



**July - August 2016**

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES  
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES  
HIV/HCV COINFECTION  
COMPLEMENTARY AND ALTERNATIVE MEDICINE  
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS  
LIVER CANCER

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**CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

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**[Ledipasvir/sofosbuvir-based treatment of patients with chronic genotype-1 HCV infection and cirrhosis: results from two Phase II studies.](#)**

Lawitz E1, Poordad F, Hyland RH, et al. Antivir Ther. 2016 Jun 27. doi: 10.3851/IMP3062. [Epub ahead of print]

**BACKGROUND:** Ledipasvir/sofosbuvir ± ribavirin administered for 12 weeks to patients with genotype 1 hepatitis C virus (HCV) infection and compensated cirrhosis is effective and well-tolerated. The Phase II TRILOGY-1 and TRILOGY-2 studies investigated whether ledipasvir/sofosbuvir plus the non-nucleotide NS5B inhibitor GS-9669 or the NS3/4A protease inhibitor vedoprevir could reduce treatment duration and/or eliminate the need for ribavirin in genotype 1 HCV-infected patients with compensated cirrhosis. **METHODS:** In TRILOGY-1, 100 cirrhotic patients were randomized (1:1:1) to 8 weeks of ledipasvir/sofosbuvir plus ribavirin, ledipasvir/sofosbuvir plus GS-9669 250 mg or ledipasvir/sofosbuvir plus GS-9669 500 mg. In TRILOGY-2, 46 previously treated cirrhotic patients were randomized (1:1) to 8 weeks of ledipasvir/sofosbuvir plus vedoprevir ± ribavirin. The co-primary endpoints were the proportion of patients with sustained virologic response 12 weeks after treatment discontinuation (SVR12) and safety. **RESULTS:** In both studies, most patients were male (each 65%) and white (92-96%), infected with HCV genotype 1a (62-70%) and had IL28B non-CC genotypes (82-87%). In total, 37-39% of patients were Hispanic or Latino. SVR12 rates were similar across treatment arms in TRILOGY-1 (82-91%) and TRILOGY-2 (88-95%); no patient had on-treatment virologic failure. Two serious adverse events (acute myocardial infarction and cardiomyopathy) were reported in two patients participating in TRILOGY-1, both of whom had pre-existing cardiac conditions. Laboratory abnormalities were infrequent. **CONCLUSIONS:** All ledipasvir/sofosbuvir-based regimens were well-tolerated. To shorten therapy and eliminate ribavirin, use of a more potent third agent or a third agent with a different mechanism of action may be required.

**[An Open-Label Trial of 12-Week Simeprevir plus Peginterferon/Ribavirin \(PR\) in Treatment-Naïve Patients with Hepatitis C Virus \(HCV\) Genotype 1 \(GT1\).](#)**

Asselah T1, Moreno C2, Sarrazin C3, et al. PLoS One. 2016 Jul 18;11(7):e0158526. doi: 10.1371/journal.pone.0158526. eCollection 2016.

**BACKGROUND:** Shortening duration of peginterferon-based HCV treatment reduces associated burden for patients. Primary objectives of this study were to assess the efficacy

against the minimally acceptable response rate 12 weeks post-treatment (SVR12) and safety of simeprevir plus PR in treatment-naïve HCV GT1 patients treated for 12 weeks. Additional objectives included the investigation of potential associations of rapid viral response and baseline factors with SVR12. **METHODS:** In this Phase III, open-label study in treatment-naïve HCV GT1 patients with F0-F2 fibrosis, patients with HCV-RNA <25 IU/mL (detectable/undetectable) at Week 2, and undetectable HCV-RNA at Weeks 4 and 8, stopped all treatment at Week 12. All other patients continued PR for a further 12 weeks. Baseline factors significantly associated with SVR12 were identified through logistic regression. **RESULTS:** Of 163 patients who participated in the study, 123 (75%) qualified for 12-week treatment; of these, 81 (66%) achieved SVR12. Baseline factors positively associated with SVR12 rates in patients receiving the 12-week regimen were: IL28B CC genotype: (94% SVR12); HCV RNA  $\leq$ 800,000 IU/mL (82%); F0-F1 fibrosis (74%). Among all 163 patients, 94% experienced  $\geq$ 1 adverse event (AE), 4% a serious AE, and 2.5% discontinued due to an AE. Reduced impairment in patient-reported outcomes was observed in the 12-week vs >12-week regimen. **CONCLUSIONS:** Overall SVR12 rate (66%) was below the target of 80%, indicating that shortening of treatment with simeprevir plus PR to 12 weeks based on very early response is not effective. However, baseline factors associated with higher SVR12 rates were identified. Therefore, while Week 2 response alone is insufficient to predict efficacy, GT1 patients with favourable baseline factors may benefit from a shortened simeprevir plus PR regimen.

[Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCV-TARGET study.](#) Welzel TM1, Nelson DR2, Morelli G2, et al. Gut. 2016 Jul 13. pii: gutjnl-2016-311609. doi: 10.1136/gutjnl-2016-311609. [Epub ahead of print]

**OBJECTIVE:** Due to a high efficacy in clinical trials, sofosbuvir (SOF) and ribavirin (RBV) for 12 or 16 weeks is recommended for treatment of patients with HCV genotype (GT) 2 infection. We investigated safety and effectiveness of these regimens for GT2 in HCV-TARGET participants. **DESIGN:** HCV-TARGET, an international, prospective observational study evaluates clinical practice data on novel antiviral therapies at 44 academic and 17 community medical centres in North America and Europe. Clinical data were centrally abstracted from medical records. Selection of treatment regimen and duration was the investigator's choice. The primary efficacy outcome was sustained virological response 12 weeks after therapy (SVR12). **RESULTS:** Between December 2013 and April 2015, 321 patients completed 12 weeks (n=283) or 16 weeks (n=38) of treatment with SOF and RBV. Prior treatment experience and cirrhosis was more frequent among patients in the 16-week regimen compared with 12 weeks (52.6% vs 27.6% and 63.2% vs 21.9%, respectively). Overall, SVR12 was 88.2%. The SVR12 in patients without cirrhosis was 91.0% and 92.9% for 12 or 16 weeks of therapy, respectively. In patients with cirrhosis treated for 12 or 16 weeks, SVR12 was 79.0% and 83%. In the multivariate analysis, liver cirrhosis, lower serum albumin and RBV dose at baseline were significantly associated with SVR12. Common adverse events (AEs) included fatigue, anaemia, nausea, headache, insomnia, rash and flu-like symptoms. Discontinuation due to AEs occurred in 2.8%. **CONCLUSIONS:** In this clinical practice setting, SOF and RBV was safe and effective for treatment of patients with HCV GT2 infection.

[The relationship between liver stiffness measurement and outcome in patients with chronic hepatitis C and cirrhosis: a retrospective longitudinal hospital study.](#) Sultanik P1,2,3,4,

Kramer L2,3, Soudan D2,3, et al. Aliment Pharmacol Ther. 2016 Jul 12. doi: 10.1111/apt.13722. [Epub ahead of print]

**BACKGROUND:** There is a relationship between liver stiffness measurement (LSM) and outcome of HCV patients. **AIM:** To evaluate the performance of LSM to predict outcome of HCV patients at risk of liver-related complication. **METHODS:** We established a retrospective longitudinal cohort of 341 HCV patients with unequivocal cirrhosis. All underwent LSM and were followed from September 2006 to July 2015. Outcome measure was a composite end-point of end-stage liver disease (ESLD) and/or hepatocellular carcinoma (HCC). Cox models and areas under receiver operating characteristic (AUROC) curves were used to evaluate independent risk factors of outcome. **RESULTS:** Overall, LSM was below the 12.5 kPa threshold in 129 (37.8%) patients, including three-fourth and one-third of patients with or without a sustained virological response respectively. Liver disease progressed in 136 (39.9%) patients after a median observational period of 23.5 months. Older age, male gender, alcohol use disorders, metabolic syndrome and LSM were independent risk factors of liver disease progression. Age, alcohol use disorders and LSM were independently associated with ESLD. Age, gender and metabolic syndrome, but not LSM, were associated with HCC. The AUROC curves for disease progression, ESLD and HCC were 0.67, 0.70 and 0.58 respectively. Patients with a liver stiffness >12.5 kPa were at the highest risk of liver disease progression; below 12.5 kPa, liver stiffness was not discriminant. **CONCLUSION:** Liver stiffness measurement is not a surrogate of disease progression of HCV patients with cirrhosis. HCV patients with cirrhosis should undergo the recommended follow-up, regardless of liver stiffness measurement.

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### **Ribavirin-Free Regimen With Sofosbuvir and Velpatasvir is Associated With High Efficacy and Improvement of Patient-Reported Outcomes in Patients With Genotypes 2 and 3**

**Chronic Hepatitis C: Results From Astral-2 and 3 Clinical Trials.** Younossi ZM1, Stepanova M2, Sulkowski M3, et al. Clin Infect Dis. 2016 Jul 20. pii: ciw496. [Epub ahead of print]

**BACKGROUND:** Approved treatment regimens for genotype (GT) 2 and 3 contain sofosbuvir (SOF) and ribavirin (RBV) for 12 or 24 weeks. The impact of RBV-free pan-genotypic regimen with SOF and velpatasvir (SOF/VEL) on patient-reported outcomes (PROs) of patients with genotype 2 and 3 has not been described. **METHODS:** Patient-reported outcomes data were collected from participants of ASTRAL-2 and ASTRAL-3 studies before, during and after treatment using four PRO instruments (SF-36v2, FACIT-F, CLDQ-HCV, WPAI:SHP), and compared between the SOF/VEL and SOF+RBV groups. **RESULTS:** 818 HCV patients were included: 78% treatment-naïve, 25% cirrhosis. The rates of nearly all adverse events were lower in the RBV-free SOF/VEL group (all  $p < 0.03$ ). The SOF/VEL group also experienced improvement of their PROs by treatment week 4 (+1.8% on average across all PROs) which continued throughout treatment (+4.1%) and post-treatment (+5.5%). In contrast, the SOF+RBV group had a modest decline in their PROs starting at treatment week 4 (up to -3.7%) which lasted until the end of treatment (up to -6.4%). In multiple regression analysis, the association of a treatment regimen with end-of-treatment PROs was significant for nearly all PROs; the average beta was +5.0% for the use of the SOF/VEL (reference: SOF+RBV). **CONCLUSIONS:** Patients receiving ribavirin-free SOF/VEL report significantly better PRO scores during treatment compared to those receiving the RBV-containing regimen. Furthermore, the interferon- and ribavirin-free SOF/VEL regimen results in a rapid improvement of PROs in HCV genotypes 2 and 3 patients during treatment and after achieving sustained virologic response.

[Peripheral blood toll-like receptor 4 correlates with rapid virological response to pegylated-interferon and ribavirin therapy in hepatitis C genotype 1 patients.](#)

Lee CM<sup>1,2</sup>, Hu TH<sup>1,2</sup>, Lu SN<sup>1,2</sup>, Wang JH<sup>1,2</sup>, Hung CH<sup>1,2</sup>, Chen CH<sup>1,2</sup>, Yen YH<sup>3,4</sup>. BMC Gastroenterol. 2016 Jul 25;16(1):73. doi: 10.1186/s12876-016-0492-6.

**BACKGROUND:** Toll-like receptors (TLRs) are effectors of the innate immune system that are able to recognize hepatitis C virus (HCV) and give rise to an immune response. Failure of interferon (IFN)- $\alpha$ -based treatment is related to host immunity. Therefore, we sought to study the clinical importance of TLRs in HCV genotype 1 patients who received pegylated IFN (PEG-IFN) plus ribavirin (RBV) therapy. **METHODS:** We enrolled 79 treatment-naïve patients with HCV genotype 1. Patients completed a 24- to 48-week course of response-guided therapy. Peripheral blood monocyte (PBMC) expression of mRNA for TLRs 2, 3, 4, 7, and 9 was quantified by real-time PCR before therapy. TLR mRNA expression is shown as a log ratio relative to GAPDH mRNA ( $\log_2(-(\Delta Ct))$ ). **RESULTS:** Forty-five patients (57.0 %) showed a rapid virological response (RVR). Univariate analysis revealed that TLR 2, 3, 4, 7, and 9 were significantly lower in the RVR group than in the non-RVR group ( $P = 0.001, 0.014, < 0.001, 0.008, \text{ and } 0.001$ , respectively). Multivariate analysis revealed that  $\text{TLR } 4 < -2 \log$  (OR: 7.17, 95 % CI: 1.70-30.34,  $P = 0.007$ ) was an independent predictor for RVR. In addition, levels of TLR 2, 3, 4, 7, and 9 were positively correlated with HCV viral load ( $P = 0.009, 0.013, < 0.001, 0.007, \text{ and } 0.001$ , respectively). **CONCLUSIONS:** A low level of TLR 4 mRNA in PMBCs was correlated with RVR, which indicates that TLR4 may play a critical role in HCV recognition and activation of innate immunity. TLR expression levels were correlated with HCV viral load, indicating that TLR activation upon exposure to HCV may subsequently limit HCV replication.

[Evaluation of a Potential Interaction Between New Regimens to Treat Hepatitis C and Warfarin.](#)

DeCarolis DD<sup>1</sup>, Westanmo AD<sup>2</sup>, Chen YC<sup>3</sup>, Boese AL<sup>2</sup>, Walquist MA<sup>2</sup>, Rector TS<sup>3</sup>. Ann Pharmacother. 2016 Jul 26. pii: 1060028016660325. [Epub ahead of print]

**OBJECTIVE:** New regimens to treat hepatitis C virus infection have expanded the eligible patient population to include more patients receiving concurrent warfarin. The primary objective of this study was to assess whether a drug interaction occurs when these regimens are added to warfarin therapy. **METHODS:** This was a retrospective cohort design using a nationwide database of the Veterans Affairs Health System. Patients on warfarin therapy treated with sofosbuvir or ombitasvir, paritaprevir-ritonavir, and dasabuvir (OBV-PTV/r-DSV) from March 2014 through October 2015 were identified. The warfarin dose response was calculated using a warfarin sensitivity index (WSI) defined as the steady-state INR divided by the mean daily warfarin dose. The primary outcome was the change in WSI from hepatitis C treatment initiation to completion. **RESULTS:** The final sample consisted of 271 patients. The WSI decreased 23% from a mean baseline value of 0.53 to 0.39 (decrease of 0.14; 95% CI = 0.11 to 0.16;  $P < 0.001$ ). OBV-PTV/r-DSV produced a significantly greater decrease than any sofosbuvir regimen. Concurrent ribavirin accounted for an additional decrease in warfarin sensitivity of -0.09 (95% CI = -0.06 to -0.12;  $P < 0.001$ ). The percentage of subtherapeutic INR results increased from 26% prior to hepatitis C treatment to 58% during treatment. **CONCLUSIONS:** Results indicate a clinically significant reduction in warfarin dose-response when hepatitis C treatment regimens were added to warfarin. They were most profound with OBV-PTV/r-DSV. Ribavirin was associated with an additive effect. Clinicians should be aware of this potential drug interaction to closely monitor and minimize subtherapeutic levels of anticoagulation.



### [Risk Factors and Clinical Characteristics of the Depressive State Induced by Pegylated Interferon Therapy in Patients with Hepatitis C Virus Infection: A Prospective Study.](#)

Kawase K1, Kondo K1, Saito T1, et al. *Psychiatry Clin Neurosci*. 2016 Jul 29. doi: 10.1111/pcn.12424. [Epub ahead of print]

**AIM:** Pegylated interferon (PegIFN) therapies for hepatitis C virus (HCV) infection often induce a depressive state. This study aimed to identify the risk factors for and clinical characteristics of PegIFN-induced depressive state. **METHODS:** Sixty-nine subjects with HCV who received PegIFN therapy were enrolled. Before beginning therapy, all subjects were evaluated using the Neuroticism-Extraversion-Openness Five-Factor Inventory and the List of Threatening Events Questionnaire. Beck Depression Inventory (BDI) was also evaluated at baseline, 2-4 weeks after initiating therapy, and every 4 weeks thereafter. **RESULTS:** During the study, 18 subjects (24.3%) developed a depressive state ( $BDI \geq 10$ ). A bimodal peak of onset was observed during early (2-8 weeks) and late (after 20 weeks) therapy phases. Moreover, we observed that baseline BDI scores [odds ratio (OR) = 1.40,  $P = 0.0104$ ] and neuroticism [OR = 1.14,  $P = 0.0275$ ] were significant risk factors for developing a depressive state. To determine the specific characteristics of this condition, we compared the BDI subscales between the "PegIFN-induced" and "general" depressive state reported previously. We found that the score at "somatic symptoms" were higher in the "PegIFN-induced" group. **CONCLUSION:** Our results indicate the following: (1) PegIFN-induced depressive state most frequently develops during the first 8 weeks of therapy, (2) baseline BDI and neuroticism scores are risk factors for PegIFN-induced depressive state, and (3) the core symptoms of PegIFN-induced depressive state are different from those of "general" depression.

### [Hepatitis C - Assessment to Treatment Trial \(HepCATT\) in primary care: study protocol for a cluster randomised controlled trial.](#) Roberts K1, Macleod J1, Metcalfe C1,2, et al. *Trials*. 2016 Jul 29;17(1):366.

**BACKGROUND:** Public Health England (PHE) estimates that there are upwards of 160,000 individuals in England and Wales with chronic hepatitis C virus (HCV) infection, but until now only around 100,000 laboratory diagnoses have been reported to PHE and of these 28,000 have been treated. Targeted case-finding in primary care is estimated to be cost-effective; however, there has been no robust randomised controlled trial evidence available of specific interventions. Therefore, this study aims to develop and conduct a complex intervention within primary care and to evaluate this approach using a cluster randomised controlled trial. **METHODS/DESIGN:** A total of 46 general practices in South West England will be randomised in a 1:1 ratio to receive either a complex intervention comprising: educational training on HCV for the practice; poster and leaflet display in the practice waiting rooms to raise awareness and encourage opportunistic testing; a HCV risk prediction algorithm based on information on possible risk markers in the electronic patient record run using Audit + software (BMJ Informatica). The audit will then be used to recall and offer patients a HCV test. Control practices will follow usual care. The effectiveness of the intervention will be measured by comparing number and rates of HCV testing, the number and proportion of patients testing positive, onward referral, rates of specialist assessment and treatment in control and intervention practices. Intervention costs and health service utilisation will be recorded to estimate the NHS cost per new HCV diagnosis and new HCV patient initiating treatment. Longer-term cost-effectiveness of the intervention in improving quality-adjusted life years (QALYs) will be extrapolated using a pre-existing dynamic

health economic model. Patients' and health care workers' experiences and acceptability of the intervention will be explored through semi-structured qualitative interviews.

### [Liver stiffness measurement using acoustic radiation force impulse elastography in hepatitis C virus-infected patients with a sustained virological response.](#)

Tachi Y1, Hirai T1, Kojima Y1, Miyata A1, Ohara K1, Ishizu Y2, Honda T2, Kuzuya T2, Hayashi K2, Ishigami M2, Goto H2. *Aliment Pharmacol Ther.* 2016 Aug;44(4):346-55. doi: 10.1111/apt.13695. Epub 2016 Jun 13.

**BACKGROUND:** Acoustic radiation force impulse (ARFI) elastography is a non-invasive method for measuring liver stiffness. However, there are no reports evaluating the value of ARFI elastography for liver fibrosis in chronic hepatitis C patients with a sustained virological response (SVR). **AIM:** To investigate the diagnostic performance of ARFI elastography for the assessment of liver fibrosis in hepatitis C virus (HCV) infected patients with an SVR.

**METHODS:** In this prospective study, we enrolled 336 patients: 121 HCV patients with an SVR (44.6% women) and 215 patients with HCV (47.9% women). ARFI elastography measurements of all patients were performed on the same day of liver biopsy. **RESULTS:** The diagnostic accuracies, expressed as areas under the receiver operating characteristic curves for ARFI elastography, in HCV patients with an SVR and those in patients with HCV were 0.818 and 0.875 for the diagnosis of significant fibrosis ( $\geq$ F2), 0.909 and 0.888 for the diagnosis of severe fibrosis ( $\geq$ F3), and 0.981 and 0.890 for the diagnosis of liver cirrhosis (F4), respectively. The optimum cut-off values for ARFI elastography were 1.26 m/s for  $\geq$ F2, 1.31 m/s for  $\geq$ F3 and 1.49 m/s for F4 in HCV patients with an SVR. The liver stiffness values were lower in patients with SVR compared with those in patients with HCV at the same stage of fibrosis. The liver stiffness values were affected by the necroinflammatory activity and the time after SVR.

**CONCLUSION:** Acoustic radiation force impulse elastography is an acceptable method for predicting the severity of fibrosis in patients with hepatitis C virus and a sustained viral response.

### [Pharmacokinetics, efficacy and safety of daclatasvir plus asunaprevir in dialysis patients with chronic hepatitis C: pilot study.](#)

Kawakami Y1,2, Imamura M1,2, Ikeda H3, et al. *J Viral Hepat.* 2016 Jun 27. doi: 10.1111/jvh.12553. [Epub ahead of print]

The aim of this study was to evaluate the pharmacokinetic profile of daclatasvir (DCV) and asunaprevir (ASV) dual therapy in haemodialysis patients infected with hepatitis C virus (HCV). Eighteen haemodialysis patients and 54 patients with normal renal function were treated with DCV and ASV dual therapy for 24 weeks. We evaluated the pharmacokinetic profiles of DCV and ASV and examined the rate of sustained virological response 12 weeks after the end of treatment (SVR<sub>12</sub>) and incidence of adverse events during treatment of haemodialysis patients infected with chronic HCV genotype 1 infection. To adjust for potential differences in baseline characteristics between haemodialysis patients and patients with normal renal function, we used propensity scores case-control matching methods. Area under the plasma concentration time curve from 0 to 6 h (AUC<sub>0-6 h</sub>) of DCV was slightly lower in haemodialysis patients than in patients with normal renal function ( $P > 0.6$ ). AUC<sub>0-6 h</sub> of ASV was significantly lower in haemodialysis patients ( $P = 0.012$ ). SVR<sub>12</sub> rates were 100% (18/18) for haemodialysis and 96.2% (52/54) for patients with normal renal function. Changes in mean log<sub>10</sub> HCV RNA levels and viral response were higher in haemodialysis patients compared to patients with normal renal function. No discontinuations due to adverse events occurred. In conclusion, DCV and ASV dual

therapy for HCV infection is effective and safe with similar results in haemodialysis patients compared to patients with normal renal function.

### [Development and Preliminary Evaluation of an Integrated Cognitive-Behavior Treatment for Chronic Pain and Substance Use Disorder in Patients with the Hepatitis C Virus.](#)

Morasco BJ1, Greaves DW2, Lovejoy TI3, Turk DC4, Dobscha SK3, Hauser P5. Pain Med. 2016 Jun 27. pii: pnw076. [Epub ahead of print]

**OBJECTIVE:** Individuals with the hepatitis C virus (HCV) have high rates of both chronic pain and substance use disorder (SUD). Despite high comorbidity, there are limited data available on effective methods of treatment for co-occurring chronic pain and SUD. In this study, we sought to develop and conduct preliminary testing of an integrated cognitive-behavior therapy (CBT) for chronic pain and SUD in patients with HCV. **DESIGN:** Descriptive, including pretreatment, posttreatment, and follow-up testing. **SETTING AND PATIENTS:** Outpatient clinic as part of one VA Medical Center. **PARTICIPANTS:** Veterans with chronic pain, SUD, and HCV. **INTERVENTION:** Eight-session integrated group CBT for chronic pain and SUD in patients with HCV. **METHODS:** Participants completed standardized measures of pain, function, depression severity, and alcohol and substance use at baseline, post-treatment, and 3-month follow-up. **RESULTS:** Generalized estimating equations identified improvements in pain interference, reducing cravings for alcohol and other substances, and decreasing past-month alcohol and substance use. The proportion of participants who met diagnostic criteria for current SUD demonstrated a four-fold decrease over the course of the study from 24% at baseline to 15% at post-treatment and 6% at 3-month follow-up. On response to a global impression of change, 94% of participants noted improvement from baseline. **CONCLUSIONS:** Results from this pilot study suggest that a customized CBT for patients with both chronic pain and SUD (CBT-cp.sud) may be beneficial in improving important pain and addiction-related outcomes in patients with HCV. Larger scale investigations of this intervention appear warranted.

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## **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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### [Hepatitis C virus depends on E-cadherin as an entry factor and regulates its expression in epithelial-to-mesenchymal transition.](#)

Li Q1, Sodroski C2, Lowey B2, Schweitzer CJ2, Cha H2, Zhang F2, Liang TJ1. Proc Natl Acad Sci U S A. 2016 Jul 5;113(27):7620-5. doi: 10.1073/pnas.1602701113. Epub 2016 Jun 13.

Hepatitis C virus (HCV) enters the host cell through interactions with a cascade of cellular factors. Although significant progress has been made in understanding HCV entry, the precise mechanisms by which HCV exploits the receptor complex and host machinery to enter the cell remain unclear. This intricate process of viral entry likely depends on additional yet-to-be-defined cellular molecules. Recently, by applying integrative functional genomics approaches, we identified and interrogated distinct sets of host dependencies in the complete HCV life cycle. Viral entry assays using HCV pseudoparticles (HCVpps) of various genotypes uncovered multiple previously unappreciated host factors, including E-cadherin, that mediate HCV entry. E-cadherin silencing significantly inhibited HCV infection in Huh7.5.1 cells, HepG2/miR122/CD81 cells, and primary human hepatocytes at a postbinding entry step. Knockdown of E-cadherin, however, had no effect on HCV RNA replication or internal

ribosomal entry site (IRES)-mediated translation. In addition, an E-cadherin monoclonal antibody effectively blocked HCV entry and infection in hepatocytes. Mechanistic studies demonstrated that E-cadherin is closely associated with claudin-1 (CLDN1) and occludin (OCLN) on the cell membrane. Depletion of E-cadherin drastically diminished the cell-surface distribution of these two tight junction proteins in various hepatic cell lines, indicating that E-cadherin plays an important regulatory role in CLDN1/OCLN localization on the cell surface. Furthermore, loss of E-cadherin expression in hepatocytes is associated with HCV-induced epithelial-to-mesenchymal transition (EMT), providing an important link between HCV infection and liver cancer. Our data indicate that a dynamic interplay among E-cadherin, tight junctions, and EMT exists and mediates an important function in HCV entry.

**Hepatitis C Virus RNA-Dependent RNA Polymerase Interacts with the Akt/PKB Kinase and Induces Its Subcellular Relocalization.**

Valero ML1, Sabariego R2, Cimas FJ3, et al. Antimicrob Agents Chemother. 2016 May 23;60(6):3540-50. doi: 10.1128/AAC.03019-15. Print 2016 Jun.

Hepatitis C virus (HCV) interacts with cellular components and modulates their activities for its own benefit. These interactions have been postulated as a target for antiviral treatment, and some candidate molecules are currently in clinical trials. The multifunctional cellular kinase Akt/protein kinase B (PKB) must be activated to increase the efficacy of HCV entry but is rapidly inactivated as the viral replication cycle progresses. Viral components have been postulated to be responsible for Akt/PKB inactivation, but the underlying mechanism remained elusive. In this study, we show that HCV polymerase NS5B interacts with Akt/PKB. In the presence of transiently expressed NS5B or in replicon- or virus-infected cells, NS5B changes the cellular localization of Akt/PKB from the cytoplasm to the perinuclear region. Sequestration of Akt/PKB by NS5B could explain its exclusion from its participation in early Akt/PKB inactivation. The NS5B-Akt/PKB interaction represents a new regulatory step in the HCV infection cycle, opening possibilities for new therapeutic options.

**Variant ITPA Phenotypes are Associated with Increased Ribavirin Triphosphate Levels.**

Jimmerson LC1, Urban TJ2, Truesdale A3, et al. J Clin Pharmacol. 2016 Jun 28. doi: 10.1002/jcph.783. [Epub ahead of print]

Individuals with lower inosine triphosphatase (ITPA) enzyme activity have a reduced likelihood of experiencing hemolytic anemia during hepatitis C virus (HCV) treatment containing ribavirin (RBV). Given ITPA degrades purines and RBV is a purine analog, it is conceivable that ITPA activity may affect intracellular RBV concentrations. Here, we assessed the association between ITPA activity phenotype and concentrations of RBV triphosphate (RBV-TP) in red blood cells (RBCs) during HCV treatment. RBV-TP was quantified in the RBCs of 177 HCV-infected individuals at a median (range) of 84 (19-336) days into HCV treatment that included RBV. Mean (SD) RBV-TP concentrations were 92.8 (51.6), 101.3 (53.5), 184.8 (84.5), and 197.7 (64.6) pmol/106 cells for 100%, 60%, 30%, and  $\leq 10\%$  ITPA activity groups, respectively ( $p < 0.0001$ ). Overall, RBV-TP was approximately 2-fold higher in patients with  $\leq 30\%$  ITPA activity compared to 100% activity ( $p < 0.0001$ ). Despite higher RBV-TP levels, individuals with variant ITPA phenotypes had less anemia. The 100% activity group had, on average, a -2.20 g/dL drop in hemoglobin vs. -1.43 g/dL ( $p = 0.04$ ) for 60% activity, -1.14 g/dL ( $p = 0.008$ ) for 30% activity, and -0.70 g/dL ( $p = 0.06$ ) for  $\leq 10\%$  activity. This finding of higher RBV-TP concentrations in RBCs in ITPA variants was unexpected given ITPA activity deficient



individuals have a reduced likelihood of RBV-induced anemia. It also refutes the hypothesis that the mechanism by which ITPA variants are protected against anemia is due to lower RBV-TP levels in RBCs.

**[Impact of resistance-associated variant dominance on treatment in patients with HCV genotype 1b receiving daclatasvir/asunaprevir.](#)**

Ikeda H1, Watanabe T1, Okuse C1,2, et al. J Med Virol. 2016 Jun 22. doi: 10.1002/jmv.24608. [Epub ahead of print]

Sustained virological responses (SVR) by daclatasvir (DCV) and asunaprevir (ASV) therapy for genotype 1b hepatitis C virus (HCV) infected patients has been significantly affected by pre-existence of Y93 H resistance-associated variants (RAVs) in the non-structural protein 5A (NS5A) region. The aim of this study was to elucidate the dominance of naturally occurring RAVs in viral quasispecies on treatment outcomes in patients with HCV. In total, 138 patients were prospectively selected from 152 patients treated with DCV and ASV, where evaluation of treatment outcomes at 12 weeks post-treatment was possible. Pre-treatment RAVs in the non-structural protein 3 and NS5A regions were detected by polymerase chain reaction (PCR)-Invader assays, and the ratio of Y93H RAVs in viral quasispecies was measured by quantitative PCR-Invader assay. Among 25 patients detected the Y93H RAV, the Y93H ratio was 1-25% in 5 patients, 26-75% in 7 patients, and  $\geq 76\%$  in 13 patients. Overall, SVR at 12 weeks after the completion of treatment (SVR12) was 91% (125/138), and those with Y93H ratios of  $< 1\%$ , 1-25%, 26-75%, and  $\geq 76\%$  were 99%, 100%, 71%, and 23%, respectively. Thus, the SVR12 decreased as the HCV Y93H ratio increased ( $P < 0.0001$ ). The dominance of pre-treatment RAVs of DCV and ASV affected its treatment outcomes, suggesting that evaluating the dominance of HCV RAVs could be required for every other direct-acting antiviral agent treatments.

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## **HIV/HCV COINFECTION**

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**[Ledipasvir and sofosbuvir for HCV-infection in patients coinfecting with HBV.](#)** Gane EJ1, Hyland RH, An D, Svarovskaia ES, Brainard D, McHutchison JG. Antivir Ther. 2016 Jul 1. doi: 10.3851/IMP3066. [Epub ahead of print]

**BACKGROUND:** Currently there are no all-oral treatment regimens for hepatitis C virus (HCV) in patients coinfecting with hepatitis B virus (HBV). In this pilot study, we evaluated whether ledipasvir and sofosbuvir therapy can suppress HCV infection in patients coinfecting with HBV. **METHODS:** Patients with HBV and genotype 1 HCV received 90 mg ledipasvir and 400 mg sofosbuvir daily for 12 weeks. The efficacy endpoint was sustained virologic response (HCV RNA  $< 15$  IU/mL) 12 weeks after the end of treatment. **RESULTS:** Of the 8 patients enrolled, 6 (75%) were male, 5 (63%) were Polynesian, 7 (88%) had the CC IL28B genotype, and 2 (25%) had cirrhosis. All 8 patients (100%; 95% CI, 63-100%) reached the primary endpoint of HCV RNA  $< 15$  IU/mL 12 weeks after treatment. In 7 of 8 patients (88%), serum HBV DNA levels increased during treatment, but none of the increases were greater than 20,000 IU/mL, and none were associated with clinical HBV flares or required treatment. The most common adverse events were viral infection (63%), fatigue (25%), and upper respiratory tract infection (25%). No patients had serious adverse events and none discontinued treatment for any reason. **CONCLUSIONS:** In this small sample, 12 weeks of ledipasvir-sofosbuvir was a safe and effective treatment for genotype 1 HCV infection in patients coinfecting with HBV. Larger studies with longer follow-up are warranted.

**CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core Research Group: 2016 Updated Canadian HIV/Hepatitis C Adult Guidelines for Management and Treatment.** Hull M1, Shafran S2, Wong A3, et al. Can J Infect Dis Med Microbiol.

2016;2016:4385643. doi: 10.1155/2016/4385643. Epub 2016 Jul 4.

**BACKGROUND:** Hepatitis C virus (HCV) coinfection occurs in 20-30% of Canadians living with HIV and is responsible for a heavy burden of morbidity and mortality. **PURPOSE:** To update national standards for management of HCV-HIV coinfecting adults in the Canadian context with evolving evidence for and accessibility of effective and tolerable DAA therapies. The document addresses patient workup and treatment preparation, antiviral recommendations overall and in specific populations, and drug-drug interactions. **METHODS:** A standing working group with HIV-HCV expertise was convened by The Canadian Institute of Health Research HIV Trials Network to review recently published HCV antiviral data and update Canadian HIV-HCV Coinfection Guidelines. **RESULTS:** The gap in sustained virologic response between HCV monoinfection and HIV-HCV coinfection has been eliminated with newer HCV antiviral regimens. All coinfecting individuals should be assessed for interferon-free, Direct Acting Antiviral HCV therapy. Regimens vary in content, duration, and success based largely on genotype. Reimbursement restrictions forcing the use of pegylated interferon is not acceptable if optimal patient care is to be provided. **DISCUSSION:** Recommendations may not supersede individual clinical judgement. Treatment advances published since December 2015 are not considered in this document.

**Improving treatment and liver fibrosis outcomes with metformin in HCV-HIV co-infected and HCV mono-infected patients with insulin resistance: study protocol for a randomized controlled trial.** Doyle MA<sup>1,2,3</sup>, Singer J<sup>4</sup>, Lee T<sup>4</sup>, Muir M<sup>5</sup>, Cooper C<sup>6,5,4</sup>. Trials. 2016 Jul

20;17(1):331. doi: 10.1186/s13063-016-1454-6.

**BACKGROUND:** Approximately 180 million people worldwide, (3 % of the world's population) are infected with hepatitis C (HCV). Insulin resistance (IR) and type 2 diabetes (T2DM) are common extrahepatic manifestations of chronic HCV infection and associated with poor treatment and liver-related outcomes. The presence of these metabolic complications have been associated with poor response to interferon-based HCV antiviral therapy and increased risk of liver-related outcomes. Metformin, an insulin sensitizer is known to improve HCV treatment response and has been associated with a reduced risk of developing hepatocellular carcinoma (HCC). This study will evaluate the effect of metformin on preventing progression or promoting regression of liver fibrosis, rate of virologic cure (SVR) and other metabolic measures in HCV-HIV co-infected and HCV mono-infected study participants who have IR and are planning on initiating HCV treatment. **METHODS:** This study is a prospective 48-week single-centre, randomized, open-label, controlled trial of HIV-HCV co-infected and HCV mono-infected patients with IR (HOMA-IR  $\geq 2.0$ ) who are planning to initiate HCV antiviral therapy. Sixty participants will be recruited from The Ottawa Hospital Viral Hepatitis Clinic. Participants will be randomized in a 1:1 ratio to either arm 1, metformin 2 g (1 g twice daily) plus lifestyle, or to arm 2, lifestyle alone. The primary outcome will be the change in FibroScan® score (kPa) from baseline to week 12 (start of HCV treatment), the end of HCV treatment (week 24) and 24 weeks post HCV treatment (week 48). Secondary outcomes include changes in liver fibrosis using AST to platelet ratio index, changes in glucose and lipid levels, anthropometric measures, changes in alpha-fetoprotein levels, patient acceptability, and changes in dietary and physical activity

parameters. **DISCUSSION:** This pilot study will be the first to evaluate the role of metformin on liver fibrosis in HCV-HIV co-infected and HCV mono-infected patients with IR receiving DAA HCV treatment. If metformin is effective in reducing liver fibrosis in this patient population, this will represent a well-tolerated, easy-to-administer, inexpensive therapy that will protect against negative HCV outcomes. This study will also be an opportunity to evaluate the impact of insulin resistance and hyperglycemia on viral clearance in HCV-infected patients treated with interferon-free regimens.

**Liver fibrosis progression and clinical outcomes are intertwined: role of CD4+ T-cell count and NRTI exposure from a large cohort of HIV/HCV-coinfected patients with detectable HCV-RNA: A MASTER cohort study.** Focà E1, Fabbiani M, Prosperi M, Quiros Roldan E, et al. *Medicine (Baltimore)*. 2016 Jul;95(29):e4091. doi: 10.1097/MD.0000000000004091.

**INTRODUCTION:** Patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) suffer from faster progression of liver fibrosis (LF) and have greater risk of worse clinical outcomes. We evaluated predictors and incidence of these events in a large multicentre cohort. **METHODS:** We selected all HIV-infected patients starting a first-line combination antiretroviral therapy (cART), with detectable HCV-RNA, without exposure to interferon/ribavirin, with  $\geq 2$  fibrosis-4 index (FIB-4) classifications before cART. Kaplan-Meier analysis was used to estimate incidence of clinical events (AIDS, non-AIDS related, deaths) and LF progression (via transitions: from FIB-4 class 1 to 2 or 3, from class 2 to class 3, and worsening by 0.5 point). Multivariate Cox regression was used to assess predictors, baseline, or time updated. **RESULTS:** One thousand four hundred thirty-three patients were selected. Overall, 745 clinical events occurred, with an incidence of 7.6% over 9811 person-year of follow-up (PYFU) and a median survival time of 9.36 years. Incidence of LF progression from FIB-4 class 1 to 2 or 3 was 12.4%, and from FIB-4 class 2 to 3 was 7% with a median survival time of 5.67 and 10.35 years, respectively. At multivariate analyses, intravenous drug use and time-updated gamma-glutamyl transferase ( $\gamma$ GT) were negative predictors for any outcomes, either clinical or FIB-4 progression. Higher CD4+ T-cell protected from clinical events, and lower HIV-RNA and higher CD4+ T-cell appeared to protect from FIB-4 transitions. Moreover, independently from the viro-immunological status, current FIB-4 class 3 predicted clinical events. Occurrence of AIDS and cardiovascular/kidney events were significant predictors of 0.5 point worsening and transitions of FIB-4, respectively. Prolonged exposure to nucleos(t)ide reverse transcriptase inhibitors (NRTI) was a negative predictor for any outcomes.

**CONCLUSION:** Both clinical and LF progression in HIV/HCV-coinfected patients depend strongly on immune status. Intravenous drug users and patients with high  $\gamma$ GT (a possible proxy for alcohol abuse) are most-at-risk for both outcomes, as well those who had prolonged exposures to the NRTI class. Therefore, these patients should be prioritized for the access to anti-HCV therapy and a test-and-treat strategy should be implemented for early initiation of cART. Possible benefits of NRTI sparing regimens in HIV/HCV-coinfected patients should be investigated.

**Isolated Hepatitis B Core Antibody Status Is Not Associated With Accelerated Liver Disease Progression in HIV/Hepatitis C Coinfection.** French AL1, Hotton A, Young M, Nowicki M, Augenbraun M, Anastos K, Seaberg E, Rosenberg W, Peters MG. *J Acquir Immune Defic Syndr*. 2016 Jul 1;72(3):274-80. doi: 10.1097/QAI.0000000000000969.

**BACKGROUND:** Isolated hepatitis B core antibody (anti-HBc) is a common serologic finding in HIV-infected persons, but the clinical significance is uncertain. We studied HIV/hepatitis C virus (HCV)-infected women over time to determine whether the trajectory of liver disease progression is affected by isolated anti-HBc serologic status. **METHODS:** We performed serial enhanced liver fibrosis (ELF) markers on HIV/HCV-coinfected women to assess liver disease progression trajectory over time comparing women with isolated anti-HBc to women with either negative HB serologies, anti-HBs alone, or anti-HBc and anti-HBs. ELF, a serum marker that combines direct markers of extracellular matrix remodeling and fibrosis, was performed on serum stored biannually. Women with at least 3 ELF determinations and persistent HCV RNA positivity were included. **RESULTS:** Three hundred forty-four women, including 132 with isolated anti-HBc and 212 with other serologic findings, were included. A median of 6 (interquartile range, 5-7) biannual ELF values was available for each woman, totaling 2119 visits. ELF increased over time from a median of 9.07 for women with isolated anti-HBc and 9.10 for those without isolated anti-HBc to 9.83 and 9.88, respectively, with no difference in degree of change or slope in the mixed-effects model including age, race, CD4 count, antiretroviral therapy, and drug and alcohol use. Factors independently associated with liver disease progression were older age, lower CD4, antiretroviral therapy nonuse, and Hispanic ethnicity. **CONCLUSION:** Isolated anti-HBc serologic status was not associated with accelerated liver disease progression over a median of 9.5 years among HIV/HCV-coinfected women.

[A new 3p25 locus is associated with liver fibrosis progression in human immunodeficiency virus/hepatitis C virus-coinfected patients.](#) Ulveling D1, Le Clerc S1, Cobat A2,3, et al.

Hepatology. 2016 Jun 23. doi: 10.1002/hep.28695. [Epub ahead of print]

There is growing evidence that human genetic variants contribute to liver fibrosis in subjects with hepatitis C virus (HCV) mono-infection, but this aspect has been little investigated in patients coinfected with HCV and human immunodeficiency virus (HIV). We performed the first genome-wide association study of liver fibrosis progression in patients coinfected with HCV and HIV, using the well-characterized French National Agency for Research on AIDS and Viral Hepatitis CO13 HEPAVIH cohort. Liver fibrosis was assessed by elastography (FibroScan), providing a quantitative fibrosis score. After quality control, a genome-wide association study was conducted on 289 Caucasian patients, for a total of 8,426,597 genotyped (Illumina Omni2.5 BeadChip) or reliably imputed single-nucleotide polymorphisms. Single-nucleotide polymorphisms with P values  $<10^{-6}$  were investigated in two independent replication cohorts of European patients infected with HCV alone. Two signals of genome-wide significance ( $P < 5 \times 10^{-8}$ ) were obtained. The first, on chromosome 3p25 and corresponding to rs61183828 ( $P = 3.8 \times 10^{-9}$ ), was replicated in the two independent cohorts of patients with HCV mono-infection. The cluster of single-nucleotide polymorphisms in linkage disequilibrium with rs61183828 was located close to two genes involved in mechanisms affecting both cell signaling and cell structure (CAV3) or HCV replication (RAD18). The second signal, obtained with rs11790131 ( $P = 9.3 \times 10^{-9}$ ) on chromosome region 9p22, was not replicated. **CONCLUSION:** Our genome-wide association study identified a new locus associated with liver fibrosis severity in patients with HIV/HCV coinfection, on chromosome 3p25, a finding that was replicated in patients with HCV mono-infection; these results provide new relevant hypotheses for the pathogenesis of liver fibrosis in patients with HIV/HCV coinfection that may help define new targets for drug development or new prognostic tests, to improve patient care. (Hepatology 2016).



**High rates of hepatitis C virus (HCV) cure using direct-acting antivirals in HIV/HCV-coinfected patients: a real-world perspective.**

Hawkins C1, Grant J2, Ammerman LR3, Palella F2, Mclaughlin M4, Green R5, Mcgregor D2, Stosor V2. J Antimicrob Chemother. 2016 Jun 20. pii: dkw203. [Epub ahead of print]

**OBJECTIVES:** There are few data on the real-world experience of FDA-approved oral hepatitis C virus (HCV) direct-acting antiviral (DAA) drug combinations in HIV/HCV-coinfected patients. We evaluated the safety and efficacy of DAA therapies in a cohort of HIV/HCV patients in a large urban clinic in Chicago. **METHODS:** HIV/HCV-coinfected adults ( $\geq 18$  years) enrolled in the Northwestern University Viral Hepatitis Registry between January 2013 and June 2015 were analysed. Treated patients received one of the following DAA combinations: sofosbuvir/ledipasvir, sofosbuvir/ribavirin, sofosbuvir/simeprevir or paritaprevir/ritonavir/ombitasvir/dasabuvir $\pm$ ribavirin. The primary outcome was sustained virological response at 12 weeks after DAA completion (SVR12). **RESULTS:** Seventy-seven HIV/HCV patients were evaluated for DAA therapy. Most patients were male (62/77, 81%) and infected with HCV genotype 1 (67/77, 87%). Some 32/77 (42%) were cirrhotic and 29/77 (38%) had received prior treatment with an IFN-containing regimen. DAA therapy was more likely to be started in Caucasians than persons of other ethnicities ( $P=0.01$ ). The overall SVR12 rate was 92% in 52 patients who completed therapy and had follow-up by the end of the study: sofosbuvir/simeprevir, 32/33 (97%); sofosbuvir/ribavirin, 4/7 (57%); sofosbuvir/ledipasvir, 11/11 (100%); and paritaprevir/ritonavir/ombitasvir/dasabuvir, 1/1 (100%). Four patients relapsed after therapy with sofosbuvir/simeprevir ( $n=1$ ) or sofosbuvir/ribavirin ( $n=3$ ). Adverse events were uncommon and did not result in DAA treatment interruption or discontinuation. **CONCLUSIONS:** The HCV DAA combinations of sofosbuvir/ledipasvir and sofosbuvir/simeprevir were highly effective and well tolerated in this diverse population of HIV/HCV-coinfected patients, many of whom had advanced liver disease. HIV coinfection should not be considered a barrier to successful HCV treatment with DAAs.

**All-oral Direct-acting Antiviral Regimens in HIV/Hepatitis C Virus-coinfected Patients With Cirrhosis Are Efficient and Safe: Real-life Results From the Prospective ANRS CO13-HEPAVIH Cohort.**

Sogni P1, Gilbert C2, Lacombe K3, et al. Clin Infect Dis. 2016 Jun 17. pii: ciw379. [Epub ahead of print]

**BACKGROUND:** Human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients with cirrhosis have long been considered to be difficult to treat, and real-life efficacy and tolerance data with all-oral direct-acting antiviral (DAA) combinations in these patients are scarce. **METHODS:** Cirrhotic HIV/HCV-coinfected patients enrolled in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) CO13 HEPAVIH cohort initiating an all-oral DAA regimen were consecutively included. A negative HCV RNA result at 12 weeks of follow-up or thereafter was assumed as a sustained virologic response (SVR12). Adjusted exact logistic regression was used to study factors associated with treatment outcome. **RESULTS:** We included 189 patients who initiated an all-oral DAA regimen with the following characteristics: median age 53.2 years; 74.6% male; Centers for Disease Control and Prevention classification A/B/C: 37%/31%/32%; Child-Pugh class A/B/C: 91%/8%/1%; 87% with HIV RNA  $<50$  copies/mL; 99% on antiretrovirals; median CD4 count: 489 cells/ $\mu$ L; HCV treatment naive 29%; HCV genotype 1/2/3/4: 58%/4%/17%/21%. Sofosbuvir (SOF) + daclatasvir  $\pm$  ribavirin (RBV) was used in 123 patients, SOF + RBV in 30, SOF + simeprevir in 11, and SOF +



ledipasvir in 23. An SVR12 was reported in 93.1% of the patients (95% confidence interval, 88.5%-96.3%). In adjusted analyses, no difference was found between 12 or 24 weeks of treatment, in patients receiving RBV or not, and in treatment-naïve vs experienced patients. Premature stop of DAA was reported for 8 patients. One patient died during treatment (unknown cause), and 12 other patients developed liver-related events. **CONCLUSIONS:** In this prospective real-life cohort, all-oral DAA regimens were well tolerated and associated with a high virologic efficacy in cirrhotic HIV/HCV-coinfected patients. This should not alleviate the surveillance for liver-related events in these patients.

**[Hepatitis C treatment initiation in HIV-HCV coinfecting patients.](#)** Cotte L1,2, Pugliese P3, Valantin MA4,5, et al. BMC Infect Dis. 2016 Jul 22;16:345. doi: 10.1186/s12879-016-1681-1.

**BACKGROUND:** There are few data regarding HCV treatment initiation among HIV/HCV coinfecting patients. The objective of this study was to analyze the changing patterns of HCV coinfection and HCV treatment initiation over time in a large French cohort of HIV/HCV coinfecting patients at the beginning of DAA's era and to analyze factors associated with treatment initiation. **METHODS:** All HIV/HCV coinfecting patients enrolled during 2000-2012 were analyzed. HCV status was defined per calendar year as naïve, spontaneous cure, sustained virological response (SVR), failure or reinfection. HCV treatment initiation rate was determined per year. Trends over time were analyzed using Chi-2 test for trend and linear regression analysis. The effect of covariates on treatment initiation over time was analyzed using generalized estimating equations. **RESULTS:** Among 34,308 HIV-infected patients enrolled between 2000 and 2012, 5,562 were HCV coinfecting. HCV prevalence declined from 38.4 to 15.1 %. HCV treatment initiation rate fluctuated from 5.6 to 7.4 %/year from 2000 to 2007, dropped to 5.6 % in 2011 and increased to 8.5 % in 2012 due to the use of first-generation DAAs (29.1 % of initiations in 2012). Cumulative HCV treatment initiation rate increased from 14.8 % in 2000 to 54.7 % in 2012. HCV cure rate increased from 12.4 to 45.2 %. Older age, male gender, male homosexuality, high CD4, undetectable HIV-RNA, CDC stage A-B, and severe fibrosis/cirrhosis were associated with a higher treatment initiation rate. The role of HCV genotype 1, CDC stage, fibrosis and recent HCV infection on treatment initiation rate changed over time. **CONCLUSION:** A high rate of HCV treatment initiation was observed at the beginning of DAAs era in HIV/HCV coinfecting patients. Given the very high efficacy of new DAA-based regimens and if treatment initiation keeps increasing, HCV prevalence among HIV patients will drastically decrease during the forthcoming years.

Free Article

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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**[Advance in studies on traditional Chinese medicines to treat infection with the hepatitis B virus and hepatitis C virus.](#)** Xia J1, Inagaki Y, Song P, Sawakami T, Kokudo N, Hasegawa K, Sakamoto Y, Tang W. Biosci Trends. 2016 Jun 25. [Epub ahead of print]

Traditional Chinese medicine (TCM), as a type of complementary and alternative medicine (CAM), is a sophisticated and time-honored form of healthcare in China. Many TCMs are widely used to treat hepatitis B and hepatitis C in countries like China, Japan, and South Korea. Since conventional clinical preparations like interferon- $\alpha$  cause obvious dose-dependent adverse reactions and drug resistance, TCMs and related bioactive compounds have garnered increasing attention from physicians and medical researchers. Thus far, a number of TCMs and compounds

have been used to inhibit the hepatitis B virus (HBV) or hepatitis C virus (HCV) in vitro, in vivo, and even in clinical trials. The current review summarizes TCMs and related compounds that have been used to inhibit HBV or HCV. Most of these medicines are derived from herbs. HepG2.2.15 cells have been used to study HBV in vitro and Huh7.5 cells have been similarly used to study HCV. Ducks have been used to study the anti-HBV effect of new medication in vivo, but there are few animal models for anti-HCV research at the present time. Thus far, a number of preclinical studies have been conducted but few clinical trials have been conducted. In addition, a few chemically modified compounds have displayed greater efficacy than natural products. However, advances in TCM research are hampered by mechanisms of action of many bioactive compounds that have yet to be identified. In short, TCMs and related active compounds are a CAM that could be used to treat HBV and HCV infections.

**[The wild Egyptian artichoke as a promising functional food for the treatment of hepatitis C virus as revealed via UPLC-MS and clinical trials.](#)** Elsebai MF1, Abass K2, Hakkola J3, Atawia AR4, Farag MA5. *Food Funct.* 2016 Jul 13;7(7):3006-16. doi: 10.1039/c6fo00656f.

Infection by hepatitis C virus (HCV) and its subsequent complications are a major cause of mortality worldwide. The water extract of the wild Egyptian artichoke (WEA) (*Cynara cardunculus* L. var. *sylvestris* (Lam.) Fiori) leaves is a freely available herbal product that is used for treatment of HCV-infection complications such as jaundice and ascites. The purpose of this study was to evaluate whether WEA exhibits activity against HCV, identify bioactive chemicals in its extract and to tentatively examine the potential inhibitory interactions of WEA with human drug-metabolizing enzymes. The current pilot clinical trial revealed that the water extract of a WEA plant decreased the HCV viral load below the detection level in 12 out of 15 patients. Furthermore, the liver enzymes ALT and AST, as well as the level of bilirubin were normalized. The total WEA extract inhibited CYP2B6 (OH-BUP) and CYP2C19 (5-OH-OME) with high affinity,  $IC_{50} \sim 20 \mu\text{g ml}^{-1}$ , while moderate inhibitory interactions were observed for CYP1A2, CYP2D6, CYP2E1 and CYP3A4. Results presented herein suggest that the WEA exhibits strong antiviral activity against HCV and may be useful for its treatment. Compared to the artichoke product "Hepar SL Forte®", WEA was found to be more enriched in sesquiterpenes versus the abundance of phenolic compounds, especially flavonoids in Hepar SL Forte® as revealed via UPLC-MS analysis coupled to chemometrics.

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

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**[Desirable Characteristics of Hepatitis C Treatment Regimens: A Review of What We Have and What We Need.](#)** Bidell MR1, McLaughlin M2,3, Faragon J4, Morse C1, Patel N5. *Infect Dis Ther.* 2016 Jul 6. [Epub ahead of print]

There have been dramatic advancements in the treatment of chronic hepatitis C (HCV) infection. This is largely due to the approval of several direct-acting antiviral agents (DAAs) from a variety of medication classes with novel mechanisms of action. These therapies are a welcomed advancement given their improved efficacy and tolerability compared to pegylated interferon and ribavirin (RBV)-based regimens. These convenient, all-oral regimens treat a variety of genotypes and often offer high cure rates in a variety of HCV-infected populations. While there are several benefits associated with these therapies, there are also notable shortcomings. Shortcomings include diminished response or need for adjunctive RBV in difficult-to-treat populations (decompensated cirrhosis, active substance abuse patients, advanced kidney disease, etc.),

activity against select genotypes, substantial drug-drug interaction potential, and high cost. Therefore, while current DAA-based therapies have several favorable attributes, each also has its limitations. The purpose of this review is to (1) identify the characteristics of an ideal HCV treatment regimen, (2) describe desirable features of existing regimens, (3) summarize limitations of existing regimens, and (4) introduce promising emerging therapies. This manuscript will serve as a guide for evaluating the caliber of future HCV treatment regimens.

[Hepatology After Hepatitis C](#). Fitz JG1. Dig Dis. 2016;34(5):603-6. doi: 10.1159/000445276. Epub 2016 Jun 22.

The ~90% probability of curing individual patients with hepatitis C virus (HCV) using direct-acting antivirals represents one of the most dramatic medical success stories of the modern era, and the journey from viral discovery to treatment occurred over just ~25 years. The realities of the global burden of disease (2-3% of the world's population is infected), limited access to care and cost of treatment mean that HCV will continue to be a major problem for the next 25 years. But what if HCV (and hepatitis B) could be eradicated? Since liver transplantation and HCV management have been the mainstays of academic hepatology practice, where do we go from here? Unfortunately, we are in an era where the incidence and prevalence of liver diseases around the globe is increasing, and death from complications of cirrhosis is now among the top 10 causes in most countries; so hepatologists are expected to play a major role in the future. Despite remarkable progress, success at the population level is limited by the resource-intensive nature of caring for patients with end-stage disease. Accordingly, the major advances in the next decade are likely to focus on (i) the earlier identification of individuals and populations at higher risk for liver diseases, and (ii) initiation in high-risk populations of specific strategies for early detection and treatment of fibrosis, cancer and cirrhosis. The answers will lie in large part in the further exploration of the human genome in carefully phenotyped patients. Risk variants in the PNPLA3 gene represent the best example to date. The risk variants are common and are enriched in certain populations around the globe; and individuals that possess risk variants are more likely to have liver injury from fatty liver disease (even as children), alcohol and viral hepatitis. Further, those with liver injury are more likely to progress to cirrhosis and hepatoma. Similarly, in those with established liver disease, use of biomarkers and other strategies for early detection of fibrosis and hepatoma will pay dividends as the next generation of treatments focusing on (i) anti-fibrotic strategies and (ii) liver regeneration move to the forefront. There remains an important need to invest in hepatology as a growth industry even after the (unlikely) eradication of HCV.

[Access to treatment for hepatitis C virus infection: time to put patients first](#). Edlin BR1. Lancet Infect Dis. 2016 Jul 12. pii: S1473-3099(16)30005-6. doi: 10.1016/S1473-3099(16)30005-6. [Epub ahead of print]

Sound health policy puts patients first. Antiviral regimens approved in 2014 revolutionised treatment of hepatitis C virus (HCV) infection. Most patients can now be cured. These new regimens, however, were priced at US\$83 320-150 000 for a 3-month course. Public and private payers in the USA responded by limiting coverage to patients with advanced fibrosis or cirrhosis, keeping the drugs from being used to prevent those stages. These restrictions defy medical guidelines, lack scientific justification, and undermine public health efforts to stem transmission. Instead of reducing barriers to care, the system has erected new ones. As drug makers and payers battle over billions of dollars, the needs of patients have been cast aside. Physicians and

governments have a duty to make sure health policy is driven by the needs of patients and public health. In this Personal View, I call upon these groups to lead the creation of a national consensus among all stakeholders that will allow the advances in therapeutics for HCV infection to be put to work to end the epidemic.

### [Survival effects of physical activity on mortality among persons with liver disease.](#)

Loprinzi PD1, VanWagner LB2. *Prev Med Rep.* 2015 Dec 29;3:132-4. doi: 10.1016/j.pmedr.2015.12.011. eCollection 2016.

Physical activity is protective of premature mortality and those with liver disease are at an increased risk of early mortality. It is thus plausible to suggest that physical activity may have survival benefits among those with liver disease, but this has yet to be investigated. In a national sample, we examine the prospective association of objectively-measured physical activity on all-cause mortality among those with liver disease. Data from the 2003-2006 National Health and Nutrition Examination Survey (with follow-up through 2011) were evaluated (analyzed in 2015). Physical activity was assessed via accelerometry over 7 days. Liver disease was assessed via self-report of physician diagnosis. Covariates included age, gender, race-ethnicity, serum cotinine, income-to-poverty ratio, C-reactive protein, cholesterol medication use, blood pressure medication use, alcohol behavior, self-reported liver disease status, serum alanine aminotransferase (ALT), serum gamma-glutamyltransferase (GGT) and comorbid illness. The sample included 162 adults who self-reported a physician-diagnosis of liver disease. The unweighted median follow-up period was 80.0 months (IQR = 68-91; SD = 18.0). In the sample, 12,815 person-months occurred with a mortality incidence rate of 1.09 deaths per 1000 person-months. After adjustments, for every 10 min/day increase in moderate-to-vigorous physical activity (MVPA), participants had an 89% reduced risk of all-cause mortality (HR<sub>adjusted</sub> = 0.11; 95% CI: 0.02-0.47; P = 0.004). There was no evidence of moderation by alcohol behavior, ALT, GGT or Hepatitis C virus status. These findings demonstrate that modest increases in MVPA may have survival benefits among those with a self-reported liver condition.

### [The time and cost investment required to obtain and initiate direct-acting antiviral therapy.](#)

Loy V1, Benyashvili T, Adams W, Pavkov D, O'Mahoney M, Cotler SJ. *Antivir Ther.* 2016 Jul 14. doi: 10.3851/IMP3068. [Epub ahead of print]

**BACKGROUND:** Obtaining direct acting antiviral (DAA) medications for treatment of hepatitis C virus infection (HCV) is labor-intensive for providers. The purpose of this study was to assess the amount of unbillable time and to estimate the financial burden of obtaining DAAs for HCV. **METHODS:** Patients prescribed DAA therapy from 9/30/2014- 3/19/2015 at an academic hepatology practice were enrolled prospectively. Providers recorded the amount of time required to obtain HCV therapy for each patient. **RESULTS:** 79 patients were consented, 27 of whom were excluded due to incomplete data or deferment of therapy. In our patient population 56% of patients had private insurance, 27% Medicare and 15% Medicaid. The median time spent per patient was 92.5 minutes (80.00 - 108.80 IQR). The median cost spent per patient was \$78.85 (66.75- 94.30 IQR). **CONCLUSIONS:** Development of a streamlined process to reduce the time and cost for physicians to obtain DAAs is needed. Removing this barrier will encourage physicians to adopt HCV treatment to address the large number of patients in need.

**Ten-year follow-up analysis of chronic hepatitis C patients after getting sustained virological response to pegylated interferon- $\alpha$  and ribavirin therapy.**

Wang X<sup>1,2</sup>, Gao F<sup>3</sup>, Yuan G<sup>1</sup>, et al. J Viral Hepat. 2016 Jul 24. doi: 10.1111/jvh.12574. [Epub ahead of print] There is little data on the long-term follow-up outcomes of chronic hepatitis C patients achieving sustained virological response (SVR) after treatment with pegylated interferon- $\alpha$  plus ribavirin. We prospectively investigated the overall clinical, biochemical, virological and histological outcomes in a ten-year cohort study of 325 patients with chronic hepatitis C achieving SVR to pegylated interferon- $\alpha$  and ribavirin therapy. Patients underwent consistent clinical, biochemical and virological evaluation every six months, and patients with pretherapy Ishak fibrosis score  $\geq 2$  were invited to accept a second liver biopsy at the last follow-up. Liver biopsy specimens were evaluated using Ishak's scoring system. At the end of follow-up, five patients developed decompensated liver cirrhosis. One patient (0.3%) with pretherapy cirrhosis was diagnosed with hepatocellular carcinoma (HCC). A total of 305 patients (94%) had normal serum ALT and AST levels during the entire period of follow-up. Twenty-seven patients (8%) had conclusive evidence of virological relapse. Among the 117 patients with paired pretherapy and long-term follow-up biopsies, 96 (82%) had a decreased fibrosis score. Ninety-nine (79%) had a decrease in combined inflammation score. Thirty-seven (32%) had normal or nearly normal livers on long-term follow-up biopsy. SVR achieved with PEG-IFN- $\alpha$  and RBV combination therapy is durable, while late virological relapse may still occur in some patients. Clinical outcomes for patients who obtain SVR are excellent, although the patients with cirrhosis are still at a low risk of hepatocellular carcinoma.

**Examining the link between psychological distress, mental health disorders and sharing behaviors among cocaine users.**

Lévesque A<sup>1</sup>, Roy É<sup>2</sup>, Jutras-Aswad D<sup>3</sup>, Zang G<sup>4</sup>, Arsenault AA<sup>1</sup>, Bruneau J<sup>5</sup>. Addict Behav. 2016 Nov;62:54-9. doi: 10.1016/j.addbeh.2016.06.004. Epub 2016 Jun 7.

**BACKGROUND:** Psychiatric problems and cocaine use are associated with heightened vulnerability for HIV and Hepatitis C infections. Little is known regarding the relationship between psychiatric symptoms, psychiatric diagnoses and injection risk behaviors among cocaine users. We examined the association between psychological distress and injection material sharing among cocaine users, while accounting for comorbid anxious and mood disorders. **METHODS:** Participants included cocaine users who inject drugs recruited in a prospective cohort study in Montreal, Canada. Diagnosis of mood and anxiety disorders in the year preceding baseline were established using the Composite International Diagnostic Interview (CIDI) questionnaire. Psychological distress based on the Kessler scale and injection material sharing in the past 3 months were assessed at baseline and at each of the five follow-up visits at 3-month intervals. Statistical analyses were conducted using generalized estimation equation. **RESULTS:** Of the 387 participants (84.5% male; 80.1%,  $\geq 30$ y.o.), 35% reported severe psychological distress, 43% qualified for an anxiety disorder diagnosis and 29% for a mood disorder diagnosis at baseline. Psychological distress was not associated with any injection risk behavior when adjusting for socio-demographic and psychiatric disorders. Participants with anxiety disorders were more likely to share needle (adjusted odds ratio: 1.89, 95% CI: 1.17-3.03). Sharing of injection material other than needle was not associated with psychiatric disorders or with psychological distress in multivariate analyses. **CONCLUSIONS:** Anxiety disorders are associated with needle sharing among cocaine users. Our results suggest the



importance of screening for anxiety disorders as part of preventive interventions to decrease blood-borne viruses' transmission.

**Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort.**

Setiawan VW<sup>1,2</sup>, Stram DO<sup>1</sup>, Porcel J<sup>2</sup>, Lu SC<sup>3</sup>, Le Marchand L<sup>4</sup>, Nouredin M<sup>3,5</sup>. *Hepatology*. 2016 Jun 15. doi: 10.1002/hep.28677. [Epub ahead of print]

Chronic liver disease (CLD) and cirrhosis are major sources of morbidity and mortality in the United States. Little is known about the epidemiology of these two diseases in ethnic minority populations in the United States. We examined the prevalence of CLD and cirrhosis by underlying etiologies among African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the Multiethnic Cohort. CLD and cirrhosis cases were identified using Medicare claims between 1999 and 2012 among the fee-for-service participants (n = 106,458). We used International Classification of Diseases Ninth Revision codes, body mass index, history of diabetes mellitus, and alcohol consumption from questionnaires to identify underlying etiologies. A total of 5,783 CLD (3,575 CLD without cirrhosis and 2,208 cirrhosis) cases were identified. The prevalence of CLD ranged from 3.9% in African Americans and Native Hawaiians to 4.1% in whites, 6.7% in Latinos, and 6.9% in Japanese. Nonalcoholic fatty liver disease (NAFLD) was the most common cause of CLD in all ethnic groups combined (52%), followed by alcoholic liver disease (21%). NAFLD was the most common cause of cirrhosis in the entire cohort. By ethnicity, NAFLD was the most common cause of cirrhosis in Japanese Americans, Native Hawaiians, and Latinos, accounting for 32% of cases. Alcoholic liver disease was the most common cause of cirrhosis in whites (38.2%), while hepatitis C virus was the most common cause in African Americans (29.8%). **CONCLUSIONS:** We showed racial/ethnic variations in the prevalence of CLD and cirrhosis by underlying etiology; NAFLD was the most common cause of CLD and cirrhosis in the entire cohort, and the high prevalence of NAFLD among Japanese Americans and Native Hawaiians is a novel finding, warranting further studies to elucidate the causes. (*Hepatology* 2016).

**Risk-taking behavior and impulsivity among HCV-infected patients.** Dantas-Duarte A1, Morais-de-Jesus M1, Nunes AP1, et al. *Psychiatry Res*. 2016 Jun 22;243:75-80. doi: 10.1016/j.psychres.2016.04.114. [Epub ahead of print]

The association between risk behaviors and hepatitis C virus (HCV) has been extensively studied. It is also proved that impulsivity is associated with risk behaviors. However, there is a lack of studies investigating the association between HCV and impulsivity, a characteristic that can contribute directly to these risk behaviors. This study aimed to investigate HCV-infected individuals' impulsivity and whether this feature mediates risk behavior. Adult patients with liver diseases (n=269) were divided into two groups: viral group (n=157) - patients with HCV and nonviral group (n=112). Risk behaviors were evaluated by a sociodemographic questionnaire. Impulsivity was assessed through Barratt Impulsiveness Scale - BIS-11. Psychiatric comorbidities were investigated by the Mini International Neuropsychiatric Interview 5.0.0. The viral group patients had higher impulsivity than the nonviral group in all domains: attentional impulsivity, motor impulsivity, and nonplanning. Risk behaviors were also shown to be associated with impulsivity levels. Our results suggest that HCV-infected patients are more impulsive than individuals with other liver diseases, even when analyses are controlled for the

presence of comorbid mental disorders. In addition, at-risk behavior was significantly mediated by impulsivity.

**Cost-Effectiveness of Genotype 1 Chronic Hepatitis C Virus Treatments in Patients Coinfected with Human Immunodeficiency Virus in the United States.**

Saab S1, Virabhak S2, Parisé H2, Johnson S2, Wang A3, Misurski D4, Gonzalez YS4, Juday T4. Adv Ther. 2016 Jun 24. [Epub ahead of print]

**INTRODUCTION:** New treatments for chronic hepatitis C virus (HCV) are highly effective in patients coinfecting with human immunodeficiency virus (HIV). This study estimated the cost-effectiveness of treatments for genotype 1 (GT1) HCV in HIV-coinfecting patients. **METHODS:** A Markov model based on HCV natural history was used. The base-case analysis included both treatment-naïve and -experienced patients. Alternatives were ombitasvir/paritaprevir/ritonavir, dasabuvir with or without ribavirin (3D ± R) for 12 or 24 weeks, sofosbuvir plus peginterferon and R (SOF + PR) for 12 weeks, SOF + R for 24 weeks, and no treatment (NT). A subgroup analysis restricted to treatment-naïve, non-cirrhotic patients compared 3D ± R for 12 weeks to SOF plus ledipasvir (LDV) for 12 weeks and NT. Transition probabilities, utilities, and costs were obtained from the published literature. Outcomes were measured over a lifetime horizon and included rates of compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver-related death, total costs, life-years, quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER). **RESULTS:** In the base-case, SOF + R was dominated by both SOF + PR and 3D ± R. Compared to SOF + PR, 3D ± R had an ICER of \$45,581. The lifetime rates of liver morbidity and mortality were lower among those treated with 3D ± R compared to SOF + PR, SOF + R, or NT. In the subgroup analysis, 3D ± R was cost-effective compared to NT at a threshold of \$50,000 per QALY (ICER \$27,496). SOF/LDV had an ICER of \$104,489 per QALY gained compared to 3D ± R. **CONCLUSION:** In the GT1 HCV population coinfecting with HIV, 3D ± R was cost-effective compared to NT, SOF + R, and SOF + PR. In the treatment-naïve sub-population, 3D ± R was cost-effective compared to NT and SOF/LDV.

**Nonprescription syringe sales: Resistant pharmacists' attitudes and practices.** Chiarello E1. Drug Alcohol Depend. 2016 Jun 27. pii: S0376-8716(16)30170-3. doi: 10.1016/j.drugalcdep.2016.06.023. [Epub ahead of print]

**OBJECTIVES:** To examine barriers to nonprescription syringe sales (NPSS) in pharmacies by examining resistant pharmacists' willingness to provide syringes to people who inject drugs (PWID) and their current practices for provision or refusal. **METHODS:** Qualitative, semi-structured, in-depth interviews with community pharmacists in California, Kansas, Mississippi, and New Jersey. Participants include seventeen community pharmacists who expressed ethical concerns about providing syringes drawn from a larger sample of 71 community pharmacists participating in a study of ethical decision-making. Analysis captures pharmacists' descriptions of their experiences providing syringes to suspected PWID. **RESULTS:** Pharmacists who identified syringes as a key ethical issue exhibited significant ambivalence about providing syringes to PWID. Most of these pharmacists were aware of harm reduction logics, but endorsed them to varying degrees. Moral concerns about supplying PWID with syringes were mediated by law and organizational policy. Many pharmacists who considered syringes an ethical challenge allayed their concerns by creating informal policy and engaging in deterrence practices designed to dissuade PWID from coming to the pharmacy. **CONCLUSIONS:** ZZAs heroin abuse rates

continue to rise, pharmacists are undoubtedly integral allies in the fight to prevent the spread of communicable diseases like HIV/AIDS and Hepatitis C. Education should be aimed at identifying barriers to NPSS resulting from resistant pharmacists' attitudes and practices. Increased education paired with favorable law and organizational policy and decentralization of syringe provision could increase access to clean needles and decrease public health risks.

[Accessibility to Oral Antiviral Therapy for Patients with Chronic Hepatitis C in the United States.](#) Saab S1, Jimenez M2, Fong T2, Wu C2, Bau S2, Jamal Z2, Grotts J2, Elashoff D2. J Clin Transl Hepatol. 2016 Jun 28;4(2):76-82. doi: 10.14218/JCTH.2016.00011. Epub 2016 Jun 15.

**BACKGROUND:** Hepatitis C (HCV) direct acting antiviral agents (DAAs) are safe, effective, and tolerable. Most contraindications to interferon-based treatment are no longer applicable. The aims of this study were to understand the predictors of approval to drug accessibility.

**METHODS:** We studied all consecutive patients with HCV prescribed DAAs between October 2014 and July 2015. Data on demographic, socio-economic status, comorbidities, baseline laboratory values, and assessment of liver disease severity, insurance, and specialty pharmacy type were collected. Multivariate analyses were performed to identify predictors of prescription approval. **RESULTS:** In total, 410 patients were prescribed DAAs between October 2014 and July 2015. Of those, 332 (81%) patients were insurance approved for therapy. Of the 332 patients accepted, 251 were accepted after the first prescription attempt, and 38 were accepted after the second and third attempts. The number of attempts for the other 43 approved patients was unknown. Older age ( $p = 0.001$ ), employment ( $p = 0.001$ ), lack of comorbidities ( $p = 0.02$ ), liver transplantation ( $p = 0.018$ ), and advanced liver disease ( $p = 0.001$ ) were more likely associated with obtaining approval. Household income was not associated with insurance approval. In the multivariate analysis, Medicare insurance (odds ratio [OR] 2.67, 95% confidence interval [CI] 0.96-7.20), lack of nonliver comorbidities (OR 2.72, 95% CI 1.35-5.43), and the presence of advanced liver disease (OR 1.82, 95% CI 1.04-3.24) independently predicted drug approval.

**CONCLUSION:** Despite the availability of DAAs for HCV, barriers from insurance carriers continue to impair widespread use. Patients with advanced liver disease, Medicare, and without comorbidities are most likely to be insurance approved for DAAs.

[Biomarkers of Hepatic Fibrosis in Chronic Hepatitis C: A Comparison of 10 Biomarkers Using 2 Different Assays for Hyaluronic Acid.](#) Tanwar S1, Trembling PM, Hogan BJ, et al. J Clin Gastroenterol. 2016 Jul 1. [Epub ahead of print]

**BACKGROUND:** Advancing fibrosis is regarded as the most important factor when stratifying patients with chronic hepatitis C for retreatment. **GOALS:** (1) To compare the performance of 10 biomarkers of fibrosis, including patented tests, among patients with chronic hepatitis C and treatment failure; and (2) to assess the impact on biomarker performance of using 2 different assays of hyaluronic acid (HA). **STUDY:** For 80 patients, liver histology (Metavir) was compared with biomarker scores using sera obtained within 6 months of liver biopsy (indirect biomarkers: AST:ALT ratio, APRI, Forns index, FIB-4, Fibrometer V3G; direct biomarkers: ELF, Fibrospect II, Hyaluronic acid-HA, Fibrometer V2G, Hepascore). Direct biomarker scores were calculated using 2 validated assays for HA (ELISA and radiometric). **RESULTS:** Using the ELISA assay for HA to calculate the direct panels, all 10 of the biomarkers exhibited comparable overall discriminatory performance (unweighted Obuchowski measure, ordROC 0.92-0.94,  $P$ -value $>0.05$ ) except AST:ALT ratio and APRI (ordROC 0.86-0.88,  $P$ -value $<0.05$ ).

For the detection of moderate (F2-4) and advanced (F3-4) fibrosis, the AUROC of Fibrometer 2G were significantly higher than AST:ALT ratio and APRI but none of the other biomarkers. Good correlation was observed between the 2 HA assays (intraclass correlation coefficient=0.873) with the ELISA assay exhibiting superior diagnostic performance (ordROC 0.92 vs. 0.88, P-value=0.003). Importantly, the performance of many of the direct biomarkers at their diagnostic thresholds was heavily influenced by the choice of HA assay. **CONCLUSIONS:** Although many biomarkers exhibited good diagnostic performance for the detection of advancing fibrosis, our results indicate that diagnostic performance may be significantly affected by the selection of individual component assays.

**The citizen scientist: Community-academic partnerships through Translational Advisory Boards.** Patel DI1, Winkler P2, Botello J3, Villarreal J4, Puga F5. Patient Educ Couns. 2016 Jul 5. pii: S0738-3991(16)30308-1. doi: 10.1016/j.pec.2016.07.013. [Epub ahead of print]

**OBJECTIVE:** To describe the effectiveness of engaging patient partners as "citizen scientists" in the research process to boost patient centered outcomes research in underrepresented populations. **METHODS:** Translational Advisory Boards in South Texas have effectively collaborated with University researchers to develop community-based patient centered research. Here we describe innovative approaches in research to engage patients and offer practical methods to enhance partnerships between patients and researchers to facilitate patient engagement. **RESULTS:** Three health issues identified by the TABs were diabetes, obesity and teen pregnancy. Examples of other community inspired research topics include air and water quality, methicillin-resistant staphylococcus aureus, intimate partner violence, chronic pain, and human papilloma virus and hepatitis C vaccinations. **CONCLUSION:** Patient engagement of underrepresented populations is inverse to the vast disparities they experience. In order to adequately address our nation's deficits in providing equitable healthcare, we must fully integrate disparate partners into the research process. By engaging community champions, academic health centers can fully integrate meaningful interventions on topics of interest to the catchment area in which they serve. **PRACTICE IMPLICATIONS:** These lessons can be used in developing local and regional collaborations across the country to boost active participation of patient stakeholder in PCOR to reduce healthcare disparities and improve our healthcare systems.

**Performance of Risk-Based and Birth-Cohort Strategies for Identifying Hepatitis C Virus Infection Among People Entering Prison, Wisconsin, 2014.** Stockman LJ1, Greer J2, Holzmacher R2, et al. Public Health Rep. 2016 Jul-Aug;131(4):544-51.

**OBJECTIVES:** The prevalence of hepatitis C virus (HCV) infection among young adults is rising in Wisconsin. We examined the prevalence of HCV infection among male and female inmates entering two Wisconsin prisons and evaluated existing and alternate risk-based strategies for identifying HCV infection at intake. **METHODS:** We added HCV testing to the intake procedures for all 1,239 adults prison entrants at the Wisconsin Department of Corrections (WDOC) from November 3, 2014, to January 31, 2015. We identified risk factors associated with HCV infection during the routine intake examination and calculated the sensitivity and specificity of risk-based testing strategies for identifying HCV infection. **RESULTS:** The prevalence of HCV antibody among prison entrants was 12.5% (95% confidence interval [CI] 10.7, 14.4) overall and was almost two times higher at the women's facility (21.3%, 95% CI 15.4, 27.2) than at the men's facility (11.0%, 95% CI 0.0, 12.9) (p<0.001). The sensitivity and

specificity of the WDOC risk-based criteria were 88% (95% CI 83, 93) and 80% (95% CI 78, 83), respectively. Adding a new criterion, the 1945-1965 birth cohort, to the risk-based criteria improved the sensitivity to 92% (95% CI 88, 96) and lowered the specificity to 71% (95% CI 68, 74). Compared with entrants without these risk factors, HCV antibody prevalence was significantly higher among prison entrants who had the following risk factors: injection drug use (prevalence ratio [PR] = 9.9, 95% CI 7.4, 13.2), liver disease (PR=9.7, 95% CI 7.8, 12.0), and elevated levels of alanine transaminase (PR=3.6, 95% CI 2.7, 4.9). **CONCLUSION:** The WDOC risk criteria for HCV testing identified 88% of HCV infections among prison entrants. Including the 1945-1965 birth cohort as a criterion along with the other WDOC risk criteria increased the sensitivity of targeted testing to 92%. These findings may be informative to jurisdictions where universal HCV testing is not feasible because of resource limitations.

[Collaborative Care for Depression in Chronic Hepatitis C Clinics.](#) Kanwal F1, Pyne JM1, Tavakoli-Tabasi S1, et al. Psychiatr Serv. 2016 Jul 1:appips201400474. [Epub ahead of print]

**OBJECTIVE:** Depression is highly prevalent yet underdiagnosed and undertreated among patients with chronic hepatitis C virus (HCV) infection. Collaborative care models have improved depression outcomes in primary care settings, and this study aimed to provide more information on testing such methods in specialty HCV care. **METHODS:** Hepatitis C Translating Initiatives for Depression Into Effective Solutions (HEPTIDES) was a randomized controlled trial that tested a collaborative depression care model in HCV clinics at four Veterans Affairs facilities. The HEPTIDES intervention consisted of an offsite depression care team (depression care manager, pharmacist, and psychiatrist) that delivered collaborative care. Participant interview data were collected at baseline and at six months. The outcome was depression severity measured with the Hopkins Symptom Checklist (SCL-20) and reported as treatment response ( $\geq 50\%$  decrease in SCL-20 item score), remission (mean SCL-20 item score  $< .5$ ), and depression-free days (DFDs). **RESULTS:** Baseline screening identified 263 HCV-infected patients with depression. In unadjusted analyses, intervention participants' reports trended toward more treatment response (19% versus 13%) and remission (12% versus 6%), but total number of DFDs (50.9) was similar to that of usual care participants (50.7). These trends did not reach statistical significance for the overall sample in the adjusted analyses: response (odds ratio [OR]=2.02, 95% confidence interval [CI]=.98-4.20), remission (OR=2.63, CI=1.00-6.94), and DFDs ( $\beta=7.6$  days, CI=-.99 to 16.2). However, the intervention was effective in improving all three outcomes for patients who did not meet criteria for remission at baseline (SCL-20 score  $> .5$ , N=245). **CONCLUSIONS:** Depression collaborative care resulted in modest improvements in HCV patient depression outcomes. Future research should investigate intervention modifications to improve outcomes in specialty HCV clinics.

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## LIVER CANCER

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[Association of long noncoding RNA and c-JUN expression in hepatocellular carcinoma.](#)

El-Tawdi AH1, Matboli M2, El-Nakeep S3, Azazy AE4, Abdel-Rahman O5. Expert Rev Gastroenterol Hepatol. 2016 Jul;10(7):869-77. doi: 10.1080/17474124.2016.1193003. Epub 2016 Jun 6.

**BACKGROUND:** Long noncoding RNAs(lncRNAs) have emerged as key elements in modulating gene expression in different biological contexts. **PATIENTS AND METHODS:** We used quantitative real-time PCR (Qpcr) to evaluate the expression of lncRNA-UCA1 and C-



JUN in serum of 70 patients with hepatocellular carcinoma (HCC), 32 patients chronic hepatitis C (CHC) and 38 healthy subjects and their correlation with different clinicopathological factors. **RESULTS:** The expression of lncRNA-UCA1 and C-JUN was positive in 91.4% HCC patients with strong discriminating power between HCC and healthy subjects and CHC patients as well. The median follow up period was 29 months. The survival analysis showed that both lncRNA-UCA1 and C-JUN were independent prognostic factors. Of note, we identified C-JUN expression changes consistent with the lncRNA-UCA1 target regulation. **CONCLUSION:** This information sheds light on the possible role of lncRNA-UCA1 and C-JUN mRNA as promising diagnostic and prognostic markers as well as potential therapeutic targets in HCC.

**Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals.** Conti F1, Buonfiglioli F1, Scuteri A2, et al. J Hepatol. 2016 Jun 24. pii: S0168-8278(16)30303-8. doi: 10.1016/j.jhep.2016.06.015. [Epub ahead of print]

**BACKGROUND & AIMS:** Hepatocellular carcinoma (HCC) represents a serious complication of HCV-related cirrhosis. New direct-acting antivirals (DAA) cure HCV infection in over 90% of patients. The aim of this study was to evaluate the early occurrence and recurrence of HCC in cirrhotic patients treated with DAA. **METHODS:** We analysed 344 consecutive cirrhotic patients, without HCC, who were treated with DAA, and followed for 24 weeks. Fifty-nine patients had previous HCC. **RESULTS:** DAA therapy induced sustained virological response in 91% of patients. During 24-week follow-up, HCC was detected in 26 patients (7.6%, 95% CI: 4.99-10.84): 17 of 59 patients (28.81%, 95% CI: 17.76-42.07) with previous HCC and 9 of 285 patients (3.16%, 95% CI: 1.45-5.90) without previous HCC. Child-Pugh Class B, more severe liver fibrosis, lower platelet count, and previous HCC were significantly associated with HCC development, at univariate analysis. At multivariate analysis, Child-Pugh class ( $p=0.03$ , OR: 4.18, 95% CI: 1.17-14.8) and history of HCC ( $p<0.0001$ , OR: 12.0, 95% CI: 4.02-35.74) resulted independently associated with HCC development. Among the 59 patients with previous HCC, younger age and more severe liver fibrosis were significantly associated with HCC recurrence, both at univariate and at multivariate analysis. **CONCLUSIONS:** In patients with HCV-related cirrhosis, DAA-induced resolution of HCV infection does not seem to reduce occurrence of HCC, and patients previously treated for HCC have still a high risk of tumour recurrence, in the short term. For these reasons, all cirrhotic patients should be closely monitored and followed during and after antiviral therapy. **LAY SUMMARY:** New direct-acting antivirals are able to eradicate HCV infection in over 90% of patients with advanced liver disease. Unfortunately, the occurrence of liver cancer is not reduced in effectively treated cirrhotic patients. In addition, patients previously treated for HCC have still a high risk of tumour recurrence in the short term, despite DAA treatment.

**Serum PAI-1 and PAI-1 4G/5G Polymorphism in Hepatitis C Virus-Induced Cirrhosis and Hepatitis C Virus-Induced Hepatocellular Carcinoma patients.** El Edel RH1, Essa ES1, Essa AS2, Hegazy SA1, El Rowedy DI1. Viral Immunol. 2016 Jul 26. [Epub ahead of print]

Association between variable agent-induced hepatocellular carcinoma (HCC) and both PAI-1 4G/5G polymorphism and plasminogen activator inhibitor (PAI-1) levels compared to healthy controls have been reported in earlier studies. We aimed to assess serum PAI-1 and PAI-1 4G/5G polymorphism in hepatitis C virus (HCV)-induced HCC, HCV-induced liver cirrhosis, and viral infection-free apparently healthy control subjects. Forty nine HCC, 52 cirrhosis, and 105 controls

were genotyped for PAI-1 4G/5G using an allele-specific polymerase chain reaction analysis. In addition, for 31 HCC, 24 cirrhosis, and 28 controls, serum PAI-1 level was measured by enzyme-linked immunosorbent assay (ELISA). There was no significant difference in PAI-1 4G/5G genotype distribution between cirrhosis and controls ( $p = 0.33$ ,  $p = 0.15$ , and  $p = 0.38$  for the codominant, dominant, and recessive models, respectively) or between HCC and cirrhosis ( $p = 0.5$ ,  $p = 0.24$ , and  $p = 0.69$  for the codominant, dominant, and recessive models, respectively). Serum PAI-1 was significantly higher in cirrhosis than controls and significantly lower in HCC than cirrhosis ( $p < 0.001$  for both). Serum PAI-1 did not differ significantly among the three PAI-1 4G/5G genotypes in controls, cirrhosis, and HCC ( $p = 0.29$ ,  $p = 0.28$ , and  $p = 0.73$  respectively). We documented higher serum PAI-1 in HCV-induced HCC than viral infection-free controls, but interestingly, lower than HCV-induced liver cirrhosis patients. This was not genotype related. Further studies will be needed to clearly elucidate the underlying mechanism.

**[Serum metabolome profiles characterized by patients with hepatocellular carcinoma associated with hepatitis B and C.](#)** Saito T1, Sugimoto M1, Okumoto K1, et al. *World J Gastroenterol.* 2016 Jul 21;22(27):6224-34. doi: 10.3748/wjg.v22.i27.6224.

**AIM:** To clarify the characteristics of metabolite profiles in virus-related hepatocellular carcinoma (HCC) patients using serum metabolome analysis. **METHODS:** The serum levels of low-molecular-weight metabolites in 68 patients with HCC were quantified using capillary electrophoresis chromatography and mass spectrometry. Thirty and 38 of the patients suffered from hepatitis B virus-related HCC (HCC-B) and hepatitis C virus-related HCC (HCC-C), respectively. **RESULTS:** The main metabolites characteristic of HCC were those associated with glutathione metabolism, notably 13  $\gamma$ -glutamyl peptides, which are by-products of glutathione induction. Two major profiles, i.e., concentration patterns, of metabolites were identified in HCC patients, and these were classified into two groups: an HCC-B group and an HCC-C group including some of the HCC-B cases. The receiver operating characteristic curve for the multiple logistic regression model discriminating HCC-B from HCC-C incorporating the concentrations of glutamic acid, methionine and  $\gamma$ -glutamyl-glycine-glycine showed a highly significant area under the curve value of 0.94 (95%CI: 0.89-1.0,  $P < 0.0001$ ). **CONCLUSION:** The serum levels of  $\gamma$ -glutamyl peptides, as well as their concentration patterns, contribute to the development of potential biomarkers for virus-related HCC. The difference in metabolite profiles between HCC-B and HCC-C may reflect the respective metabolic reactions that underlie the different pathogeneses of these two types of HCC.

**[Evaluation of Circulatory RNA-Based Biomarker Panel in Hepatocellular Carcinoma.](#)** El-Tawdi AH1, Matboli M2, Shehata HH3, Tash F3, El-Khazragy N4, Azazy Ael-S5, Abdel-Rahman O6. *Mol Diagn Ther.* 2016 Jun;20(3):265-77. doi: 10.1007/s40291-016-0200-9.

**BACKGROUND:** The circulating transcriptome (coding and non-coding) plays a critical role in cancer. Novel accurate strategies for early detection of hepatocellular carcinoma (HCC) are strongly needed. **PATIENTS AND METHODS:** We chose an HCC-specific RNA-based biomarker panel based on the integration of differential lysosomal-associated membrane protein 2 (LAMP2) gene expression with its selected epigenetic regulators using bioinformatic methods. This was followed by RT-qPCR validation in serum of 78 patients with HCC, 36 patients with chronic hepatitis C (CHC) infection and 44 healthy volunteers. We used risk-score analysis to evaluate the diagnostic efficacy of the serum profiling system. Moreover, in twenty of the 78

HCC cases involved in the study we examined the expression of RNA-based biomarker panel in both HCC and adjacent non-tumor tissues and assessed their correlation with the serum level of this panel. **RESULTS:** The four ribonucleic acid (RNA)-based biomarker panel [long non-coding RNA-C terminal binding protein, androgen responsive (lncRNA-CTBP), microRNA-16-2 (miR-16-2), microRNA-21-5-P (miR-21-5p) and LAMP2], had high sensitivity and specificity for discriminating HCC from healthy controls and also from CHC patients. Among these four RNAs, serum miR-16-2 and miR-21-5p were independent prognostic factors. **CONCLUSION:** The circulatory RNA-based biomarker panel can serve as a potential biomarker for HCC diagnosis and prognosis.

**Impact of HCV core gene quasispecies on hepatocellular carcinoma risk among HALT-C trial patients.** El-Shamy A1, Pendleton M2, Eng FJ1, Doyle EH1, Bashir A2, Branch AD1. Sci Rep. 2016 Jun 1;6:27025. doi: 10.1038/srep27025.

Mutations at positions 70 and/or 91 in the core protein of genotype-1b, hepatitis C virus (HCV) are associated with hepatocellular carcinoma (HCC) risk in Asian patients. To evaluate this in a US population, the relationship between the percentage of 70 and/or 91 mutant HCV quasispecies in baseline serum samples of chronic HCV patients from the HALT-C trial and the incidence of HCC was determined by deep sequencing. Quasispecies percentage cut-points,  $\geq 42\%$  of non-arginine at 70 (non-R(70)) or  $\geq 98.5\%$  of non-leucine at 91 (non-L(91)) had optimal sensitivity at discerning higher or lower HCC risk. In baseline samples, 88.5% of chronic HCV patients who later developed HCC and 68.8% of matched HCC-free control patients had  $\geq 42\%$  non-R(70) quasispecies ( $P = 0.06$ ). Furthermore, 30.8% of patients who developed HCC and 54.7% of matched HCC-free patients had quasispecies with  $\geq 98.5\%$  non-L(91) ( $P = 0.06$ ). By Kaplan-Meier analysis, HCC incidence was higher, but not statistically significant, among patients with quasispecies  $\geq 42\%$  non-R(70) ( $P = 0.08$ ), while HCC incidence was significantly reduced among patients with quasispecies  $\geq 98.5\%$  non-L(91) ( $P = 0.01$ ). In a Cox regression model, non-R(70)  $\geq 42\%$  was associated with increased HCC risk. This study of US patients indicates the potential utility of HCV quasispecies analysis as a non-invasive biomarker of HCC risk.