated with HCC on age-adjusted analysis (OR 2.42, 95% CI 1.03-5.69, $P=0.043$). Core substitutions R70Q and L91M were mainly found in genotype 1b isolates. Furthermore, a borderline level of statistical significance association was found among the presence of amino acid Glutamine (Q) in the position 70 and IFNL3 genotype AG ($P=0.054$). **CONCLUSIONS:** the screening of these polymorphisms and functional studies would be useful in clinical practice for identifying groups at high risk of HCC development.

[Altered glycosylation, expression of serum haptoglobin and alpha-1-antitrypsin in chronic hepatitis C, hepatitis C induced liver cirrhosis and hepatocellular carcinoma patients.](#)

Mondal G1, Saroha A2, Bose PP3, Chatterjee BP4. *Glycoconj J*. 2016 Mar 31. [Epub ahead of print]

Liver cirrhosis with hepatitis C viral infection (HCV-LC) causes high risk to develop hepatocellular carcinoma (HCC). Besides diagnosis of liver cirrhosis by biochemical test, imaging techniques, assessment of structural liver damage by biopsy shows several disadvantages. Our aim was to monitor the changes in the expression level of serum proteins and their glycosylation pattern among chronic hepatitis C (HCV-CH), HCV-LC and HCC patients with respect to controls. 2D gel electrophoresis of HCV-CH, HCV-LC and HCC patients' sera showed several protein spots, which were identified by LC-MS. The change in the expression of two prominent protein spots, haptoglobin (Hp) and alpha 1-antitrypsin (AAT) was evaluated by western blot and ELISA. The changes in glycosylation pattern of these serum proteins were assayed using different lectins. Increased level of Hp and AAT was observed in HCV-LC and HCC patients' group whereas those were found to be present less in HCV-CH patient groups

with respect to control as determined by ELISA using monoclonal antibodies. Decreased level of sialylation in both Hp and AAT was observed in HCV-LC and HCV-CH patients' group whereas increased level of sialylation was observed in HCC patient groups by ELISA using Sambucus nigra agglutinin. On the other hand increased level of fucosylation in two serum glycoproteins was observed in HCV-LC and HCC patients' group using Lens culinaris agglutinin. High glycan branching was found in HCV-LC and HCC patient groups in Hp but not in HCV-CH as determined by Datura stramonium agglutinin. However, there was no such change observed in glycan branching in AAT of HCV-CH and HCV-LC patients' groups, to the contrary high glycan branching was observed in HCC patients' group. Increased level of exposed galactose in both serum proteins was observed in both HCC patients' group as determined by Ricinus communis agglutinin. The present glycoproteomics study could predict the progression of HCV-CH, HCV-LC and HCC without the need of liver biopsy.

Epidermal Growth Factor Receptor-Dependent Mutual Amplification between Netrin-1 and the Hepatitis C Virus.

Plissonnier ML1, Lahlali T1, Michelet M1, et al. PLoS Biol. 2016 Mar 31;14(3):e1002421. doi: 10.1371/journal.pbio.1002421. eCollection 2016.

Hepatitis C virus (HCV) is an oncogenic virus associated with the onset of hepatocellular carcinoma (HCC). The present study investigated the possible link between HCV infection and Netrin-1, a ligand for dependence receptors that sustains tumorigenesis, in particular in inflammation-associated tumors. We show that Netrin-1 expression is significantly elevated in HCV+ liver biopsies compared to hepatitis B virus (HBV+) and uninfected samples. Furthermore, Netrin-1 was upregulated in all histological stages of HCV+ hepatic lesions, from minimal liver fibrosis to cirrhosis and HCC, compared to histologically matched HCV- tissues. Both cirrhosis and HCV contributed to the induction of Netrin-1 expression, whereas anti-HCV treatment resulted in a reduction of Netrin-1 expression. In vitro, HCV increased the level and translation of Netrin-1 in a NS5A-La-related protein 1 (LARP1)-dependent fashion. Knockdown and forced expression experiments identified the receptor uncoordinated receptor-5 (UNC5A) as an antagonist of the Netrin-1 signal, though it did not affect the death of HCV-infected cells. Netrin-1 enhanced infectivity of HCV particles and promoted viral entry by increasing the activation and decreasing the recycling of the epidermal growth factor receptor (EGFR), a protein that is dysregulated in HCC. Netrin-1 and HCV are, therefore, reciprocal inducers in vitro and in patients, as seen from the increase in viral morphogenesis and viral entry, both phenomena converging toward an increase in the level of infectivity of HCV virions. This functional association involving a cancer-related virus and Netrin-1 argues for evaluating the implication of UNC5 receptor ligands in other oncogenic microbial species.

Hepatitis C treatment failure is associated with increased risk of hepatocellular carcinoma.

Lu M1, Li J1, Rupp LB2, et al. J Viral Hepat. 2016 Mar 30. doi: 10.1111/jvh.12538. [Epub ahead of print]

Sustained virological response (SVR) to antiviral therapy for hepatitis C (HCV) reduces risk of hepatocellular carcinoma (HCC), but there is little information regarding how treatment failure (TF) compares to lack of treatment. We evaluated the impact of treatment status on risk of HCC using data from the Chronic Hepatitis Cohort Study (CHeCS-an observational study based in four large US health systems, with up to 7 years of follow-up on patients). Multivariable analyses were used to adjust for bias in treatment selection, as well as other covariates, followed

by sensitivity analyses. Among 10 091 HCV patients, 3681 (36%) received treatment, 2099 (57%) experienced treatment failure (TF), and 1582 (43%) of these achieved sustained virological response (SVR). TF patients demonstrated almost twice the risk of HCC than untreated patients [adjusted hazard ratio (aHR) = 1.95, 95% confidence interval (CI) 1.50-2.53]; this risk persisted across all stages of fibrosis. Several sensitivity analyses validated these results. Although African Americans were at increased risk of treatment failure, they were at lower risk for HCC and all-cause mortality compared to White patients. SVR patients had lower risk of HCC than TF patients (aHR = 0.48, CI 0.31-0.73), whereas treatment - regardless of outcome - reduced all-cause mortality (aHR = 0.45, CI 0.34-0.60 for SVR patients; aHR = 0.78, CI 0.65-0.93 for TF patients).

Bone Metastases of Hepatocellular Carcinoma: Appearance on MRI Using a Standard Abdominal Protocol. Velloni F1, Ramalho M1,2, AlObaidy M1,3, Matos AP1,2, Altun E1, Semelka RC1. AJR Am J Roentgenol. 2016 Mar 21:1-10. [Epub ahead of print]

OBJECTIVE: The purpose of this study is to describe the MRI features of hepatocellular carcinoma (HCC) bone metastases. **MATERIALS AND METHODS:** Thirty-three consecutive patients were included. Two radiologists performed qualitative and quantitative analysis. The coordinator searched for clinical and epidemiologic features related to patients and their primary liver tumors. Earlier MRI studies were also reviewed to determine whether bone metastases were already present and prospectively identified. Descriptive statistics and the Lin concordance correlation coefficient were used. **RESULTS:** Chronic hepatitis C virus infection was the most common cause of liver disease (20/32; 62.5%), and diffuse and multifocal HCC were the most frequent types of liver HCCs (28/33; 84.8%). Most lesions were located at the spine (109/155; 70.3%), with high signal intensity on fat-suppressed T1-weighted (54/62; 87.1%) and T2-weighted (53/62; 85.5%) images. Bone metastases were predominantly nodular (48/62; 77.4%), confined to the vertebral body (40/60; 66.7%), and best visualized at the arterial phase (40/62; 64.5%). The ring pattern of enhancement was present in 23 of 62 lesions, and the remaining lesions showed diffuse enhancement. Thirty-five of 62 (56.4%) bone metastases showed arterial peak of enhancement. In 13 of 33 (39.9%) patients, bone metastases were not prospectively reported. **CONCLUSION:** Most patients with bone metastases had chronic hepatitis C virus infection and diffuse or multifocal HCC. Metastases are most commonly appreciated as hypervascular focal moderately intensely enhancing nodular masses on the hepatic arterial dominant phase images, with concomitant moderately high signal intensity on fat-suppressed T1- and T2-weighted images.

Hepatitis B Surface Antigen Loss and Hepatocellular Carcinoma Development in Patients With Dual Hepatitis B and C Infection. Yang WT1, Wu LW, Tseng TC, et al. Medicine (Baltimore). 2016 Mar;95(10):e2995. doi: 10.1097/MD.0000000000002995.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are 2 major causes of chronic viral hepatitis. It is still unclear how HCV coinfection affects HBV replication and clinical outcomes in HBV/HCV coinfecting patients. We conducted a longitudinal study, which enrolled 111 patients with HBV/HCV coinfection and 111 propensity score-matched controls with HBV mono-infection. Both groups had comparable baseline age, sex, fibrosis stage, levels of HBV DNA, and HBV surface antigen (HBsAg). The HCV coinfection and other host/viral factors were correlated with various outcomes, including HBsAg loss and cirrhosis/hepatocellular carcinoma (HCC) development. After a 10-year follow-up, we found that HCV coinfection itself

was not associated with HBsAg loss. However, coinfecting patients with alanine aminotransferase (ALT) level >80U/L had a higher chance of HBsAg loss than those with ALT level ≤80U/L [hazard ratio (95% confidence interval): 4.41 (1.75-11.15)] or matched controls with HBV monoinfection [hazard ratio (95% confidence interval): 3.40 (1.54-7.50)]. Besides, both HCV coinfection and higher ALT levels were associated with higher HCC risks and the HCC risks remained even after HBsAg loss in HBV/HCV coinfecting patient. HCV coinfection is not associated with HBsAg loss. A higher ALT level is a major determinant of HBsAg loss in patients with HBV/HCV coinfection. Both HCV coinfection and a higher ALT level were independent risk factors of HCC.

Should surveillance for liver cancer be modified in hepatitis c patients after treatment-related cirrhosis regression? D'Ambrosio R1, Colombo M1. Liver Int. 2016 Mar 3. doi: 10.1111/liv.13106. [Epub ahead of print]

Surveillance of hepatocellular carcinoma (HCC) with abdominal ultrasound (US) is recommended for patients with advanced liver fibrosis due to hepatitis C virus (HCV) infections who achieve a sustained virological response (SVR) to antiviral therapy. HCC, in fact, may still develop following SVR as a consequence of long standing carcinogenic activity of either HCV or hepatic fibrosis whereas HCC risk in non-viremic patients may also be driven by cofactors like alcohol abuse or diabetes. This explains the debate on whether surveillance for HCC should be continued in patients with documented cirrhosis regression following a SVR, too. While regression of cirrhosis was documented to occur in a majority of patients with compensated cirrhosis 5 years after an SVR to interferon, it should be noted that this clinical benefit could be the consequence of treating a selected population with well-compensated liver disease who in fact were interferon able. This may not be the case for most real-life patients with advanced cirrhosis receiving direct antivirals, in whom liver fibrosis may have reached a point of no return thus potentially preventing recovery of a normal liver architecture following SVR. Both invasive and non-invasive tools have suboptimal diagnostic accuracy for fibrosis regression in non-viremic patients, and this prompts to follow international societies' recommendation to perform surveillance in patients with advanced liver fibrosis achieving a SVR, independently on liver histology outcome.

Direct costs of care for hepatocellular carcinoma in patients with hepatitis C cirrhosis.

Tapper EB1, Catana AM1, Sethi N1, Mansuri D1, Sethi S1, Vong A1, Afdhal NH1. Cancer. 2016 Mar 15;122(6):852-8. doi: 10.1002/cncr.29855. Epub 2015 Dec 30.

BACKGROUND: Hepatitis C virus (HCV) is the commonest cause of hepatocellular carcinoma (HCC) in the United States. The benefits of HCV therapy may be measured in part by the prevention of HCC and other complications of cirrhosis. The true cost of care of the HCV patient with HCC is unknown. **METHODS:** One hundred patients were randomly selected from a cohort of all HCC patients with HCV at a US transplant center between 2003 and 2013. Patients were categorized by the primary treatment modality, Barcelona class, and ultimate transplant status. Costs included the unit costs of procedures, imaging, hospitalizations, medications, and all subsequent care of the HCC patient until either death or the end of follow-up. Associations with survival and cost were assessed in multivariate regression models. **RESULTS:** Overall costs included a median of \$176,456 (interquartile range [IQR], \$84,489-\$292,192) per patient or \$6279 (IQR, \$4043-\$9720) per patient-month of observation. The median costs per patient-month were \$7492 (IQR, \$5137-\$11,057) for transplant patients and \$4830 for nontransplant

patients. The highest median monthly costs were for transplant patients with Barcelona A4 disease (\$11,349) and patients who received chemoembolization whether they underwent transplantation (\$10,244) or not (\$8853). Transarterial chemoembolization and radiofrequency ablation were independently associated with a 28% increase and a 22% decrease in costs, respectively, with adjustments for the severity of liver disease and Barcelona class.

CONCLUSIONS: These data represent real-world estimates of the cost of HCC care provided at a transplant center and should inform economic studies of HCV therapy.

[Fine Particle Pollution, Alanine Transaminase, and Liver Cancer: A Taiwanese Prospective Cohort Study \(REVEAL-HBV\).](#) Pan WC1, Wu CD1, Chen MJ1, Huang YT1, Chen CJ1, Su HJ1, Yang HI2. J Natl Cancer Inst. 2015 Nov 11;108(3). pii: djv341. doi: 10.1093/jnci/djv341. Print 2016 Mar.

BACKGROUND: Exposure to fine particulate matter (PM_{2.5}) may promote hepatic tumorigenesis through low-grade inflammation. Therefore, we assessed the association of long-term exposure levels of PM_{2.5} and subsequent risk of hepatocellular carcinoma (HCC) and investigated the mediation effect of inflammation as represented by alanine aminotransferase (ALT) on this association. **METHODS:** Between 1991 and 1992, we recruited 23 820 participants in Taiwan with no history of HCC. Case patients of HCC were ascertained through computerized data linkage with the National Cancer Registry and death certification systems. Participants' exposures to PM_{2.5} were based on a four-year average retrieved from stationary monitoring sites. Cox proportional hazards models were used to assess the association between PM_{2.5} exposure and HCC incidence. Mediation effects of ALT on PM_{2.5}-associated HCC incidence were estimated. **RESULTS:** A total of 464 HCC cases were newly diagnosed with a median follow-up of 16.9 years. Statistically significantly increasing trends between PM_{2.5} exposures and ALT were observed on the Main Island and Penghu Islets. The adjusted hazard ratio (HR) for HCC on the Penghu Islets was 1.22 (95% confidence interval [CI] = 1.02 to 1.47) per PM_{2.5} interquartile range (IQR) increment (0.73 µg/m³) exposure. We also found a positive association between PM_{2.5} exposure (per IQR increment, 13.1 µg/m³) and HCC incidence on the Main Island. Furthermore, ALT had a statistically significant mediation effect on PM_{2.5}-associated HCC incidence (HR = 1.17, 95% CI = 1.02 to 1.52 on the Main Island; HR = 1.04, 95% CI = 1.03 to 1.07 on the Penghu Islets) per PM_{2.5} IQR increment. **CONCLUSIONS:** Long-term PM_{2.5} exposure increased the risk for liver cancer, and chronic inflammation of the liver may underlie the pathogenesis.

[Altered glycosylation, expression of serum haptoglobin and alpha-1-antitrypsin in chronic hepatitis C, hepatitis C induced liver cirrhosis and hepatocellular carcinoma patients.](#)

Mondal G1, Saroha A2, Bose PP3, Chatterjee BP4. Glycoconj J. 2016 Apr;33(2):209-18. doi: 10.1007/s10719-016-9658-2. Epub 2016 Mar 31.

Liver cirrhosis with hepatitis C viral infection (HCV-LC) causes high risk to develop hepatocellular carcinoma (HCC). Besides diagnosis of liver cirrhosis by biochemical test, imaging techniques, assessment of structural liver damage by biopsy shows several disadvantages. Our aim was to monitor the changes in the expression level of serum proteins and their glycosylation pattern among chronic hepatitis C (HCV-CH), HCV-LC and HCC patients with respect to controls. 2D gel electrophoresis of HCV-CH, HCV-LC and HCC patients' sera showed several protein spots, which were identified by LC-MS. The change in the expression of two prominent protein spots, haptoglobin (Hp) and alpha 1-antitrypsin (AAT) was evaluated by

western blot and ELISA. The changes in glycosylation pattern of these serum proteins were assayed using different lectins. Increased level of Hp and AAT was observed in HCV-LC and HCC patients' group whereas those were found to be present less in HCV-CH patient groups with respect to control as determined by ELISA using monoclonal antibodies. Decreased level of sialylation in both Hp and AAT was observed in HCV-LC and HCV-CH patients' group whereas increased level of sialylation was observed in HCC patient groups by ELISA using Sambucus nigra agglutinin. On the other hand increased level of fucosylation in two serum glycoproteins was observed in HCV-LC and HCC patients' group using Lens culinaris agglutinin. High glycan branching was found in HCV-LC and HCC patient groups in Hp but not in HCV-CH as determined by Datura stramonium agglutinin. However, there was no such change observed in glycan branching in AAT of HCV-CH and HCV-LC patients' groups, to the contrary high glycan branching was observed in HCC patients' group. Increased level of exposed galactose in both serum proteins was observed in both HCC patients' group as determined by Ricinus communis agglutinin. The present glycoproteomics study could predict the progression of HCV-CH, HCV-LC and HCC without the need of liver biopsy.

Elastin Fiber Accumulation in Liver Correlates with the Development of Hepatocellular Carcinoma.

Yasui Y1, Abe T2, Kurosaki M1, Higuchi M1, et al. PLoS One. 2016 Apr 29;11(4):e0154558. doi: 10.1371/journal.pone.0154558. eCollection 2016.

BACKGROUND & AIMS: The fibrosis stage, which is evaluated by the distribution pattern of collagen fibers, is a major predictor for the development of hepatocellular carcinoma (HCC) for patients with hepatitis C. Meanwhile, the role of elastin fibers has not yet been elucidated. The present study was conducted to determine the significance of quantifying both collagen and elastin fibers. **METHODS:** We enrolled 189 consecutive patients with hepatitis C and advanced fibrosis. Using Elastica van Gieson-stained whole-slide images of pretreatment liver biopsies, collagen and elastin fibers were evaluated pixel by pixel (0.46 $\mu\text{m}/\text{pixel}$) using an automated computational method. Consequently, fiber amount and cumulative incidences of HCC within 3 years were analyzed. **RESULTS:** There was a significant correlation between collagen and elastin fibers, whereas variation in elastin fiber was greater than in collagen fiber. Both collagen fiber ($p = 0.008$) and elastin fiber ($p < 0.001$) were significantly correlated with F stage. In total, 30 patients developed HCC during follow-up. Patients who have higher elastin fiber ($p = 0.002$) in addition to higher collagen fiber ($p = 0.05$) showed significantly higher incidences of HCC. With regard to elastin fiber, this difference remained significant in F3 patients. Furthermore, for patients with a higher collagen fiber amount, higher elastin was a significant predictor for HCC development ($p = 0.02$). **CONCLUSIONS:** Computational analysis is a novel technique for quantification of fibers with the added value of conventional staging. Elastin fiber is a predictor for the development of HCC independently of collagen fiber and F stage

Hepatitis C virus core protein regulates OCT4 expression and promotes cell cycle progression in hepatocellular carcinoma.

Zhou JJ1, Meng Z1, Zhou Y1, et al. Oncol Rep. 2016 Apr 27. doi: 10.3892/or.2016.4775. [Epub ahead of print]

Hepatitis C virus (HCV) core protein plays an important role in the development of hepatocellular carcinoma. octamer-binding protein 4 (OCT4) is critically essential for the pluripotency and self-renewal of embryonic stem cells. Abnormal expression of OCT4 has been detected in several human solid tumors. However, the relationship between HCV core and OCT4 remains uncertain. In the present study, we found that HCV core is capable of upregulating

OCT4 expression. The effect of HCV core-induced OCT4 overexpression was abolished by RNAi-mediated silencing of HCV core. In addition, HCV core-induced OCT4 overexpression resulted in enhanced cell proliferation and cell cycle progression. Inhibition of OCT4 reduced the CCND1 expression and induced G0/G1 cell cycle arrest. Furthermore, OCT4 protein directly binds to CCND1 promoter and transactivates CCND1. These findings suggest that HCV core protein regulates OCT4 expression and promotes cell cycle progression in hepatocellular carcinoma providing new insight into the mechanism of hepatocarcinogenesis by HCV infection.

[Hepatitis C Virus Protein Interaction Network Analysis Based on Hepatocellular](#)

[Carcinoma](#). Han Y1, Niu J2, Wang D3, Li Y1,3. PLoS One. 2016 Apr 26;11(4):e0153882. doi: 10.1371/journal.pone.0153882. eCollection 2016.

Epidemiological studies have validated the association between hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC). An increasing number of studies show that protein-protein interactions (PPIs) between HCV proteins and host proteins play a vital role in infection and mediate HCC progression. In this work, we collected all published interaction between HCV and human proteins, which include 455 unique human proteins participating in 524 HCV-human interactions. Then, we construct the HCV-human and HCV-HCC protein interaction networks, which display the biological knowledge regarding the mechanism of HCV pathogenesis, particularly with respect to pathogenesis of HCC. Through in-depth analysis of the HCV-HCC interaction network, we found that interactors are enriched in the JAK/STAT, p53, MAPK, TNF, Wnt, and cell cycle pathways. Using a random walk with restart algorithm, we predicted the importance of each protein in the HCV-HCC network and found that AKT1 may play a key role in the HCC progression. Moreover, we found that NS5A promotes HCC cells proliferation and metastasis by activating AKT/GSK3 β / β -catenin pathway. This work provides a basis for a detailed map tracking new cellular interactions of HCV and identifying potential targets for HCV-related hepatocellular carcinoma treatment.

[Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution.](#)

Reig M1, Mariño Z2, Perelló C3, et al. J Hepatol. 2016 Apr 12. pii: S0168-8278(16)30113-1. doi: 10.1016/j.jhep.2016.04.008. [Epub ahead of print]

BACKGROUND AND AIMS: The success of direct acting antivirals against hepatitis C is a major breakthrough in Hepatology. Until now, however, there are very few data on the effect of HCV eradication in patients who have already developed hepatocellular carcinoma.

METHODS: The study included patients with HCV infection and prior history of treated hepatocellular carcinoma who achieved complete response and lacked 'non-characterized nodules' at the time they underwent anti-HCV treatment with all-oral direct acting antivirals in 4 hospitals. Patients receiving interferon as part of the antiviral regimen were excluded. The baseline characteristics, laboratory and radiologic tumor response were registered in all patients before starting antiviral therapy and during the follow-up according to the clinical practice policy.

RESULTS: Between 2014 and 2015, 103 patients with prior hepatocellular carcinoma received DAA, 58 of them met the inclusion criteria. After a median follow-up of 5.7 months, 3 patients died and 16 developed radiologic tumor recurrence (27.6%). The pattern of recurrence was: intrahepatic growth (3 patients), new intrahepatic lesion (1 nodule in 5 patients, up to 3 nodules less or equal to 3 cm in 4 cases and multifocal in one patient) and infiltrative ill-defined

hepatocellular carcinoma and/or extra-hepatic lesions in 3 patients. **CONCLUSIONS:** Our data show an unexpected high rate and pattern of tumor recurrence coinciding with HCV clearance and, though based in a very small cohort of patients, should be taken as a note of caution and prime a large scale assessment that exceeds the individual investigators capacity. **LAY SUMMARY:** High rate of cancer recurrence after DAA treatment in patients with prior hepatocellular carcinoma. Disruption of immune surveillance may facilitate the emergence of metastatic clones.