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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

No clinically meaningful pharmacokinetic interaction between the hepatitis C virus inhibitors elbasvir and grazoprevir and the oral contraceptives ethinyl estradiol and levonorgestrel. Marshall WL1, Feng HP1, Caro L1, et al. Eur J Clin Pharmacol. 2017 Feb 24. doi: 10.1007/s00228-017-2216-4. [Epub ahead of print]
PURPOSE: Oral contraceptive pills (OCPs) are an important element of hepatitis C virus (HCV) treatment in women of childbearing potential. These studies evaluated the safety and pharmacokinetic interactions between elbasvir (EBR) and grazoprevir (GZR) and ethinyl estradiol/levonorgestrel (EE/LNG). **METHODS:** Both studies were open-label, single-site, two-period, fixed-sequence, one-way interaction studies. In period 1, subjects received one tablet of EE/LNG (0.03 mg/0.15 mg). In period 2, subjects received EBR (50 mg once daily) for 13 days or GZR (200 mg once daily) for 10 days, with one tablet of EE/LNG on day 7 (GZR group) or 10 (EBR group). Each study enrolled 20 healthy, nonsmoking adult females. **RESULTS:** There was no clinically meaningful effect of multiple doses of EBR or GZR on the pharmacokinetics of EE or LNG. Geometric mean ratios (GMRs) for AUC0-∞ and Cmax in the presence and absence of EBR were 1.01 and 1.10 for EE and 1.14 and 1.02 for LNG, with 90% confidence intervals (CIs) that were contained in the interval [0.80, 1.25]. Similarly, the AUC0-∞ and Cmax GMRs in the presence and absence of GZR were 1.10 and 1.05 for EE and 1.23 and 0.93 for LNG, respectively. The 90% CIs for EE AUC0-∞ and for EE and LNG Cmax were contained in the interval [0.80, 1.25]; however, the 90% CI for the LNG AUC0-∞ [1.15, 1.32] slightly exceeded the upper bound. **CONCLUSIONS:** These results suggest that EBR/GZR can be co-administered to female patients with HCV of childbearing potential who are on OCPs to prevent pregnancy.

Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real world cohort. Calleja JL1, Crespo J2, Rincón D3, et al. J Hepatol. 2017 Feb 8. pii: S0168-8278(17)30063-6. doi: 10.1016/j.jhep.2017.01.028. [Epub ahead of print]

BACKGROUND AND AIMS: Clinical trials evaluating second-generation direct-acting antiviral agents (DAAs) have shown excellent rates of sustained virologic response (SVR) and good safety profiles in patients with chronic hepatitis C virus (HCV) genotype 1 infection. We aimed to investigate the effectiveness and safety of two oral DAA combination regimens, ombitasvir/paritaprevir/ritonavir plus dasabuvir (OMV/PTV/r+DSV) and ledipasvir/sofosbuvir (LDV/SOF), in real-world clinical practice. **METHODS:** Data from HCV genotype 1 patients treated with either OMV/PTV/r+DSV±ribavirin (RBV) (n=1,567) or LDV/SOF±RBV (n=1,758) in 35 centers across Spain between April 1, 2015 and February 28, 2016 were recorded in a large national database. Demographic, clinical and virological data were analyzed. Details of serious adverse events (SAEs) were recorded. **RESULTS:** The two cohorts are not matched with respect to baseline characteristics and cannot be compared directly. The SVR12 rate was 96.8% with OMV/PTVr/DSV±RBV and 95.8% with LDV/SOF±RBV. No significant differences were observed in SVR according to HCV subgenotype (p=0.321 [OMV/PTV/r+DSV±RBV] and p=0.174 [LDV/SOF]) or degree of fibrosis (p=0.548 [OMV/PTV/r/DSV±RBV] and p=0.085 [LDV/SOF]). Only baseline albumin level was significantly associated with failure to achieve SVR ($p<0.05$) on multivariate analysis. Rates of SAEs and SAE-associated treatment discontinuation were 5.4% and 1.7%, in the OMV/PTV/r+DSV subcohort and 5.5% and 1.5% in the LDV/SOF subcohort, respectively. Hepatocellular carcinoma (HCC) recurred in 30% of patients with a complete response to therapy for previous HCC. Incident HCC was reported in 0.93%. **CONCLUSIONS:** In this large cohort of patients managed in the real-world setting in Spain, OMV/PTV/r+DSV and LDV/SOF achieved high rates of SVR12, comparable to those observed in randomized controlled trials, with similarly good safety profiles. **LAY SUMMARY:** In clinical trials, second-generation direct acting antiviral agents (DAAs) have been shown to cure over 90% of patients chronically infected with the genotype 1 hepatitis C virus and have been better tolerated than previous treatment regimens. However, patients enrolled in clinical trials do not reflect the real patient population encountered in routine practice. The current study, which includes almost 4,000 patients, demonstrates comparable rates of cure with two increasingly used DAA combinations as those observed in the clinical trial environment, confirming that clinical trial findings with DAAs translate into the real-world setting, where patient populations are more diverse and complex.

Risk of hepatitis C virus related hepatocellular carcinoma between subjects with spontaneous and treatment-induced viral clearance. Huang CF1,2, Yeh ML1,2, et al. Oncotarget. 2017 Feb 1. doi: 10.18632/oncotarget.14937. [Epub ahead of print]
BACKGROUND/AIMS: Both spontaneous hepatitis C virus (HCV) clearance and the achievement of sustained virological response (SVR) by anti-viral therapy greatly reduce the incidence of hepatocellular carcinoma (HCC). The current study aimed to compare the risk of HCC between the two patient groups. **METHODS:** A total of 313 subjects with spontaneous HCV clearance (SC) and 564 age- and sex-matched patients in the treatment-induced SVR group were enrolled for analysis. **RESULTS:** Nineteen (2.2%) of the 877 patients developed HCC during 6,963 person-years of follow-up. Fourteen (2.5%) SVR patients and 5 (1.6%) SC patients developed HCC (P=0.004). Cox regression analysis of factors predictive of HCC included SVR (versus SC: hazard ratio [HR]/ 95% confidence interval [CI]: 5.83/1.27-26.88), diabetes (HR/CI:3.41/1.21-9.58), and age (HR/CI: 1.07/1.01-1.14). Of the 564 SVR patients, eleven (5.9%) of the 187 patients with fibrosis stage 2-4 (F2-4) and 2 (0.9%) of the 226 patients with F01 developed HCC (P=0.01). Compared to SC subjects, only SVR patients with F2-4 (P<0.001)

but not F0-1(P=0.60) had a higher risk of HCC development. Cox-regression analysis using liver fibrosis as a variable demonstrated that factors associated with HCC included SVR with F2-4 (versus SC: HR/CI: 10.06/2.20-45.98), diabetes (HR/CI:3.23/1.14-9.19), and age (HR/CI: 1.08 1.02-1.15). **CONCLUSIONS:** Compared to subjects with spontaneous viral clearance, subjects with antiviral treatment-induced HCV viral clearance remain at high risk for HCC development, especially if they have significant hepatic fibrosis. These results may provide important information for decision-making regarding the prioritization of current direct antiviral agents in resource-limited countries.

The Safety and Efficacy of Baclofen to Reduce Alcohol Use in Veterans with Chronic Hepatitis C: A Randomized Clinical Trial. Hauser P1,2,3,4, Fuller B5,6, Ho SB7,8, Thuras P9,10, Kern S1, Dieperink E9,10. Addiction. 2017 Feb 13. doi: 10.1111/add.13787. [Epub ahead of print]

BACKGROUND AND AIMS: Alcohol use disorders (AUDs) are common among people with chronic hepatitis C (HCV) and accelerate the development of fibrosis and cirrhosis caused by HCV. Baclofen, a gamma-aminobutyric acid (GABA) beta-receptor agonist, differs from medications for AUDs currently approved by the United States (US) Federal Drug Administration (FDA) as it is metabolized primarily through the kidneys. The primary outcome of this study was to compare baclofen with a placebo in the percentage of days abstinent from alcohol. **DESIGN:** A double-blind, placebo-controlled randomized trial. **SETTING:** Hepatology linics in 4 separate US Veteran Affairs Medical Centers in the USA. **PARTICIPANTS:** One hundred eighty Veteran men and women older than 18 years with chronic HCV, a co-morbid AUD and current alcohol use. **INTERVENTION AND COMPARATOR:** Oral baclofen was given at dosages of 0 [placebo] or 30 mg/day over 12 weeks with concomitant manual-guided counseling. **MEASUREMENTS:** The primary measurement was percentage of days abstinent during the 12-week study period between the baclofen and placebo groups (measured by timeline follow back or TLFB). Secondary measurements were the percentage of Veterans who achieved complete abstinence, the percentage of Veterans who achieved no heavy drinking between weeks 4 and 12 of the study, alcohol craving, anxiety, depression, and post-traumatic stress disorder (PTSD). **FINDINGS:** Primary outcome: Compared with placebo, baclofen did not improve the percentage of days abstinent. For all subjects there were significant reductions from baseline to 12 weeks in percentage of days abstinent from 37.0% (SE = 2.7) to 68.6% (SE = 2.8) ($F(1,151.1 = 66.1$ $p < 0.001$)). However, there was no statistically significant difference between groups for change in percentage of days abstinent over the 12-week study period [absolute difference 1.3% (-9.1%- 11.7%)] ($F(1,152.6) = 0.005$, $p = 0.95$). **SECONDARY OUTCOMES:** Subjects who completed the first 4 weeks of the study, 8.9% (15/168) achieved complete abstinence; 10.1% (9/89) in the placebo group and 7.6% (6/79) in the baclofen group ($X2 (1) = 0.33$, OR = 0.73 (0.24 -2.15). The percentage of no heavy drinking for all subjects between week 4 and 12 was 20.2% (34/168) but no statistically significant differences were found between placebo 15.7% (14/89) and baclofen 25.3% (20/79), ($X2 (1) = 2.38$, OR = 1.82 (0.85 - 3.90). There were significant reductions for all subjects in all other secondary variables over the course of the study but no differences between groups. Measures of various biomarkers of alcohol use did not change significantly through the course of the study for either the baclofen or placebo groups. **CONCLUSIONS:** Baclofen administered at 30 mg/day does not appear to be superior to placebo in increasing abstinence or in reducing alcohol use, cravings for alcohol or anxiety among people with alcohol use disorder.

Daclatasvir and asunaprevir for genotype 1b chronic hepatitis C patients with chronic kidney disease. Kondo C1, Atsukawa M1, Tsubota A2, et al. Hepatol Res. 2017 Feb 22. doi: 10.1111/hepr.12879. [Epub ahead of print]
AIM: To evaluate the efficacy and safety of daclatasvir and asunaprevir combined therapy in genotype 1b chronic hepatitis C (CHC) patients with non-dialysis chronic kidney disease (CKD). **METHODS:** In a multicenter collaborative study, 249 patients received 60 mg of daclatasvir (NS5A inhibitor) once a day and 100 mg of asunaprevir (NS3/4A protease inhibitor) twice a day for 24 weeks between September 2014 and September 2015 and were subjected to this analysis. Virological responses and adverse events in non-dialysis patients with CKD (stage 3-5, excluding 5D: dialysis), which was defined as estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m2 , were compared with those in patients without CKD. **RESULTS:** Overall, the rates of rapid viral response (RVR), end-of-treatment response (ETR), and sustained viral response (SVR) were 76.7%, 91.2%, and 86.3%, respectively. Among 55 patients with CKD, the RVR, ETR, and SVR rates were 76.4%, 87.3%, and 83.6%, respectively. Among 194 patients without CKD, they were 76.8, 92.3, and 87.1%, respectively. There were no significant differences in the virological response rates between the two groups (P = 0.999, 0.282, and 0.509, respectively). The baseline eGFR level did not affect the achievement of SVR. The incidence of adverse events in patients with and without CKD were 21.8% and 13.9%, respectively (not significant, P = 0.142). **CONCLUSION:** The efficacy and safety of daclatasvir and asunaprevir combined therapy in genotype 1b CHC patients with non-dialysis CKD are not inferior to those in patients without CKD.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Novel 5-arylthio-5H-chromenopyridines as a new class of anti-fibrotic agents. Patil R1, Ghosh A2, Sun Cao P3, Sommer RD4, Grice KA5, Waris G6, Patil S7. Bioorg Med Chem Lett. 2017 Mar 1;27(5):1129-1135. doi: 10.1016/j.bmcl.2017.01.089. Epub 2017 Feb 1.
Liver fibrosis is a critical wound healing response to chronic liver injury such as hepatitis C virus (HCV) infection. If persistent, liver fibrosis can lead to cirrhosis and hepatocellular carcinoma (HCC). The development of new therapies for preventing liver fibrosis and its progression to cancer associated with HCV infection remains a critical challenge. Identification of novel anti-fibrotic compounds will provide opportunities for innovative therapeutic intervention of HCV-mediated liver fibrosis. We designed and synthesized a focused set of 5-arylthio-5H-chromenopyridines as a new class of anti-fibrotic agents. Liver fibrosis assays demonstrated that the compounds 3a and 3c show inhibitory activity towards human hepatic stellate cells (LX2) activation at 10μM. The HCV NS3 and NS5A proteins in HCV subgenome-expressing cells were also significantly reduced in cells treated with 3a and 3c, suggesting the possible inhibitory role of the compounds in HCV translation/replication activities. We have also examined the reactivity of these compounds with medicinally-relevant metal compounds such as platinum and gold. The reactivity of these complexes with metals and during Mass Spectrometry suggests that CS bond cleavage is relatively facile.

25-hydroxy Vitamin D Suppresses Hepatitis C Virus Replication and Contributes to Rapid Virological Response of Treatment Efficacy. Huang JF1,2,3, Ko YM1, Huang CF1,3,4, et al. Hepatol Res. 2017 Feb 22. doi: 10.1111/hepr.12878. [Epub ahead of print]

AIM: 25-hydroxy vitamin D (Vit D) plays a role in treatment outcomes in chronic hepatitis C virus (HCV) infection (CHC). We aimed to clarify HCV replication is inhibited by Vit D in HCV replicon cells. Clinical implication was assessed for rapid virological response (RVR) and sustained virological response (SVR) among those patients receiving anti-viral therapy. **METHODS:** Cell survival and viral loads were observed in Con1 (genotype-1b) and J6/JFH (genotype-2a) cells treated with different doses of Vit D. Three groups of patients with different treatment responses were recruited to assess their Vit D levels: Group A (RVR-/SVR-); Group B (RVR+/SVR-); Group C (RVR+/SVR+). **RESULTS:** The viral load of Con1 cells decreased by 69%, 80%, and 86%, in 1 μM, 5 μM, and 10 μM Vit D, respectively ($p < 0.0001$). In J6/JFH cells, it decreased by 12%, 55%, and 80.5% in 1 μM, 5 μM, and 10 μM Vit D, respectively ($p < 0.0001$). There was a significant increase of Vit D between CHC groups, ranging from 4.4 ± 5.6 ng/mL of group A ($n = 44$), 17.2 ± 11.6 ng/mL of group B ($n = 44$), to 32.5 ± 37.5 ng/mL of group C ($n = 44$) ($P < 0.001$). Advanced fibrosis (odds ratio = 0.13, 95% confidence interval = 0.04-0.41, $P < 0.001$) and Vit D deficiency (<10 ng/mL) (odds ratio = 0.11, 95% confidence interval = 0.03-0.43, $P = 0.001$) were predictive of SVR in the multivariate regression analysis. **CONCLUSION:** Vit D decreases HCV replication and also contributes to early treatment viral kinetics.

Extra-epitopic hepatitis C virus polymorphisms confer resistance to broadly neutralizing antibodies by modulating binding to scavenger receptor B1. El-Diwany R1, Cohen VJ1, Mankowski MC1, et al. PLoS Pathog. 2017 Feb 24;13(2):e1006235. doi: 10.1371/journal.ppat.1006235. [Epub ahead of print]

Broadly-neutralizing monoclonal antibodies (bNAbs) may guide vaccine development for highly variable viruses including hepatitis C virus (HCV), since they target conserved viral epitopes that could serve as vaccine antigens. However, HCV resistance to bNAbs could reduce the efficacy of a vaccine. HC33.4 and AR4A are two of the most potent anti-HCV human bNAbs characterized to date, binding to highly conserved epitopes near the amino- and carboxy-terminus of HCV envelope (E2) protein, respectively. Given their distinct epitopes, it was surprising that these bNAbs showed similar neutralization profiles across a panel of natural HCV isolates, suggesting that some viral polymorphisms may confer resistance to both bNAbs. To investigate this resistance, we developed a large, diverse panel of natural HCV envelope variants and a novel computational method to identify bNAb resistance polymorphisms in envelope proteins (E1 and E2). By measuring neutralization of a panel of HCV pseudoparticles by 10 μg/mL of each bNAb, we identified E1E2 variants with resistance to one or both bNAbs, despite 100% conservation of the AR4A binding epitope across the panel. We discovered polymorphisms outside of either binding epitope that modulate resistance to both bNAbs by altering E2 binding to the HCV co-receptor, scavenger receptor B1 (SR-B1). This study is focused on a mode of neutralization escape not addressed by conventional analysis of epitope conservation, highlighting the contribution of extra-epitopic polymorphisms to bNAb resistance and presenting a novel mechanism by which HCV might persist even in the face of an antibody response targeting multiple conserved epitopes.

Clinical Pharmacokinetics of Paritaprevir. Menon RM1, Polepally AR2, Khatri A2, Awni WM2, Dutta S2. Clin Pharmacokinet. 2017 Feb 25. doi: 10.1007/s40262-017-0520-x. [Epub ahead of print]

Paritaprevir is a potent hepatitis C virus (HCV) nonstructural (NS) protein 3/4A protease inhibitor that is used in combination with other direct-acting antivirals (DAAs) for the treatment of chronic HCV infection. Paritaprevir is primarily metabolized by cytochrome P450 (CYP) 3A4 and is administered with a low dose of ritonavir to achieve drug concentrations suitable for once-daily dosing. Coadministration of paritaprevir with ritonavir increases the half-life of single-dose paritaprevir from approximately 3 h to 5-8 h, doubles the time to maximum plasma concentration (T max) from 2.3 to 4.7 h, and increases exposures 30-fold for maximum observed plasma concentration (C max), 50-fold for area under the plasma concentration-time curve (AUC), and >300-fold for trough concentration (C 24). Paritaprevir displays highly variable, nonlinear pharmacokinetics, with C max and AUC increasing in a greater than dose proportional manner when administered with or without ritonavir. In the presence of ritonavir, paritaprevir is excreted mostly unchanged in feces via biliary excretion. Paritaprevir exposures are higher in Japanese subjects compared with Caucasian subjects; however, no dose adjustment is needed for Japanese patients as the higher exposures are safe and well tolerated. The pharmacokinetic characteristics of paritaprevir are similar between healthy subjects and HCV-infected patients, and are not appreciably altered by mild or moderate hepatic impairment or mild, moderate, or severe renal impairment, including those on dialysis. Paritaprevir exposures are increased in patients with severe hepatic impairment. Although the presence of a low dose of ritonavir in paritaprevir-containing regimens increases the likelihood of drug-drug interactions, results from several drug interaction studies demonstrated that paritaprevir-containing regimens can be coadministered with many comedications that are commonly prescribed in HCV-infected patients.
PMID: 28236252 [PubMed - as supplied by publisher]

Human ES Cell-derived Hepatoblasts are an Optimal Lineage Stage for HCV Infection.
Yan F1,2, Wang Y1, Zhang W1, et al. Hepatology. 2017 Feb 25. doi: 10.1002/hep.29134. [Epub ahead of print]
Maturation of hepatic cells can be gradually acquired through multiple stages of hepatic lineage specification, while little is known if the dynamics of HCV infection are maturationally lineage dependent. We investigated the susceptibility to HCV at multiple stages comprising human embryonic stem cells (hESCs), definitive endodermal cells (hDECs), hepatic stem cells (hHpSCs), hepatoblasts (hHBs) and mature hepatocytes (hHeps). Susceptibility to infection occurred initially at the stage of hHpSC, however, hHBs proved to have the highest permissiveness and infectivity compared with all other stages. The HBs' susceptibility to HCV correlated with the translocation of occludin (OCLN), as HCV receptor, from cytoplasm to plasma membrane of HBs. Vascular endothelial cell growth factor (VEGF) enhanced the HCV susceptibility of hHBs through re-arrangement of OCLN by dephosphorylation of OCLN; this minimized hHB's polarization and prevented hHBs from further maturation. The transcription profiles of different hepatic lineage stages indicated that expression of innate immune response genes were correlated with hepatic maturation; interferon β (IFNβ) played an important role in protecting hHBs from HCV infection. HCV-infected hHBs were able to engraft and integrate into the livers of Fah-/-Rag2-/- (F/R) mice and maintained at hHB phenotype for over 12 weeks during the time when HCV antigen was evident. After suppression of IFNβ in hHBs, HCV infection was significantly enhanced in the engrafted humanized liver tissue of host mice.

HIV/HCV COINFECTION

Human immunodeficiency virus-infected and uninfected adults with non-genotype 3 hepatitis C virus have less hepatic steatosis than adults with neither infection.
Price JC1, Ma Y1, Scherzer R1,2, Korn N3, Tillinghast K3, Peters MG1, Noworolski SM3, Tien PC1,2. Hepatology. 2017 Mar;65(3):853-863. doi: 10.1002/hep.28968. Epub 2017 Feb 3.
Hepatic steatosis (HS) is common in individuals with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections, but the independent contributions of HCV and HIV to HS are unclear. Magnetic resonance imaging and spectroscopy were used to measure visceral adipose tissue (VAT) and liver fat fraction (LFF) (total lipids/[total lipids + water]) in 356 adults: 57 with HCV monoinfection, 70 with HIV/HCV coinfection, 122 with HIV monoinfection, and 107 with neither infection. Participants who were infected with HCV genotype 3 were excluded because of the genotype's reported steatogenic effects. For prevalence estimates, HS was defined as LFF $\geq$ 0.05. We estimated the association of HIV and HCV status with LFF using multivariable linear regression, adjusting for demographics, lifestyle, and metabolic factors including the homeostasis model assessment estimate of insulin resistance (HOMA-IR) and liver fibrosis defined using the aspartate aminotransferase-to-platelet ratio index (APRI). The prevalence of HS was highest in the uninfected (33%) and HIV-monoinfected (28%), followed by the HCV-monoinfected (19%) and HIV/HCV-coinfected (11%) (P = 0.003 across groups). Compared with uninfected participants-and after adjusting for demographics, lifestyle, and metabolic factors-HIV monoinfection, HCV monoinfection, and HIV/HCV coinfection were associated with 19% (95% confidence interval [CI], -39% to 6%), 38% (95% CI, -55% to -12%), and 42% (95% CI, -59% to -18%) lower LFF, respectively. HCV monoinfection and HIV/HCV coinfection remained strongly associated with lower LFF after further adjusting for APRI, and results were unchanged after excluding subjects with suspected cirrhosis. Among the entire cohort, Hispanic ethnicity, male sex, VAT, and HOMA-IR were independently associated with greater LFF. **CONCLUSION:** Contrary to expectations, HIV/HCV-coinfected and HCV-monoinfected adults had significantly less liver fat than uninfected adults, even after adjusting for demographics, lifestyle, metabolic factors, and hepatic fibrosis. Our findings suggest that non-genotype 3 HCV infection may be protective against HS. The mechanisms by which this occurs and the impact of HCV treatment on HS requires further investigation. (Hepatology 2017;65:853-863).

Phase 3 trial of first generation protease inhibitor therapy for hepatitis C virus/human immunodeficiency virus coinfection. Sherman KE1, Kang M1, Sterling R1, et al. World J Hepatol. 2017 Feb 8;9(4):217-223. doi: 10.4254/wjh.v9.i4.217.
AIM: To evaluate efficacy/safety of hepatitis C virus (HCV) protease inhibitor boceprevir with pegylated interferon (PEG-IFN) alfa and weight-based ribavirin (RBV) in a phase 3 trial.
METHODS: A prospective, multicenter, phase 3, open-label, single-arm study of PEG-IFN alfa, weight-based RBV, and boceprevir, with a PEG-IFN/RBV lead-in phase was performed. The HCV/human immunodeficiency virus coinfected study population included treatment naïve (TN) and treatment experienced (TE) patients. Treatment duration ranged from 28 to 48 wk dependent upon response-guided criteria. All patients had HCV Genotype 1 with a viral load > 10000 IU/mL. Compensated cirrhosis was allowed. Sample size was determined to establish superiority to historical (PEG-IFN plus RBV) rates in sustained viral response (SVR). **RESULTS:** A total of 257 enrolled participants were analyzed (135 TN and 122 TE). In the TN group, 81.5% were male and 54.1% were black. In the TE group, 76.2% were male and 47.5% were white. Overall SVR12 rates (HCV RNA < lower limit of quantification, target not detected, target not detected)

were 35.6% in TN and 30.3% in TE. Response rates at SVR24 were 28% in TN and 10% in TE, and exceeded those in historical controls. The highest rate was observed in TN non-cirrhotic participants (36.8% and the lowest in TE cirrhotics (26.3%). Cirrhotic TN participants had a 27.8% SVR12 rate and 32.1% of TE non-cirrhotics achieved SVR12. Significantly lower response rates were observed among black participants; in the TE, SVR12 was 39.7% in white participants but only 13.2% of black subjects (P = 0.002). Among the TN, SVR12 was 42.1% among whites and 27.4% among blacks (P = 0.09). **CONCLUSION:** The trial met its hypothesis of improved SVR compared to historical controls but overall SVR rates were low. All-oral HCV treatments will mitigate these difficulties.

Update in HIV-hepatitis C virus coinfection in the direct acting antiviral era. Meissner EG1. Curr Opin Gastroenterol. 2017 Feb 23. doi: 10.1097/MOG.0000000000000347. [Epub ahead of print]
PURPOSE OF REVIEW: Availability of direct acting antivirals (DAAs) that demonstrate remarkable clinical efficacy and safety has revolutionized the ability to treat chronic infection with hepatitis C virus (HCV). An equal measure of clinical success has now been achieved in persons coinfected with HCV and the HIV, a historically harder to cure cohort with interferon-based therapy. Global goals include identifying all HIV-HCV-infected persons, gaining access to DAA therapy, preventing de novo and reinfection, and managing the sequelae of chronic infection. This review will discuss advances in the field of HIV-HCV coinfection reported during the last 18 months, and will suggest areas for future investigation. **RECENT FINDINGS:** An expanding body of literature has enhanced our understanding of the clinical and epidemiologic issues surrounding HIV-HCV coinfection. DAA therapy for HCV is highly efficacious in HIV-HCV-coinfected persons if drug-drug interactions are appropriately considered. **SUMMARY:** Eradicating HCV infection in persons with HIV coinfection can be achieved safely and effectively with available DAAs. Economic and social approaches to enable access and delivery of curative HCV therapy to HIV-infected persons require continued research and resource allocation.

Reactivation of hepatitis B in patients of chronic hepatitis C with hepatitis B virus infection treated with direct acting antivirals. Yeh ML1,2,3, Huang CF2,3, Hsieh MH2,3,4, Ko YM2, et al. J Gastroenterol Hepatol. 2017 Feb 23. doi: 10.1111/jgh.13771. [Epub ahead of print]
BACKGROUND AND AIMS: Hepatitis B virus (HBV) may reactivate when treating chronic hepatitis C (CHC) with direct acting antivirals (DAA). We aim to investigate the risk of HBV reactivation during DAA therapy. **METHODS:** CHC patients receiving pan-oral DAA therapy from Dec. 2013 to Aug. 2016 were evaluated. Fifty-seven patients that had a past HBV infection (negative hepatitis B surface antigen (HBsAg)) and positive hepatitis B core antibody (Anti-HBc)) and 7 patients that had a current HBV infection (positive HBsAg) were enrolled. Serum HBV and hepatitis C virus (HCV) markers were regularly measured. The endpoints were the HCV sustained virological response (SVR) and the HBV virological/clinical reactivation. **RESULTS:** The overall SVR12 rate was 96.9%, and 2 patients, one with positive HBsAg, had a relapse of HCV. No episodes of HBV virological reactivation were observed among the patients with a past HBV infection. For the 7 patients with a current HBV infection, HBV virological reactivation was found in 4 (57.1%) of the 7 patients. Clinical reactivation of HBV was observed in one patient with pre-treatment detectable HBV DNA and recovered after entecavir administration. For the other 3 patients with HBV virological reactivation, the reappearance of

low level HBV DNA without clinical reactivation was observed. HBsAg levels demonstrated only small fluctuations in all the patients. **CONCLUSIONS:** There was a minimal impact of Anti-HBc seropositivity on HCV efficacy and safety. For CHC patients with current HBV infection, the risk of HBV reactivation was present and monitoring the HBV DNA level during therapy is warranted.

Telaprevir-containing triple therapy in acute HCV coinfection: The CHAT Study.
Boesecke C1,2, Singh GK3, Scholten SH4, et al. Antivir Ther. 2017 Feb 27. doi: 10.3851/IMP3143. [Epub ahead of print]
BACKGROUND: No published randomised controlled data on the use of direct acting antivirals (DAA) in acute hepatitis C (AHC) coinfection exist. However, with the AHC epidemic ongoing among men who have sex with men (MSM) these are urgently needed. **METHODS:** The CHAT study is a randomised controlled trial of pegylated interferon + ribavirin (PR) plus telaprevir (TVR) for 12-24 weeks versus PR alone for 24-48 weeks in the response guided treatment of patients with AHC genotype (GT) 1 infection and HIV-1 co-infection in Germany and Great Britain. **RESULTS:** 34 patients were included: 15 were randomized to the PR arm (arm 1), 19 to the TVR + PR arm (arm 2). All patients were MSM, median age was 40 years. 55% had IL28B C/C GT. Median baseline HCV-RNA was 291,227 IU/mL, median ALT 105 U/l. 85% received cART, all had baseline HIV-RNA <40 copies/mL. Overall SVR12 rate was 79.4% (27/34). SVR12 was seen in 12/15 (80%) in arm 1 and in 15/19 (79.8%) in arm 2. Of the 4 patients without SVR in arm 2 one experienced viraI breakthrough, 2 were non-responders; in one case HCV protease inhibitor associated mutations were selected under TVR (V36M, R155K). **CONCLUSIONS:** Due to moderate response rates and additional toxicities 1st generation HCV PIs should not be used in treating acute HCV. While not being licensed recent study data and guidelines support the use of dual DAA therapy but optimal treatment duration in acute HCV needs further investigation.

Low Plasma Zinc Is Associated with Higher Mitochondrial Oxidative Stress and Faster Liver Fibrosis Development in the Miami Adult Studies in HIV Cohort.
Martinez SS1, Campa A1, Li Y1, Fleetwood C2, Stewart T3, Ramamoorthy V4, Baum MK5. J Nutr. 2017 Feb 22. pii: jn243832. doi: 10.3945/jn.116.243832. [Epub ahead of print]
BACKGROUND: Oxidative stress and reduced antioxidants may be a trigger for liver fibrogenesis. Reducing oxidative stress through higher antioxidant concentration may be a potential antifibrotic target. **OBJECTIVE:** We aimed to investigate longitudinally whether plasma zinc, an antioxidant, is related to mitochondrial oxidative stress and the progression of liver fibrosis in the Miami Adult Studies in HIV (MASH) cohort. **METHODS**: A prospective observational cohort study was conducted in 487 predominantly African American HIV-monoinfected and HIV/hepatitis C virus (HCV)-coinfected adults with a mean ± SD age of 47.08 ± 7.67 y from the MASH cohort and followed for a median of 34 mo. Blood was collected for plasma zinc and measures were used to calculate the fibrosis-4 (FIB-4) score (aspartate amino transferase, alanine aminotransferase, and platelets). Plasma zinc deficiency was defined as <0.75 mg/L. Total DNA was extracted from peripheral blood mononuclear cells and mitochondrial DNA (mtDNA) 8-hydroxyguanosine (8-oxo-dG) was determined. Adjusted mixed models were used to assess the relations between zinc, stage of liver disease, and oxidative stress over time and compared between HIV and HIV/HCV groups. **RESULTS:** Zinc concentrations (β: -0.368, SE = 0.172; P = 0.033) and deficiency were associated with lower FIB-4 scores over

time (β: 0.381, SE = 0.118; P = 0.001). Compared with those who were not zinc deficient, zinc-deficient participants had an increased risk of having more-progressed liver disease (OR: 1.91; 95% CI: 1.15, 3.16; P = 0.012). Higher mtDNA 8-oxo-dG was associated with zinc deficiency (β: 0.049, SE = 0.024; P = 0.044) and higher FIB-4 scores over time (β: 0.597, SE = 0.168, P < 0.001). **CONCLUSIONS**: Lower plasma zinc concentrations were associated with liver fibrosis progression and mitochondrial oxidative stress in the HIV and HIV/HCV groups. Zinc may play a role in the impact of liver disease outcomes.

Liver stiffness predicts variceal bleeding in HIV/HCV-coinfected patients with compensated cirrhosis. Merchante N1, Rivero-Juárez A, Téllez F, et al. AIDS. 2017 Feb 20;31(4):493-500. doi: 10.1097/QAD.0000000000001358.
BACKGROUND: A liver stiffness below 21 kPa has a high negative predictive value to exclude the presence of esophageal varices at risk of bleeding in HIV/hepatitis C virus (HCV)-coinfected patients. Consequently, upper gastrointestinal endoscopy (UGE) for the screening of esophageal varices could be avoided in these patients. However, this strategy has not been widely accepted due to concerns about its safety. **OBJECTIVE:** To assess the ability of liver stiffness to predict the risk of portal hypertensive gastrointestinal bleeding (PHGB) in HIV/HCV-coinfected patients with compensated cirrhosis. **METHODS:** Prospective study of 446 HIV/HCV-coinfected patients with a new diagnosis of cirrhosis and no previous decompensation. All patients underwent a UGE for the screening of esophageal varices at entry in the cohort before November 2009. From this date, UGE was not recommended in patients with liver stiffness below 21 kPa. The time from diagnosis of cirrhosis to the emergence of PHGB was evaluated. **RESULTS:** After a median (quartile1-quartile3) follow-up of 49 (25-68) months, 15 (3.4%, 95% confidence interval 1.7-5%) patients developed a first PHGB episode. In all cases, baseline liver stiffness was at least 21 kPa. Thus, the negative predictive value of a liver stiffness below 21 kPa to predict PHGB during follow-up was 100%. At the time of the bleeding episode, liver stiffness was above this threshold in all patients. **CONCLUSIONS:** Liver stiffness identifies HIV/HCV-coinfected patients with compensated cirrhosis with a very low risk of PHGB. In fact, no individual with liver stiffness below 21 kPa developed this outcome. Our results confirm that UGE can be safely spared in patients with liver stiffness below 21 kPa.

Efficacy and safety of daclatasvir plus pegylated-interferon alfa 2a and ribavirin in previously untreated HCV subjects coinfected with HIV and HCV genotype-1: a Phase III, open-label study. Sulkowski MS1, Fessel WJ2, Lazzarin A3, et al. Hepatol Int. 2017 Feb 16. doi: 10.1007/s12072-017-9788-z. [Epub ahead of print]
BACKGROUND: Daclatasvir (DCV) is a potent, pangenotypic, hepatitis C virus (HCV) non-structural protein 5A inhibitor with low potential for drug interactions with antiretroviral therapy (ART). We evaluated the safety and efficacy of DCV plus peginterferon alfa-2a/ribavirin (PegIFN/RBV) in HIV-1/HCV genotype-1-coinfected patients. **METHODS:** AI444043 (NCT01471574), an open-label, Phase III, single-arm, response-guided treatment (RGT) study included 301 patients. They received DCV doses of 30, 60 or 90 mg once daily (depending on concomitant ART), plus weight-based RBV (<75 kg, 1000 mg/day; or ≥75 kg, 1200 mg/day), and once-weekly PegIFN 180 μg, for 24 weeks. If required by RGT, PegIFN/RBV without DCV was extended for an additional 24 weeks of therapy. The primary endpoint was the proportion of patients with sustained virologic response at post-treatment Week 12 (SVR12). **RESULTS:** Overall, 224 (74%) patients achieved SVR12 and the lower bound of the 95% confidence

interval was higher than the historic SVR rate with PegIFN/RBV alone (70 vs. 29%). Most common adverse events (AEs) were fatigue, neutropenia, anemia, asthenia and headache. On-treatment serious AEs occurred in 24/301 (8%) patients; 18/301 (6%) discontinued treatment due to AE. **CONCLUSIONS:** DCV + PegIFN/RBV led to sustained HCV virologic response in the majority of HIV-1-HCV-coinfected patients, regardless of concomitant ART. HIV control was not compromised and no new safety signals were identified. This study supports DCV use in HIV-1-HCV-coinfected patients, while allowing the vast majority of patients to remain on their existing ART regimen.

Safety and effectiveness of a 12-week course of sofosbuvir and simeprevir ± ribavirin in HCV-infected patients with or without HIV infection: a multicentre observational study. Bruno G1, Saracino A2, Fabrizio C2, et. al. Int J Antimicrob Agents. 2017 Feb 2. pii: S0924-8579(17)30033-X. doi: 10.1016/j.ijantimicag.2016.11.030. [Epub ahead of print]
The combination of sofosbuvir and simeprevir ± ribavirin (SOF + SMV ± RBV) for hepatitis C virus (HCV) treatment has been associated with high rates of sustained virological response (SVR). Few data are available regarding this regimen in HIV/HCV co-infected patients. This study evaluated the effectiveness and safety of a 12-week course of SOF + SMV ± RBV in a cohort of HCV monoinfected and HIV/HCV co-infected individuals. HCV-infected patients, with or without HIV infection, receiving a 12-week course of SOF + SMV ± RBV in four Italian centres from February to October 2015, were included in this retrospective observational study. Clinical and biochemical data were retrieved for all patients. A total of 88 individuals were evaluated: 29 (33.0%) HIV/HCV co-infected and 59 (67.0%) monoinfected. Most patients were males with HCV genotype 1b (62.5%) and 1a (25%) infection. RBV was used in 41 HCV monoinfected and 6 HIV/HCV co-infected patients. Cirrhosis was found in 67 patients (76.1%). The most common adverse events (AEs) were rash and/or pruritus (23.9%), fatigue (13.6%) and anaemia (9.1%). Serious AEs occurred in three patients (3.4%). No treatment discontinuations were observed. RBV use was associated with multiple AEs ($P = 0.02$). An overall SVR12 of 93.2% was achieved; 96.6% in HCV monoinfected and 86.2% in HIV/HCV co-infected individuals, without significance both in univariate ($P = 0.09$) and multivariate analyses ($P = 0.12$). A baseline platelet count ≥90 000/mm3 was associated with higher rates of SVR ($P = 0.005$). A 12-week course of SOF + SMV ± RBV was associated with good safety and high SVR12 rate both in HCV monoinfected and HIV-HCV co-infected individuals.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Herbal approach in the treatment of pancytopenia. Bagwe SM, Kale PP, Bhatt LK, Prabhavalkar KS. J Complement Integr Med. 2017 Feb 14. pii: /j/jcim.ahead-of-print/jcim-2016-0053/jcim-2016-0053.xml. doi: 10.1515/jcim-2016-0053. [Epub ahead of print]
Pancytopenia is a health condition in which there is a reduction in the amount of leucocytes, erythrocytes and thrombocytes. If more than one of the blood cells is low then the condition is called as bicytopenia. The pancytopenic condition is observed in treatment of diseased conditions like thalassemia and hepatitis C. Iatrogenically pancytopenia is caused by some antibiotics and anti-HCV drugs. Medical conditions like aplastic anaemia, lymphoma, copper deficiency, and so forth can also cause pancytopenia. Pancytopenia can in turn decrease the immunity of the person and thereby can be fatal. Current therapies for pancytopenia include bone marrow stimulant drugs, blood transfusion and bone marrow transplant. The current therapies are

very excruciating and have long-term side-effects. Therefore, treating these condition using herbal drugs is very important. Herbs like wheatgrass, papaya leaves and garlic are effective in treating single lineage cytopenias. The present review is focused on the potential effects of natural herbs for the treatment of pancytopenia.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

High incidence of cardiac dysfunction and response to antiviral treatment in patients with chronic hepatitis C virus infection.
Poller W1,2, Kaya Z3,4, Muche M5, et al. Clin Res Cardiol. 2017 Feb 24. doi: 10.1007/s00392-017-1086-1. [Epub ahead of print]
AIMS: Hepatitis C virus (HCV) has been associated with cardiomyopathies. Former anti-HCV therapies employing interferon could have serious side effects in patients with advanced heart failure since interferon may adversely impact upon cardiac function. We, therefore, examined whether the novel, interferon-free and highly virus-selective anti-HCV combination therapy might be applicable even in advanced or end-stage heart failure. **METHODS AND RESULTS:** In a retrospective series of HCV-positive patients admitted to our institution with suspected cardiac disease, coronary, valvular or hypertensive heart disease was diagnosed in 70/146 (47.9%). Among the others, 36/76 (47.4%) had myocardial disease: LV (32.9%)/RV (13.2%) hypertrophy, RV dysfunction (13.2%)/dilation (6.6%), severe diastolic dysfunction (7.9%), pulmonary hypertension (22.4%). One critically ill patient listed for heart transplantation (HTX) had previously not tolerated an interferon-based protocol. To still improve her chance of enduring transplant survival, we attempted an interferon-free virus-selective antiviral combination drug protocol under careful monitoring of possible side effects. Regarding clinical status she tolerated this treatment well, with the exception of transient severe hyponatremia requiring substitution. Her NYHA functional class improved from II-IV before to class II immediately after successful complete HCV elimination. **CONCLUSIONS:** Whereas prevalence of cardiac dysfunction and potential benefit from antiviral treatment was reported previously, there is lack of data regarding the response of patients with advanced heart failure. Since the highly HCV-selective drugs used above do not eliminate other cardiotropic viruses and have no direct effect on inflammation, massive improvement in such critically ill patients indicates a causal role of HCV in their cardiac failure, and of HCV elimination in their functional recovery.

Examination of the Hepatitis C Virus care continuum among individuals with an opioid use disorder in substance use treatment. Brown JL1, Gause NK2, Lewis D3, Winhusen T3. J Subst Abuse Treat. 2017 Feb 2. pii: S0740-5472(16)30426-3. doi: 10.1016/j.jsat.2017.01.017. [Epub ahead of print]
BACKGROUND: Hepatitis C Virus (HCV) risk is elevated for individuals with an opioid use disorder (OUD). Routine HCV testing is recommended for high-risk individuals, including those with an injection drug use history. HCV antibody testing addresses the first step in the HCV treatment care cascade, with uptake and completion of HCV treatment among individuals with chronic HCV as the optimal care cascade endpoint. The aim of this study was to characterize self-reported HCV treatment cascade outcomes among individuals with an OUD in outpatient medication assisted treatment (MAT). **METHODS:** Individuals receiving methadone or buprenorphine treatment (N=202, 67.8% female, M age=35.0, SD=8.4) completed a brief,

anonymous paper-and-pencil survey examining self-reported history of HCV testing, diagnosis, and treatment. Descriptive statistics characterized HCV treatment cascade outcomes. **RESULTS:** A majority (79.3%) endorsed a lifetime HCV testing history; 34.9% were tested for HCV during the past year. Of those with a lifetime HCV testing history, 42.7% indicated they have been told they have HCV (n=67/157), with 21% (n=14/67) of those individuals reporting that they have been told they have chronic HCV, and 71.4% (n=10/14) of those with chronic HCV reporting receipt of HCV treatment. **DISCUSSION:** Results underscore gaps in the HCV care continuum among individuals with OUD in MAT. Interventions to increase uptake of HCV testing, communication of HCV diagnostic and treatment information by medical providers, linkage to HCV medical care, and uptake and adherence to HCV treatment are urgently needed, particularly among individuals with an OUD in MAT.

HCV screening in a cohort of HIV infected and uninfected homeless and marginally housed women in San Francisco, California. Page K1, Yu M2, Cohen J3, Evans J2, Shumway M4, Riley ED5. BMC Public Health. 2017 Feb 7;17(1):171. doi: 10.1186/s12889-017-4102-5.
BACKGROUND: Hepatitis C virus (HCV) screening has taken on new importance as a result of updated guidelines and new curative therapies. Relatively few studies have assessed HCV infection in homeless populations, and a minority include women. We assessed prevalence and correlates of HCV exposure in a cohort of homeless and unstably housed women in San Francisco, and estimated the proportion undiagnosed. **METHODS:** A probability sample of 246 women were recruited at free meal programs, homeless shelters, and low-cost single room occupancy hotels in San Francisco; women with HIV were oversampled. At baseline, anti-HCV status was assessed using an enzyme immunoassay, and results compared in both HIV-positive and negative women. Exposures were assessed by self-report. Logistic regression was used to assess factors independently associated th HCV exposure. **RESULTS:** Among 246 women 45.9% were anti-HCV positive, of whom 61.1% were HIV coinfected; 27.4% of positives reported no prior screening. Most (72%) women were in the 'baby-boomer' birth cohort; 19% reported recent injection drug use (IDU). Factors independently associated with anti-HCV positivity were: being born in 1965 or earlier (AOR) 3.94; 95%CI: 1.88, 8.26), IDU history (AOR 4.0; 95%CI: 1.68, 9.55), and number of psychiatric diagnoses (AOR 1.16; 95%CI: 1.08, 1.25). **CONCLUSIONS:** Results fill an important gap in information regarding HCV among homeless women, and confirm the need for enhanced screening in this population where a high proportion are baby-boomers and have a history of drug use and psychiatric problems. Due to their age and risk profile, there is a high probability that women in this study have been infected for decades, and thus have significant liver disease. The association with mental illness and HCV suggests that in addition increased screening, augmenting mental health care and support may enhance treatment success.

Direct-acting antivirals are effective for chronic hepatitis C treatment in elderly patients: a real-world study of 17,487 patients. Su F1, Beste LA, Green PK, Berry K, Ioannou GN. Eur J Gastroenterol Hepatol. 2017 Feb 13. doi: 10.1097/MEG.0000000000000858. [Epub ahead of print]
BACKGROUND: The mean age of patients with chronic hepatitis C virus (HCV) infection in the USA has been increasing. Despite the increasing proportion of HCV-infected elderly patients, this group is under-represented in clinical trials of HCV treatment. **AIM:** We aimed to describe the real-world effectiveness of direct-acting antivirals (DAAs) among elderly patients.

PATIENTS AND METHODS: We retrospectively identified 17,487 HCV-infected patients who were started on treatment with sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ombitasvir/ritonavir/dasabuvir-based regimens in the Veterans Affairs Healthcare System between 1 January 2014 and 30 June 2015. We ascertained sustained virologic response (SVR) rates in patients aged below 55, 55-59, 60-64, 65-69, 70-74, and 75 years or older and performed multivariable logistic regression to determine whether age predicted SVR. **RESULTS:** Overall unadjusted SVR rates were 91.2% [95% confidence interval (CI): 89.7-92.4], 89.8% (95% CI: 88.8-90.7), 90.8% (95% CI: 90.1-91.6), 91.1% (95% CI: 90.1-91.9), 90.0% (95% CI: 86.9-92.4), and 93.8% (95% CI: 88.8-96.7) in patients aged below 55, 55-59, 60-64, 65-69, 70-74, and 75 years or older. Unadjusted SVR rates were similar in all age groups after stratifying by genotype, treatment regimen, stage of liver disease, and treatment experience. In multivariate models, age was not predictive of SVR after adjusting for confounders. **CONCLUSION:** DAAs produce high rates of SVR in all age groups, including patients in our oldest age category (≥75 years). Advanced age in and of itself should not be considered a barrier to initiating DAA treatment.

An effectiveness study of group psychoeducation for hepatitis C patients in community clinics. North CS1, Pollio DE, Sims OT, Jain MK, Brown GR, Downs DL, Lisker-Melman M, Hong BA. Eur J Gastroenterol Hepatol. 2017 Feb 13. doi: 10.1097/MEG.0000000000000860. [Epub ahead of print]
OBJECTIVE: A successful psychoeducation program for serious mental illness, PsychoEducation Responsive to Families (PERF), was modified for hepatitis C virus (HCV). An effectiveness study was carried out comparing HCV-PERF with didactic education. **PATIENTS AND METHODS:** A sample of 309 adult HCV patients was recruited from three outpatient settings and randomized (60% HCV-PERF, 40% didactic control). Groups met for 90 min bimonthly for 6 months following separate structured protocols. HCV-PERF sessions included a didactic curriculum developed uniquely for groups by member choice, with group problem-solving and support interactions. Patients were assessed at baseline, after the intervention, and 1 year later. Demographic and HCV-related variables and structured diagnostic interview data were obtained. **RESULTS:** Both groups improved significantly on major depression and alcohol and drug use, quality of life, risk behaviors, and treatment satisfaction, and worsened on disability and perceived HCV-related problems. Intervention groups did not differ on outcomes. **CONCLUSION:** Even though the active intervention did not achieve a significant improvement relative to the control condition, the observable improvements in both conditions warrant further exploration of the contributions of education and support as potentially important elements of HCV behavioral intervention. Further study is needed to identify elements common to education interventions that may be contributory to the improved outcomes over time.

Risk of End Stage Liver Disease, Hepatocellular Carcinoma and Liver-Related Death By Fibrosis Stage in the Hepatitis C Alaska Cohort. Bruden DJ1, McMahon BJ1,2, Townshend-Bulson L2, et al. Hepatology. 2017 Feb 13. doi: 10.1002/hep.29115. [Epub ahead of print]
Long-term prospective studies of the outcomes associated with HCV infection are rare and critical for assessing the potential impact of HCV treatment. Using liver biopsy as a start point, we looked at development of end stage liver disease (ESLD), hepatocellular carcinoma (HCC) and liver-related death (LRD) according to fibrosis stage, among a cohort of American Indian/Alaska Native persons in Alaska. Persons were classified as having no/mild (Ishak=0,1), moderate (Ishak=2), or severe (Ishak=3,4) fibrosis or cirrhosis (Ishak=5,6). We examined time

until development of ESLD, HCC and LRD and report survival probabilities at 3, 5, 7 and 10-years. Of 407 persons, 39%(n = 150) had no/mild fibrosis, 32%(n = 131) had moderate fibrosis, 22%(n = 88) had severe fibrosis and 9%(n = 38) had cirrhosis. The average time of follow-up was 7.3 years. Within 5 years of biopsy, 1.7% (95% confidence interval (CI):0.4,6.8) of persons with none/mild fibrosis developed ESLD compared to 7.9% (CI:4.0,15.2), 16.4% (CI:9.6,27.2) and 49.0% (CI:33.0,67.7) with moderate, severe fibrosis, and cirrhosis, respectively (p<0.01). The 5-year outcome of HCC was 1.0% (CI:0.1,7.0), 1.0% (CI 0.1,6.6), 1.1% (CI:0.2,7.7) and 13.4% (CI:4.4,36.7) among persons with none/mild, moderate fibrosis, severe fibrosis and cirrhosis, respectively (p<0.01). Five years following biopsy, 0.0% (CI:0.0,14.8) of persons with none/mild fibrosis had suffered an LRD compared to 1.0% (CI:0.2,7.5) of persons with moderate fibrosis, 4.7% (CI:1.5,14.1) with severe fibrosis and 16.3% (CI:7.0,35.1) with cirrhosis (p<0.01). Conclusion For prevention of HCC, LRD and ESLD in the short-term, HCV therapy should target those with more than mild fibrosis.

Ongoing liver inflammation in patients with chronic hepatitis C and sustained virological response. Welsch C1, Efinger M1, von Wagner M1, Herrmann E2, Zeuzem S1, Welzel TM1, Lange CM1. PLoS One. 2017 Feb 14;12(2):e0171755. doi: 10.1371/journal.pone.0171755. eCollection 2017.
BACKGROUND: Novel direct-acting antiviral DAA combination therapies tremendously improved sustained virologic response (SVR) rates in patients with chronic HCV infection. SVR is typically accompanied by normalization of liver enzymes, however, hepatic inflammation, i.e. persistently elevated aminotransferase levels may persist despite HCV eradication. Aim: To investigate prevalence and risk factors for ongoing hepatic inflammation after SVR in two large patient cohorts. **METHODS:** This post-hoc analysis was based on prospectively collected demographic and clinical data from 834 patients with SVR after HCV treatment with either PegIFN- or DAA-based treatment regimens from the PRAMA trial (n = 341) or patients treated at our outpatient clinic (n = 493). **RESULTS:** We observed an unexpected high prevalence of post-SVR inflammation, including patients who received novel IFN-free DAA-based therapies. Up to 10% of patients had ongoing elevation of aminotransferase levels and another 25% showed aminotransferase activity above the so-called healthy range. Several baseline factors were independently associated with post-SVR aminotransferase elevation. Among those, particularly male gender, advanced liver disease and markers for liver steatosis were strongly predictive for persistent ALT elevation. The use of IFN-based antiviral treatment was independently correlated with post-SVR inflammation, further supporting the overall benefit of IFN-free combination regimens. **CONCLUSION:** This is the first comprehensive study on a large patient cohort investigating the prevalence and risk factors for ongoing liver inflammation after eradication of HCV. Our data show a high proportion of patients with ongoing hepatic inflammation despite HCV eradication with potential implications for the management of approximately one third of all patients upon SVR.

Predictors of hepatitis C testing intention among African American Baby Boomers. Rashrash M1, Maneno M2, Wutoh A2, Ettienne E2, Daftary M2. J Epidemiol Glob Health. 2017 Feb 16. pii: S2210-6006(15)30054-X. doi: 10.1016/j.jegh.2016.12.005. [Epub ahead of print]
Baby Boomers (BBs) are responsible for three-quarters of hepatitis C (HCV) infections in the United States; however, HCV testing is distinctly underused by them. A cross-sectional study was conducted to assess the prevalence of HCV testing and to evaluate predictors of HCV testing

intention among African-American BBs. The study was guided by the Health Belief Model and theory of reasoned action frameworks. Of the 137 participants included in the study, 44.8% had at least a college education; 13.9% received prior to 1992 blood transfusion. Findings related to HCV testing showed that 32.1% of the participants intended to test for HCV within 6months and 43.8% had received a previous HCV test. Significant predictors of HCV testing intention within 6months included having a blood transfusion prior to 1992 [odds ratio (OR)=8.25, 95% confidence interval (CI): 2.02-33.61], perceptions of benefits (OR=1.57, 95% CI: 1.13-2.18), severity (OR=1.39, 95% CI: 1.17-1.65), and subjective norms (OR=1.42, 95% CI: 1.12-1.79). These predictors of HCV testing intention can be used to develop future HCV testing initiatives for African-American BBs.

Understanding Patient Perceptions and Risk for Hepatitis C Screening. Grannan S1. J Viral Hepat. 2017 Feb 15. doi: 10.1111/jvh.12692. [Epub ahead of print]
OBJECTIVES: The specific aims were to identify specific themes and barriers to HCV testing and to determine if testing rates increased when patients self-identify their risk factors and were offered testing. **SETTING:** The study was conducted at a Federally Qualified Health Center (FQHC) in an underserved neighborhood located in the Mountain West. **METHODS:** This descriptive study used survey and group-level electronic health record (EHR) data. Adults 18 years and older that speak and write in English or Spanish and arrived for care at a FQHC were recruited to complete a survey. The ten item survey assessed demographics, HCV risk, willingness to test, and reasons for not testing. Screening rates during survey period were compared to baseline 2014 rates using EHR data. EHR demographic, testing and incidents of positive HCV infections data was analyzed and compared with survey data. **RESULTS:** The typical participant (N=111) was female (74%), Baby Boomer (1945-1965) generation (45%), white (86%), and uninsured (54%). Top 6 self-identified risks were tattoo and/or body piercings (47.7%), Baby Boomer (36%), multiple sex partners (18%), work related exposure (8.1%), non-injection drug use (8.1%), and injection drug use (7.2%). Only 78% of Baby Boomers identified being a Baby Boomer as a risk. Eighty-one percent of participants did not want to test. Testing did not increase during study period (2.9 tests/week in 2014 and 2.1 tests/week during survey period). Main reasons not to test were "I do not have any risk factors" (30.2%), concerned with cost (15.1%), tested in the past (15.1%), other reasons (9.3%), not feeling well (5.8%). More than one main reason was selected by 17% of participants. **CONCLUSIONS:** Baby Boomers did not self-identifying risk. Also, testing incidence did not increase when patients self-identified risk and were offered testing. Many participants did not identify risk which is a barrier to testing. Additional barriers to overcome are concerns with cost and comfort in the clinic setting. This article is protected by copyright. All rights reserved.

Pharmacy Use in the First Year of the Veterans Choice Program: A Mixed-Methods Evaluation. Gellad WF1, Cunningham FE, Good CB, Thorpe JM, Thorpe CT, Bair B, Roman K, Zickmund SL. Med Care. 2017 Feb 17. doi: 10.1097/MLR.0000000000000661. [Epub ahead of print]
BACKGROUND: The Veterans Choice Program (VCP) was created to ensure timely access to health care in the Department of Veterans Affairs (VA). Under this program, medications may be ordered by select non-VA clinicians to be dispensed by VA pharmacies, creating new challenges in ensuring medication safety. **OBJECTIVES:** To examine pharmaceutical use during the first

year of the VCP and to understand barriers and facilitators for VA pharmacists to dispensing medications under the VCP. **STUDY DESIGN:** Mixed-methods evaluation. **METHODS:** We captured all prescriptions dispensed through the VCP and described the demographics of VCP users and their medications. We also conducted semistructured interviews of VA pharmacists, focusing on VA formulary management and experiences dispensing opioid and hepatitis C (HCV) medications. Codebook development and coding followed iterative qualitative methods. **RESULTS:** Overall, 17,346 Veterans received 56,426 VCP prescriptions from November 7, 2014 through November 7, 2015. The total medication cost was $27 million, 90% of which was for only 2772 HCV prescriptions. Topical eye drops and opioids represented the most commonly dispensed prescriptions (15.6% and 9.2% of all prescriptions, respectively). Pharmacists reported numerous challenges to dispensing VCP medications, including time required to contact non-VA clinicians about formulary issues, requiring controlled substance prescriptions to be hand delivered to VA pharmacies, and lack of access to laboratory data required to safely dispense medications. **CONCLUSIONS:** HCV-related medication costs predominated the first year of VCP, but this is likely to change going forward. The safe use of opioids, efficient management of nonformulary medications, and unintended new barriers to access created by the VCP must be addressed.

Impact of Renal Disease on Patients with Hepatitis C: A Retrospective Analysis of Disease Burden, Clinical Outcomes, and Health Care Utilization and Cost. Solid CA1, Peter SA, Natwick T, Guo H, Collins AJ, Arduino JM. Nephron. 2017 Feb 18. doi: 10.1159/000454684. [Epub ahead of print]

BACKGROUND/AIMS: Few studies explore the magnitude of the disease burden and health care utilization imposed by renal disease among patients with hepatitis C virus (HCV). We aimed to describe the characteristics, outcomes, and health care utilization and costs of patients with HCV with and without renal impairment. **METHODS:** This retrospective analysis used 2 administrative claims databases: the US commercially insured population in Truven Health MarketScan® data (aged 20-64 years), and the US Medicare fee-for-service population in the Medicare 20% sample (aged ≥65 years). Baseline characteristics and comorbid conditions were identified from claims during 2011; patients were followed for up to 1 year (beginning January 1, 2012) to identify health outcomes of interest and health care utilization and costs. **RESULTS:** In the MarketScan and Medicare databases, 35,965 and 10,608 patients with HCV were identified, 8.5 and 26.5% with evidence of renal disease (chronic kidney disease [CKD] or end-stage renal disease [ESRD]). Most comorbid conditions and unadjusted outcome rates increased across groups from patients with no evidence of renal disease to non-ESRD CKD to ESRD. Health care utilization followed a similar pattern, as did the costs. **CONCLUSIONS:** Our findings suggest that HCV patients with concurrent renal disease have significantly more comorbidity, a higher likelihood of negative health outcomes, and higher health care utilization and costs.

Nonprescription naloxone and syringe sales in the midst of opioid overdose and hepatitis C virus epidemics: Massachusetts, 2015. Stopka TJ, Donahue A, Hutcheson M, Green TC. J Am Pharm Assoc (2003). 2017 Feb 8. pii: S1544-3191(16)31026-3. doi: 10.1016/j.japh.2016.12.077. [Epub ahead of print]

OBJECTIVES: To determine the prevalence of nonprescription naloxone and sterile syringe sales, factors associated with nonprescription sales, geospatial access to nonprescription naloxone and syringe-selling pharmacies, and targets for potential interventions. **DESIGN:**

Cross-sectional study. **SETTING AND PARTICIPANTS:** Massachusetts has experienced steep increases in reported opioid overdoses and hepatitis C virus cases in the past decade. Pharmacists have the potential to play a substantial role in increasing access to nonprescription naloxone and sterile syringes, which can reverse opioid overdoses and decrease hepatitis C virus transmission, respectively. We completed brief telephone surveys with 809 of 1042 retail pharmacies across Massachusetts (response rate = 77.6%) during 2015 to assess experience with nonprescription sales of naloxone and sterile syringes. **OUTCOME MEASURES:** Our primary outcomes were the stocking and selling of naloxone in the pharmacy (yes or no) for nonprescription sales and nonprescription syringe sales (yes or no). We conducted multivariable regression analyses and created maps using a geographic information system to identify factors associated with nonprescription sales of naloxone and sterile syringes, and to improve our understanding of geospatial access to pharmacy-based naloxone and syringe sales. **RESULTS:** More than 97% of pharmacies reported selling sterile syringes without requiring a prescription, and 45% of pharmacies reported stocking and selling naloxone. Factors associated with nonprescription sales included hours of operation, experience with and interest in harm reduction activities, and presence in an opioid overdose hotspot. Geographic access to nonprescription sale of sterile syringes is widespread, whereas geospatial access to naloxone is limited. Training to understand the benefits, applications, and distribution needs of naloxone is of interest to surveyed pharmacists. **CONCLUSION:** Access to sterile syringes through nonprescription sales is strong across Massachusetts, and although more than 350 pharmacies (45%) reported stocking and selling naloxone to prevent opioid overdose deaths, there is much room for improvement in access and training among pharmacy staff members.

A clinician's guide to the cost and health benefits of hepatitis C cure assessed from the individual patient perspective. McEwan P1, Selvapatt N, Brown A, Thursz M, Bennett H, Webster S, Kalsekar A, Yuan Y, Brenner M, Gordon J. Eur J Gastroenterol Hepatol. 2017 Feb;29(2):208-214. doi: 10.1097/MEG.0000000000000773.
BACKGROUND AND AIMS: The hepatitis C virus (HCV) remains a considerable public health challenge. Novel direct-acting antiviral (DAA) regimens offer high cure rates and the promise of reduced HCV incidence and prevalence following the up-scaling of treatment. This has focused attention towards affordability. This study aimed to estimate the economic value of cure to evaluate the treatment costs justifiable from the patient perspective. **PATIENTS AND METHODS:** A published, validated HCV model was utilized to contrast clinical and cost outcomes for patients aged 30-70 years, stratified by METAVIR F0-F4, for (i) no treatment and (ii) successful treatment [i.e. sustained virologic response (SVR)] ignoring the cost of treatment. Regression equations were fitted and used to determine the financial expenditure justifiable to achieve a cost-neutral or a cost-effective [£20 000 per quality-adjusted life-year (QALY)] cure. Model inputs were derived from UK literature; costs and utilities were discounted at 3.5% over a lifetime horizon. **RESULTS:** To achieve cost-neutrality, the maximum discounted expenditure justifiable for SVR was £3774-43 607 across ages and fibrosis stages. Spending between £19 745 (70 years, F0) and £188 420 (30 years, F4) on SVR is expected to be cost-effective at £20 000/QALY willingness-to-pay threshold. **CONCLUSION:** Heterogeneity across HCV patients is considerable, which can obscure the relevance of conventional cohort-based economic models evaluated at the mean, particularly when considering the value of treatment at the individual patient level. By quantifying the full exposition of HCV cost-savings and health

benefits realizable following HCV cure, this study provides insight into the economic value of successful treatment from the patient perspective.

HCV Prevalence in Asian Americans in California. Lin ON1, Chang C1, Lee J2, Do A1, Martin M3,4, Martin A4,5, Nguyen MH6. J Immigr Minor Health. 2017 Feb;19(1):91-97. doi: 10.1007/s10903-016-0342-1.
The World Health Organization estimates that 170 million persons are infected with HCV worldwide, but only 22 million are from the Americas and Europe, compared to 94 million from Asia. HCV prevalence in the general US population is 1.6 %, but data for Asian Americans are limited. Our goal was to examine HCV prevalence in Asian Americans in a large ethnically diverse patient cohort seeking primary care at a free clinic in Northern California. A total of 1347 consecutive patients were seen from September 2009 to October 2012 and were studied via individual chart review using case report forms. HCV infection was defined as positive HCV antibody (anti-HCV) or HCV RNA by PCR. 699 out of 1347 patients were screened for HCV. Asian Americans comprised 57.2 % of these patients and 29 (4.1 %) patients tested positive for HCV. Of these 29 HCV-positive patients, 22 (75.9 %) were Asian, yielding a prevalence of 5.5 % for Asians and 2.3 % for non-Asians (P = 0.038). The highest HCV prevalence was seen in Vietnamese patients at 7.9 %, and 6.0 % in Chinese patients. Of the HCV-positive Asians, none had a history of intravenous drug use (IVDU), tattoos, or sexual exposure. On multivariate analysis, significant independent predictors for positive HCV infection were male gender (OR 2.53, P = 0.02) and presence of known risk factors (OR 21.1, P < 0.001). However, older age and Asian ethnicity were found to be significant predictors of HCV infection (OR 1.03, P = 0.05 and 2.31, P = 0.066, respectively). In our study, HCV prevalence in patients seeking routine primary care was 5.5 % in Asian Americans, which was over double the prevalence for non-Asians at 2.3 %. Known risk factors were also notably absent in Asian patients with HCV infection. The high prevalence of HCV in Asian-Americans is likely reflective of the higher prevalence of HCV in their countries of origin in Asia. Asian-Americans immigrants from endemic countries are at higher risk of HCV infection and should be screened for HCV, regardless of their exposure risk profile.

HEPATOCELLULAR (LIVER) CANCER

Hepatitis C virus infection triggers a tumor-like glutamine metabolism. Lévy PL1, Duponchel S1,2, Eischeid H3, et al. Hepatology. 2017 Mar;65(3):789-803. doi: 10.1002/hep.28949. Epub 2017 Feb 3.
Chronic infection with hepatitis C virus (HCV) is one of the main causes of hepatocellular carcinoma. However, the molecular mechanisms linking the infection to cancer development remain poorly understood. Here we used HCV-infected cells and liver biopsies to study how HCV modulates the glutaminolysis pathway, which is known to play an important role in cellular energetics, stress defense, and neoplastic transformation. Transcript levels of glutaminolytic factors were quantified in Huh7.5 cells or primary human hepatocytes infected with the Japanese fulminant hepatitis 1 HCV strain as well as in biopsies of chronic HCV patients. Nutrient deprivation, biochemical analysis, and metabolite quantification were performed with HCV-infected Huh7.5 cells. Furthermore, short hairpin RNA vectors and small molecule inhibitors were used to investigate the dependence of HCV replication on metabolic changes. We show that HCV modulates the transcript levels of key enzymes of glutamine metabolism in vitro and in

liver biopsies of chronic HCV patients. Consistently, HCV infection increases glutamine use and dependence. We finally show that inhibiting glutamine metabolism attenuates HCV infection and the oxidative stress associated with HCV infection. **CONCLUSION:** Our data suggest that HCV establishes glutamine dependence, which is required for viral replication, and, importantly, that glutamine addiction is a hallmark of tumor cells. While HCV induces glutaminolysis to create an environment favorable for viral replication, it predisposes the cell to transformation. Glutaminolytic enzymes may be interesting therapeutic targets for prevention of hepatocarcinogenesis in chronic hepatitis C. (Hepatology 2017;65:789-803).

Hepatocellular Carcinoma Decreases the Chance of Successful Hepatitis C Virus Therapy with Direct-Acting Antivirals. Prenner S1, VanWagner LB2, Flamm SL3, Salem R4, Lewandowski RJ5, Kulik L6. J Hepatol. 2017 Feb 1. pii: S0168-8278(17)30053-3. doi: 10.1016/j.jhep.2017.01.020. [Epub ahead of print]

BACKGROUND: The approval of all-oral direct acting antiviral (DAA) regimens for the treatment of hepatitis C virus (HCV) has led to the expansion of therapy to include patients with cirrhosis who have hepatocellular carcinoma (HCC). Data on the use of DAA's in HCV+ patients with HCC is limited. The aim of this study was to assess the efficacy of all oral-DAA regimens in HCV+ cirrhotic patients who have or had HCC compared to those without HCC.
METHODS: We conducted a retrospective cohort study of all cirrhotic patients who were treated for HCV with DAA's at our institution between January 2014 and November 2015.
RESULTS: We identified 421 HCV+ patients with cirrhosis of whom 33% had active or a history of HCC. Failure to achieve sustained virologic response (SVR) occurred in 21% of patients with HCC compared to 12% of patients without HCC (p=0.009). Of the 29 patients with HCC who did not achieve SVR, 27 (93%) occurred with active tumor present. DAA therapy in the presence of inactive tumor or after removal of tumor (resection/transplant) resulted in excellent SVR rates, similar to those without HCC (p <0.0001). In multivariable analysis, the primary predictor of DAA treatment failure was the presence of active HCC at the time of HCV treatment initiation (Adjusted Odds Ratio= 8.5, 95% confidence interval= 3.90-18.49).
CONCLUSIONS: The presence of active HCC tumor at the initiation of HCV therapy is significantly associated with all-oral DAA treatment failure. HCV treatment after curative therapies for HCC resulted in excellent SVR. **LAY SUMMARY:** The new medications for hepatitis C have excellent cure rates. However, our study shows that in patients with both liver cancer and hepatitis C, they do not achieve these cure rates. Patients with liver cancer are almost 6 times more likely to fail hepatitis C treatment than patients without liver cancer.

The role of exosomes in hepatitis, liver cirrhosis and hepatocellular carcinoma. Shen J1, Huang CK2, Yu H1, et al. J Cell Mol Med. 2017 Feb 22. doi: 10.1111/jcmm.12950. [Epub ahead of print]

Exosomes are small vesicles that were initially thought to be a mechanism for discarding unneeded membrane proteins from reticulocytes. Their mediation of intercellular communication appears to be associated with several biological functions. Current studies have shown that most mammalian cells undergo the process of exosome formation and utilize exosome-mediated cell communication. Exosomes contain various microRNAs, mRNAs and proteins. They have been reported to mediate multiple functions, such as antigen presentation, immune escape and tumour progression. This concise review highlights the findings regarding the roles of exosomes in liver diseases, particularly hepatitis B, hepatitis C, liver cirrhosis and hepatocellular carcinoma.

However, further elucidation of the contributions of exosomes to intercellular information transmission is needed. The potential medical applications of exosomes in liver diseases seem practical and will depend on the ingenuity of future investigators and their insights into exosome-mediated biological processes.

Exceptional serological and radiological response to sorafenib in 2 patients with advanced hepatocellular carcinoma and chronic hepatitis C viral infection: case report and review of the literature. Atkin C1, Earwaker P1, Pallan A2, Shetty S3, Punia P1, Ma YT4. BMC Gastroenterol. 2017 Feb 14;17(1):30. doi: 10.1186/s12876-017-0585-x.
BACKGROUND: In patients with advanced hepatocellular carcinoma (HCC), the multikinase inhibitor sorafenib is the only systemic treatment that has been shown to increase overall survival. However, similar to other tyrosine kinase inhibitors, most patients achieve disease stabilisation radiologically, and only 2-3% of patients achieve a partial response. Recent exploratory subgroup analyses of the large phase 3 trials have demonstrated that patients with chronic hepatitis C virus (HCV) infection associated HCC survive longer than those who are negative for HCV. The mechanism underlying this currently remains unknown. A small number of cases of complete response to sorafenib treatment have now been reported worldwide, however a prolonged response has only been reported in 2 cases, both of whom had HCV-related HCC. **CASE PRESENTATION:** A 55 year old gentleman was diagnosed with hepatocellular carcinoma and concomitant chronic hepatitis C viral infection. He progressed following transarterial chemoemoblisation treatment and was commenced on sorafenib treatment. His serum alphafetoprotein level normalised within 2 months of treatment and he achieved an almost complete radiological response. This response was maintained for 20 months before the patient progressed. A 75 year old lady was diagnosed with advanced hepatocellular carcinoma and concomitant chronic hepatitis C viral infection. She was commenced on sorafenib treatment but required early dose reductions due to palmar plantar erythrodysesthesia, and liver decompensation. Despite this she achieved an excellent serological and radiological response that was maintained for 24 months. **CONCLUSIONS:** Our two cases show that patients with HCV-associated HCC can attain excellent responses to sorafenib treatment that is durable. Furthermore, such exceptional responses can be achieved even with dose reductions and treatment breaks.

Hepatic Decompensation is the Major Driver of Death In HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. Cabibbo G1, Petta S1, Barbara M1, et al. J Hepatol. 2017 Feb 9. pii: S0168-8278(17)30070-3. doi: 10.1016/j.jhep.2017.01.033. [Epub ahead of print]
BACKGROUND & AIMS: A major problem in assessing the long-term outcome of HCV-infected cirrhotic patients with successfully treated Barcelona Clinic Liver Cancer (BCLC) A hepatocellular carcinoma (HCC) arises from the lack of models accounting for early changes during follow-up. Aim of study is to estimate the impact on 5-year overall survival (OS) of early (occurring within 12 months after complete radiological response) time-dependents events (HCC recurrence or hepatic decompensation) in a large cohort of successfully treated HCC patients with HCV cirrhosis. **METHODS:** A total of 328 consecutive Caucasian patients with HCV-related cirrhosis and BCLC 0/A HCC who had complete radiological response after curative resection or thermal ablation were prospectively recruited to this study. Primary endpoint of the study was 5-year OS. Independent baseline and time-dependent predictors of 5-year OS were

identified by Cox model. **RESULTS:** The observed 5-year survival rate was 44%. The observed HCC early recurrence and early hepatic decompensation rate were 21% and 10%, respectively. Early hepatic decompensation (Hazard Ratio [HR] 7.52; 95%CI:1.23-13.48) and HCC early recurrence as time-dependent covariates (HR 2.50; 95%CI:1.23-5.05), presence of esophageal varices at baseline (HR 1.66; 95%CI:1.02-2.70) and age (HR 1.04; 95%CI:1.02-1.07) were significantly associated with the 5-year OS. **CONCLUSION:** Survival in HCV-infected cirrhotic patients with successfully treated HCC is mainly influenced by early hepatic decompensation. Our study indirectly suggests that direct antiviral agents could improve OS of HCC by long-term preservation of liver function, resulting in a lower cirrhosis-related mortality and a greater change of receiving curative treatments. **LAY SUMMARY:** Survival in hepatitis C virus (HCV) infected cirrhotic patients with successfully treated Hepatocellular Carcinoma (HCC) is mainly influenced by early hepatic decompensation. HCV eradication after treatment with new direct antiviral agents could improve overall survival of HCC patients by long-term preservation of liver function.

Genome-wide Association Study Identifies TLL1 Variant Associated With Development of Hepatocellular Carcinoma After Eradication of Hepatitis C Virus Infection.

Matsuura K1, Sawai H2, Ikeo K3, et al. Gastroenterology. 2017 Feb 2. pii: S0016-5085(17)30130-0. doi: 10.1053/j.gastro.2017.01.041. [Epub ahead of print]

BACKGROUND & AIMS: There is still a risk for hepatocellular carcinoma (HCC) development after eradication of hepatitis C virus (HCV) infection with anti-viral agents. We investigated genetic factors associated with the development of HCC in patients with a sustained virologic response (SVR) to treatment for chronic HCV infection. **METHODS:** We obtained genomic DNA from 457 patients in Japan with a SVR to interferon-based treatment for chronic HCV infection from 2007 through 2015. We conducted a genome-wide association study (GWAS) followed by a replication analysis of 79 candidate single nucleotide polymorphisms (SNPs) in an independent set of 486 patients in Japan. The study endpoint was HCC diagnosis or confirmation of lack of HCC (at follow-up examinations until December 2014 in the GWAS cohort, and until January 2016 in the replication cohort). We collected clinical and laboratory data from all patients. We analyzed expression levels of candidate gene variants in human hepatic stellate cells, rats with steatohepatitis caused by a choline-deficient L-amino acid-defined diet, and a mouse model of liver injury caused by administration of carbon tetrachloride. We also analyzed expression levels in liver tissues of patients with chronic HCV infection with different stages of fibrosis or tumors vs patients without HCV infection (controls). **RESULTS:** We found a strong association between the SNP rs17047200, located within the intron of the tolloid like 1 gene (TLL1) on chromosome 4, and development of HCC; there was a genome-wide level of significance when the results of the GWAS and replication study were combined (odds ratio, 2.37; P=2.66×10-8). Multivariate analysis showed rs17047200 AT/TT to be an independent risk factor for HCC (hazard ratio, 1.78; P=.008), along with male sex, older age, lower level of albumin, advanced stage of hepatic fibrosis, presence of diabetes, and higher post-treatment level of α-fetoprotein. Combining the rs17047200 genotype with other factors, we developed prediction models for HCC development in patients with mild or advanced hepatic fibrosis. Levels of TLL1 mRNA in human hepatic stellate cells increased with activation. Levels of Tll1 mRNA increased in liver tissues of rodents with hepatic fibrogenesis, compared with controls. Levels of TLL1 mRNA increased in liver tissues of patients with progression of fibrosis. Gene expression levels of TLL1 short variants, including isoform 2, were higher in patients with

rs17047200 AT/TT. **CONCLUSION:** In a GWAS, we identified the association between the SNP rs17047200, within the intron of TLL1, and development of HCC in patients who achieved an SVR to treatment for chronic HCV infection. We found levels of Tll1/TLL1 mRNA to be increased in rodent models of liver injury and liver tissues of patients with fibrosis, compared with controls. We propose that this SNP might affect splicing of TLL1 mRNA, yielding short variants with high catalytic activity that accelerate hepatic fibrogenesis and carcinogenesis. Further studies are needed to determine how rs17047200 affects TLL1 mRNA levels, splicing, and translation, as well as the prevalence of this variant among other patients with HCC. Tests for the TLL1 SNP might be used to identify patients at risk for HCC after an SVR to treatment of HCV infection.