



**January 2017**

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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**[Post-Treatment Resistance Analysis of Hepatitis C Virus from Phase 2 and 3 Clinical Trials of Ledipasvir/ Sofosbuvir.](#)**

Wyles D1, Dvory-Sobol H2, Svarovskaia Doehle ES3, et al. J Hepatol. 2016 Dec 3. pii: S0168-8278(16)30699-7. doi: 10.1016/j.jhep.2016.11.022. [Epub ahead of print]

**BACKGROUND & AIMS:** Ledipasvir/sofosbuvir combination treatment in phase 3 clinical trials, resulted in sustained viral suppression in 94%-99% of patients. Characterization of drug resistance in treatment failures may help inform retreatment options. **METHODS:** We performed NS5A and NS5B deep sequencing of HCV from patients infected with genotype (GT) 1 who participated in ledipasvir/sofosbuvir phase 2 and 3 clinical trials. **RESULTS:** Fifty-one of 2144 (2.4%) (42 GT1a and 9 GT1b) treated patients met the criteria for resistance analysis due to virologic failure following the end of treatment. The majority of patients with virologic failure (38 of 51; 74.5%) had detectable ledipasvir-specific resistance-associated substitutions (RASs) at the time of virologic failure (1% deep sequencing cutoff). The percent of patients with NS5A RASs at virologic failure were 37.5%, 66.7%, 94.7% and 100% in patients treated for 6, 8, 12 and 24 weeks, respectively. The common substitutions detected at failure were Q30R/H, Y93H/N and/or L31M in GT1a and Y93H in GT1b. At failure, 35.3% (18/51) of virologic failure patients' viruses had 2 or more NS5A RASs and the majority of patients harbored NS5A RASs conferring 100-1000-fold (n=10) or >1000-fold (n=23) reduced susceptibility to ledipasvir. One patient in a phase 2 study with a known ledipasvir RAS at baseline (L31M) developed the S282T sofosbuvir (NS5B) RAS at failure. **CONCLUSIONS:** In GT1 HCV-infected patients treated with ledipasvir/sofosbuvir±ribavirin, virologic failure was rare. Ledipasvir resistance in NS5A was selected or enhanced in most patients with virologic failure, one of whom also developed resistance to sofosbuvir. **LAY SUMMARY:** Clinical studies have shown that combination treatment with ledipasvir/sofosbuvir efficiently cures most patients with genotype 1 hepatitis C infection. For the few patients failing treatment, we show that resistance to ledipasvir was observed in most patients, whereas resistance to sofosbuvir was less common. This has important implications for selection of optimal retreatment strategies for these patients.

**[NS5A resistance-associated variants undermine the effectiveness of ledipasvir and sofosbuvir for cirrhotic patients infected with HCV genotype 1b.](#)**

Ogawa E1, Furusyo N1, Nomura H2, et al. J Gastroenterol. 2016 Dec 2. [Epub ahead of print]

**BACKGROUND:** Little real-world cohort data has been reported for Asians who have received interferon-free regimens with sofosbuvir (SOF) for chronic hepatitis C virus (HCV) infection. We evaluated the effectiveness and safety in clinical practice of ledipasvir (LDV) plus SOF for Japanese patients infected with HCV genotype 1. **METHODS:** This large, multicenter, real-world cohort study consisted of 772 patients treatment-naïve or -experienced, with or without compensated cirrhosis, who were treated with LDV (90 mg)/SOF (400 mg) for a fixed 12-week duration. Direct sequence analysis of the NS5A genes (L31 and Y93) was performed at baseline. **RESULTS:** Almost all (99.6%) were infected with HCV genotype 1b. The overall sustained virological response 12 weeks after the end of treatment (SVR12) rate was 98.8% (763/772). Multivariable logistic regression analysis extracted male (odds ratio [OR] 6.62,  $p = 0.024$ ), cirrhosis (OR 20.1,  $p = 0.0054$ ), and baseline NS5A resistance-associated variants (RAVs) (OR 29.3,  $p = 0.0018$ ) as independently associated with treatment failure. Notably, the SVR12 rate for cirrhosis patients with baseline NS5A RAVs (87.5%, 49/56) was statistically lower than for the other groups. This tendency was found except for patients with prior daclatasvir/asunaprevir failure. All patients with treatment failure had NS5A Y93H at relapse, whether or not they had NS5A RAVs at baseline. Serious adverse effects were very rare, and discontinuation was required for only five (0.6%) patients. **CONCLUSIONS:** LDV/SOF for HCV genotype 1b was exceptionally effective, however, NS5A RAVs undermined the virological effect for cirrhosis patients. Moreover, LDV/SOF was shown to be safe, irrespective of age or fibrosis status.

[Short-duration treatment for chronic hepatitis C virus with daclatasvir, asunaprevir, beclabuvir, and sofosbuvir \(FOURward study\).](#) Sulkowski MS1, Flamm S2, Kayali Z3, et al. *Liver Int.* 2016 Dec 10. doi: 10.1111/liv.13335. [Epub ahead of print]

**BACKGROUND AND AIMS:** The phase 2, FOURward study (NCT02175966) investigated short-duration therapy (4/6 weeks) with four direct-acting antivirals (DAAs) with distinct mechanisms of action in patients infected with HCV genotype-1. **METHODS:** Non-cirrhotic patients were randomized 1:1 to DCV-TRIO (fixed-dose daclatasvir 30mg, asunaprevir 200mg and beclabuvir 75mg) twice-daily + sofosbuvir 400 mg once-daily for 4 or 6 weeks. The primary endpoint was sustained virologic response at post-treatment Week 12 (SVR12). Patients without SVR12 were offered retreatment based on the DAA resistance profile at failure; patients with resistance to  $\leq 1$  DCV-TRIO component received DCV-TRIO+RBV for 12 weeks. **RESULTS:** Twenty-eight patients with HCV genotype-1 were enrolled; 79% had genotype-1a infection and median baseline HCV-RNA levels were high ( $9 \times 10^6$  IU/mL). Most patients had undetectable HCV-RNA at end-of-treatment (96% [ $n=27/28$ ]); however, relapse occurred in 77% ( $n=10/13$ ) and 43% ( $n=6/14$ ) treated for 4 and 6 weeks, leading to SVR12 rates of 29% ( $n=4/14$ ) and 57% ( $n=8/14$ ), respectively. SVR12 was higher in patients with lower baseline HCV-RNA ( $< 2$  million IU/mL, 71% [ $n=5/7$ ];  $\geq 2$  million IU/mL, 33% [ $n=7/21$ ]). None of the 16 non-SVR12 patients had NS3 or NS5B resistance-associated substitutions (RAS) detected at failure. All 15 patients retreated with DCV-TRIO+RBV for 12 weeks achieved SVR12. All regimens were well tolerated. **CONCLUSIONS:** Short-duration treatment with four DAAs with distinct mechanisms of action was insufficient for most patients with genotype-1 infection and high baseline viremia. Non-SVR12 was not associated with emergence of NS3 or NS5B RAS and re-treatment with DCV-TRIO+RBV for 12 weeks led to SVR in all patients.

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

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**[PTC725, an NS4B-Targeting Compound, Inhibits a Hepatitis C Virus Genotype 3 Replicon, as Predicted by Genome Sequence Analysis and Determined Experimentally.](#)**

Graci JD1, Jung SP1, Pichardo J1, Lahser F2, Tong X3, Gu Z1, Colacino JM4. *Antimicrob Agents Chemother.* 2016 Nov 21;60(12):7060-7066. Print 2016 Dec.

PTC725 is a small molecule NS4B-targeting inhibitor of hepatitis C virus (HCV) genotype (gt) 1 RNA replication that lacks activity against HCV gt2. We analyzed the Los Alamos HCV sequence database to predict susceptible/resistant HCV gt's according to the prevalence of known resistance-conferring amino acids in the NS4B protein. Our analysis predicted that HCV gt3 would be highly susceptible to the activity of PTC725. Indeed, PTC725 was shown to be active against a gt3 subgenomic replicon with a 50% effective concentration of ~5 nM. De novo resistance selection identified mutations encoding amino acid substitutions mapping to the first predicted transmembrane region of NS4B, a finding consistent with results for PTC725 and other NS4B-targeting compounds against HCV gt1. This is the first report of the activity of an NS4B targeting compound against HCV gt3. In addition, we have identified previously unreported amino acid substitutions selected by PTC725 treatment which further demonstrate that these compounds target the NS4B first transmembrane region.

**[Effects of ribavirin/sofosbuvir treatment and ITPA phenotype on endogenous purines.](#)**

Jimmerson LC1, Clayton CW2, MaWhinney S2, Meissner EG3, Sims Z3, Kottlilil S3, Kiser JJ4. *Antiviral Res.* 2017 Feb;138:79-85. doi: 10.1016/j.antiviral.2016.12.005. Epub 2016 Dec 9.

Ribavirin (RBV), a purine analog, causes hemolytic anemia in some patients. In vitro, anemia appears to result from depletion of endogenous purines, but there are limited data in vivo. Single nucleotide polymorphisms in the gene encoding the inosine triphosphatase (ITPA) enzyme have been associated with protection against RBV-induced anemia and may mediate the effect of RBV treatment on endogenous purines. The purpose of this work was to determine the effect of RBV treatment on endogenous purine concentrations in individuals being treated for chronic hepatitis C virus (HCV) infection. Adenosine triphosphate (ATP), guanosine triphosphate (GTP), inosine triphosphate (ITP) and ribavirin triphosphate (RTP) were measured in whole blood obtained from 47 HCV-infected individuals at day zero (baseline), day three, day 28 and day 84 of RBV/sofosbuvir (SOF) treatment. ATP decreased -35.1% and -38.6% ( $p < 0.0001$ ) at day 28 and day 84 of treatment, respectively compared to baseline. The decrease in ATP was greater in patients with  $\leq 60\%$  ITPA activity compared to those with 100% ITPA activity (-29.4% vs. -9.6%). GTP did not change during treatment but was 16.5% ( $p = 0.01$ ) higher per 100 pmol/106 cells RTP in those with 100% ITPA activity. No significant change or effect of RTP or ITPA phenotype was noted for ITP. In summary, only ATP was reduced by RBV/SOF treatment and ITPA variants had larger reductions in ATP suggesting RBV-induced anemia is due to a different mechanism than predicted from in-vitro studies. These data emphasize the importance of characterizing the effect of nucleos(t)ide analog treatment on endogenous purines in-vivo.

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PMID: 27956135 [PubMed - in process]

**[Suppression of Host Innate Immune Response by Hepatitis C Virus via Induction of Autophagic Degradation of TRAF6.](#)**

Chan ST1, Lee J1, Narula M1, Ou JJ2. *J Virol.* 2016 Nov 14;90(23):10928-10935. Print 2016 Dec 1.

Tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) is an important adaptor molecule that mediates the TNFR family and interleukin-1 (IL-1)/Toll-like receptor (TLR) signaling cascades. These pathways are important for the host to control viral infections. In this report, we demonstrated that hepatitis C virus (HCV) depleted TRAF6 from its host cells through a posttranslational mechanism. This depletion was independent of proteasomes, as it was not affected by the proteasome inhibitor MG132, but it was suppressed by bafilomycin A1, which led to the association of TRAF6 with autophagosomes. As bafilomycin A1 is a vacuolar ATPase inhibitor that inhibits autophagic protein degradation, these results suggested that HCV depleted TRAF6 via autophagy. The degradation of TRAF6 was apparently mediated by the p62 sequestosome protein, which is a factor important for selective autophagy, as it could bind to TRAF6 and its silencing stabilized TRAF6. The depletion of TRAF6 suppressed activation of NF- $\kappa$ B and induction of proinflammatory cytokines and enhanced HCV replication. In contrast, the overexpression of TRAF6 suppressed HCV replication. These results revealed a novel mechanism that was used by HCV to disrupt the host innate immune responses for viral replication and persistence. **IMPORTANCE:** HCV can cause severe liver diseases and is one of the most important human pathogens. It establishes chronic infections in the great majority of patients that it infects, indicating that it has evolved sophisticated mechanisms to evade host immunity. TRAF6 is an important signaling molecule that mediates activation of NF- $\kappa$ B and expression of proinflammatory cytokines and interferons. In this study, we found that HCV infection suppressed the host innate immune response through the induction of autophagic degradation of TRAF6. This finding provided important information for further understanding how HCV evades host immunity to establish persistence.

**Altered Glycosylation Patterns Increase Immunogenicity of a Subunit Hepatitis C Virus Vaccine, Inducing Neutralizing Antibodies Which Confer Protection in Mice.** Li D1,2, von Schaewen M3, Wang X1,2, et al. J Virol. 2016 Nov 14;90(23):10486-10498. Print 2016 Dec 1. Hepatitis C virus (HCV) infection is a global health problem for which no vaccine is available. HCV has a highly heterogeneous RNA genome and can be classified into seven genotypes. Due to the high genetic and resultant antigenic variation among the genotypes, inducing antibodies capable of neutralizing most of the HCV genotypes by experimental vaccination has been challenging. Previous efforts focused on priming humoral immune responses with recombinant HCV envelope E2 protein produced in mammalian cells. Here, we report that a soluble form of HCV E2 (sE2) produced in insect cells possesses different glycosylation patterns and is more immunogenic, as evidenced by the induction of higher titers of broadly neutralizing antibodies (bNAbs) against cell culture-derived HCV (HCVcc) harboring structural proteins from a diverse array of HCV genotypes. We affirm that continuous and discontinuous epitopes of well-characterized bNAbs are conserved, suggesting that sE2 produced in insect cells is properly folded. In a genetically humanized mouse model, active immunization with sE2 efficiently protected against challenge with a heterologous HCV genotype. These data not only demonstrate that sE2 is a promising HCV vaccine candidate, but also highlight the importance of glycosylation patterns in developing subunit viral vaccines. **IMPORTANCE:** A prophylactic vaccine with high efficacy and low cost is urgently needed for global control of HCV infection. Induction of broadly neutralizing antibodies against most HCV genotypes has been challenging due to the antigenic diversity of the HCV genome. Here, we refined a high-yield subunit HCV vaccine that elicited broadly neutralizing antibody responses in preclinical trials. We found that soluble HCV E2 protein (sE2) produced in insect cells is distinctly glycosylated and is more

immunogenic than sE2 produced in mammalian cells, suggesting that glycosylation patterns should be taken into consideration in efforts to generate antibody-based recombinant vaccines against HCV. We further showed that sE2 vaccination confers protection against HCV infection in a genetically humanized mouse model. Thus, our work identified a promising broadly protective HCV vaccine candidate that should be considered for further preclinical and clinical development.

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## HIV/HCV COINFECTION

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[Pharmacokinetic Evaluation of Darunavir Administered Once or Twice daily in Combination with Ritonavir or the Three Direct Acting Antiviral Regimen of Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir in Adults Co-infected with Hepatitis C and Human Immunodeficiency Virus.](#) King JR1, Khatri A2, Trinh R3, Viani RM3, Ding B4, Zha J2, Menon R1. Antimicrob Agents Chemother. 2016 Dec 5. pii: AAC.02135-16. [Epub ahead of print]

**BACKGROUND:** The three-direct acting antiviral (3D) regimen containing ombitasvir, paritaprevir, ritonavir and dasabuvir ± ribavirin (RBV) is approved for treatment of HCV GT1/HIV-1 co-infection. Results of a pharmacokinetic substudy of 3D and darunavir are presented. **METHODS:** HCV/HIV-1 infected subjects were randomized to maintain a darunavir 800 mg once daily (QD) or switch to a darunavir 600 mg twice daily (BID) based antiretroviral regimen. On Study Day 1, subjects received 3D and RBV plus darunavir for 12 weeks. Pharmacokinetic parameters were compared for darunavir with and without 3D. Pharmacokinetic parameters of 3D were compared to historical data. **RESULTS:** Ten subjects received darunavir QD and 12 subjects received darunavir BID. The central value ratios (90% confidence interval [CI]) for darunavir C<sub>max</sub>, AUC<sub>24</sub> and C<sub>24</sub> administered QD with 3D vs. alone were 0.92 (0.72, 1.18), 0.83 (0.71, 0.98) and 0.64 (0.44, 0.93), respectively. The ratios (90% CI) for darunavir C<sub>max</sub>, AUC<sub>12</sub> and C<sub>12</sub> administered BID with 3D were 0.92 (0.76, 1.12), 0.88 (0.73, 1.05) and 0.73 (0.58, 0.92), respectively. Exposures of 3D were similar or slightly lower compared with historical data. All darunavir trough concentrations (C<sub>trough</sub>) associated with an HIV-1 RNA >40 copies/mL were above the darunavir EC<sub>50</sub> of 550 ng/mL for resistant virus.

**CONCLUSIONS:** The 3D regimen with darunavir QD or BID did not affect darunavir C<sub>max</sub> and AUC, whereas darunavir C<sub>trough</sub> decreased. Changes in pharmacokinetic parameters of 3D were not considered clinically significant. Episodes of intermittent HIV-1 viremia were infrequent and not associated with darunavir C<sub>trough</sub> values below 550 ng/mL. (This study has been registered at ClinicalTrials.gov under identifier NCT01939197.).

[Is Response to Anti-HCV Treatment Predictive of Mortality in HCV/HIV Positive Patients?](#) Peters L1, Cozzi-Lepri A; Hepatitis C Working Group for the Collaboration of Observational HIV Research Europe (COHERE) in EuroCoord. AIDS. 2016 Dec 21. doi: 10.1097/QAD.0000000000001378. [Epub ahead of print]

**BACKGROUND:** Long-term clinical outcomes after HCV treatment of HIV/HCV patients are not well described. We aimed to compare the risk of all-cause and liver-related death according to HCV treatment response in HIV/HCV patients in the multi-cohort study COHERE.

**METHODS:** All patients who had started PEG-interferon + ribavirin (baseline) and followed for ≥72 weeks after baseline were included. Patients were categorized into three response groups depending on treatment duration and HCV-RNA measured in the window 24-72 weeks after



baseline. Patients who received  $\geq 24$  weeks of therapy were defined as responders if their last HCV-RNA measured between 24-72 weeks after baseline was negative, and having "unknown response" if HCV-RNA was unknown. Non-responders were treated for less than 24 weeks or were HCV-RNA+ between 24-72 weeks after baseline. Mortality rates were compared using survival analysis, and Cox regression used to compare hazard ratios of death between response groups. **RESULTS:** 3,755 patients were included: 1031 (27.5%) responders, 1,639 (43.6%) non-responders and 1085 (28.9%) with unknown response. Rates (per 1,000 PYFU, 95% CI) of all-cause death were 17.59 (14.88-20.78), 10.43 (7.62-14.28) and 11.00 (8.54-14.23) for non-responders, responders and unknown responders, respectively. After adjustment, the relative hazard (non-responders vs. responders) for all-cause death, liver-related death and non-liver-related death was 1.53 (95% CI 1.06-2.22), 3.39 (95% CI 1.32-8.75) and 1.22 (95% CI 0.80-1.84), respectively. **CONCLUSION:** HIV/HCV patients with a favourable virological response to PEG-interferon + ribavirin had reduced risk of all-cause and liver-related death, while there was no difference in risk of non-liver-related death when comparing responders and non-responders.

### **Metabolic and Cardiovascular Complications in HIV/HCV-Co-infected Patients.**

Bedimo R1,2, Abodunde O3,4. *Curr HIV/AIDS Rep.* 2016 Dec;13(6):328-339.

**PURPOSE OF REVIEW:** Fifteen to thirty percent of HIV-infected persons in North America and Europe are co-infected with chronic hepatitis C (HCV). The latter is associated with a significant number of extra-hepatic metabolic complications that could compound HIV-associated increased cardiovascular risk. This article reviews the basic science and epidemiologic and clinical evidence for increased cardio-metabolic risk among HIV/HCV-co-infected patients and discusses potential underlying mechanisms. We will finally review the impact of control of HCV viremia on the cardio-metabolic morbidity and mortality of HIV/HCV-co-infected patients.

**RECENT FINDINGS:** HCV infection is associated with a number of immune-related complications such as cryoglobulinemia but also metabolic complications including dyslipidemias, hepatic steatosis, insulin resistance, diabetes, and chronic kidney disease. The incidence of these complications is higher among HIV-co-infected patients and might contribute to increased mortality. The potential mechanisms of increased cardiovascular risk among HIV/HCV-co-infected subjects include endothelial dysfunction, chronic inflammation and immune activation, the cardio-metabolic effects of HCV-induced hepatic steatosis and fibrosis or insulin resistance, and chronic kidney disease. However, epidemiologic studies show discordant findings as to whether HCV co-infection further increases the risk of atherosclerotic cardiovascular diseases (acute myocardial infarctions and strokes) among HIV-infected patients. Nonetheless, successful treatment of HCV is associated with significant improvements in cardio-metabolic risk factors including diabetes mellitus. HCV co-infection is associated with a higher incidence of metabolic complications-and likely increased risk of cardiovascular events-that might contribute to increased mortality in HIV. These appear to improve with successful HCV therapy.

### **The Role of Current and Historical Alcohol Use in Hepatic Fibrosis Among HIV-Infected Individuals.** Kim HN1, Crane HM2, Rodriguez CV2, et al. *AIDS Behav.* 2016 Dec 29. doi: 10.1007/s10461-016-1665-6. [Epub ahead of print]

We examined risk factors for advanced hepatic fibrosis [fibrosis-4 (FIB)-4  $> 3.25$ ] including both current alcohol use and a diagnosis of alcohol use disorder among HIV-infected patients. Of the

12,849 patients in our study, 2133 (17%) reported current hazardous drinking by AUDIT-C, 2321 (18%) had a diagnosis of alcohol use disorder, 2376 (18%) were co-infected with chronic hepatitis C virus (HCV); 596 (5%) had high FIB-4 scores >3.25 as did 364 (15%) of HIV/HCV coinfecting patients. In multivariable analysis, HCV (adjusted odds ratio (aOR) 6.3, 95% confidence interval (CI) 5.2-7.5), chronic hepatitis B (aOR 2.0, 95% CI 1.5-2.8), diabetes (aOR 2.3, 95% CI 1.8-2.9), current CD4 <200 cells/mm<sup>3</sup> (aOR 5.4, 95% CI 4.2-6.9) and HIV RNA >500 copies/mL (aOR 1.3, 95% CI 1.0-1.6) were significantly associated with advanced fibrosis. A diagnosis of an alcohol use disorder (aOR 1.9, 95% CI 1.6-2.3) rather than report of current hazardous alcohol use was associated with high FIB-4. However, among HIV/HCV coinfecting patients, both current hazardous drinkers (aOR 1.6, 95% CI 1.1-2.4) and current non-drinkers (aOR 1.6, 95% CI 1.2-2.0) were more likely than non-hazardous drinkers to have high FIB-4, with the latter potentially reflecting the impact of sick abstainers. These findings highlight the importance of using a longitudinal measure of alcohol exposure when evaluating the impact of alcohol on liver disease and associated outcomes.

**[The PNPLA3 Genetic Variant rs738409 Influences the Progression to Cirrhosis in HIV/Hepatitis C Virus Coinfected Patients.](#)** Núñez-Torres R<sup>1,2</sup>, Macías J<sup>1,2</sup>, Mancebo M<sup>1,2</sup>, et al. PLoS One. 2016 Dec 14;11(12):e0168265. doi: 10.1371/journal.pone.0168265. eCollection 2016.

Contradictory data about the impact of the rs738409 steatosis-related polymorphism within PNPLA3 gene on liver fibrosis progression in HIV/hepatitis C virus (HIV/HCV)-coinfecting patients have been reported. Our objective was to test whether this, and other polymorphisms previously related to fatty liver disease in HIV infection linked to SAMM50 or LPPR4 genes, influence liver fibrosis progression in HIV/HCV-coinfecting individuals. Three hundred and thirty two HIV/HCV-coinfecting patients who consecutively attended four Spanish university hospitals from November 2011 to July 2013 were included. A liver stiffness cut-off of 14.6 kPa, as determined by transient elastography, was used to diagnose cirrhosis. Liver stiffness progression was studied in 171 individuals who had two available LS determinations without anti-HCV treatment between them. Moreover, 28 HIV/HCV-coinfecting patients who underwent liver transplant, as well as 19 non-cirrhotic coinfecting individuals used as controls, were included in an additional study. Only rs738409 was associated with cirrhosis: 45 (29.6%) of 152 G allele carriers versus 36 (20.0%) of 180 CC carriers showed cirrhosis (multivariate  $p = 0.018$ ; adjusted odds ratio = 1.98; 95% confidence interval = 1.12-3.50). Also, 21 (30.4%) of 69 G allele carriers versus 16 (15.7%) of 102 CC patients showed significant liver stiffness progression (adjusted  $p$ -value = 0.015; adjusted odds ratio = 2.89; 95% confidence interval = 1.23-6.83). Finally, the proportion of rs738409 G allele carriers was significantly higher in transplanted individuals than in controls ( $p = 0.044$ , odds ratio = 3.43; 95% confidence interval = 1.01-11.70). Our results strongly suggest that the rs738409 polymorphism is associated with liver fibrosis progression in HIV/HCV-coinfecting patients.

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#### COMPLEMENTARY AND ALTERNATIVE MEDICINE

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**[Clinical efficacy of Rong-Yang-Jyh-Gan-Tang on Patients with Chronic Hepatitis C: a Double-blinded Randomized Placebo-Controlled Crossover Study.](#)** Chen FP<sup>1</sup>, Chang CM<sup>2</sup>, Wu TP<sup>2</sup>, Yang JL<sup>2</sup>, Kung YY<sup>3</sup>, Huang YH<sup>4</sup>, Su CW<sup>4</sup>, Lan KH<sup>4</sup>, Chiang SC<sup>5</sup>, Hwang SJ<sup>6</sup>. J

Ethnopharmacol. 2016 Dec 10. pii: S0378-8741(16)32323-6. doi: 10.1016/j.jep.2016.12.013. [Epub ahead of print]

**ETHNOPHARMACOLOGICAL RELEVANCE:** Traditional Chinese medicine (TCM) has been widely used by the Chinese population for treatment of chronic hepatitis. However, the efficacy of TCM for patients with chronic hepatitis has not been confirmed, mostly due to the lack of available scientific parameters such as serum viral load to evaluate treatment response. **AIM OF THE STUDY:** We evaluated the efficacy of Rong-Yang-Jyh-Gan-Tang (RYJGT, composed of Long-Dan-Xie-Gan-Tang, Jia-Wei-Xia-Yao-San, Dan-Shen, and Hou-Po) on patients with chronic hepatitis C. **MATERIALS AND METHODS:** Thirty-six patients with chronic hepatitis C who had no response to or had contraindications to interferon-ribavirin therapy were randomly allocated to receive RYJGT 15g/day or placebo for 12 weeks. After a 2-week washout period, patients were crossed over to receive placebo or RYJGT for another 12 weeks. Evaluation parameters included liver biochemistries, serum HCVRNA, side effects of RYJGT/placebo, and TCM symptoms. **RESULTS:** Of the patients who had 12-week RYJGT treatment, 51.7% had decreased serum HCVRNA levels, whereas only 25.8% patients had decreased levels in the placebo group ( $p=0.036$ ). TCM patterns of "Damp-Heat" and "Liver Qi Depression" had significantly improved after RYJGT treatment in comparison with the placebo. Logistic analyses showed that RYJGT treatment, and pre-treatment values of TCM symptoms of "Damp-Heat" and "Liver Qi Depression", were statistically significant factors in predicting the decrease in serum HCVRNA. **CONCLUSION:** Chronic hepatitis C patients who received a 12-week RYJGT treatment had significantly higher HCVRNA decrease ratio, and improved TCM symptoms of "Damp-Heat" and "Liver Qi Depression", than those who received the placebo. Our results require further larger scale clinical trials.

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#### EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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[Long-term disease and economic outcomes of prior authorization criteria for Hepatitis C treatment in Pennsylvania Medicaid.](#) Kabiri M1, Chhatwal J2, Donohue JM3, Roberts MS1, James AE4, Dunn MA5, Gellad WF6. *Healthc (Amst)*. 2016 Dec 5. pii: S2213-0764(16)30214-7. doi: 10.1016/j.hjdsi.2016.11.001. [Epub ahead of print]

**BACKGROUND:** Several highly effective but costly therapies for hepatitis C virus (HCV) are available. As a consequence of their high price, 36 state Medicaid programs limited treatment coverage to patients with more advanced HCV stages. States have only limited information available to predict the long-term impact of these decisions. **METHODS:** We adapted a validated hepatitis C microsimulation model to the Pennsylvania Medicaid population to estimate the existing HCV prevalence in Pennsylvania Medicaid and estimate the impact of various HCV drug coverage policies on disease outcomes and costs. Outcome measures included rates of advanced-stage HCV outcomes and treatment and disease costs in both Medicaid and Medicare. **RESULTS:** We estimated that 46,700 individuals in Pennsylvania Medicaid were infected with HCV in 2015, 33% of whom were still undiagnosed. By expanding treatment to include mild fibrosis stage (Metavir F2), Pennsylvania Medicaid will spend an additional \$273 million on medications in the next decade with no substantial reduction in the incidence of liver cancer or liver-related death. Medicaid patients who are not eligible for treatment under restricted policies would get treatment once they transition to the Medicare program, which would incur 10% reduction in HCV-related costs due to early treatment in Medicaid. Further expanding treatment to patients with early fibrosis stages (F0 or F1) would cost Medicaid an



additional \$693 million during the next decade but would reduce the number of individuals in need of treatment in Medicare by 46% and decrease Medicare treatment costs by 23%. In some scenarios, outcomes could worsen with eligibility expansion if there is inadequate capacity to treat all patients. **CONCLUSIONS AND RELEVANCE:** Expansion of HCV treatment coverage to less severe stages of liver disease may not substantially improve liver related outcomes for patients in Pennsylvania Medicaid in scenarios in which coverage through Medicare is widely available.

[Racial-Ethnic Disparities in Uptake of New Hepatitis C Drugs in Medicare.](#) Jung J1, Feldman R2. J Racial Ethn Health Disparities. 2016 Dec 7. [Epub ahead of print]

**BACKGROUND:** Chronic hepatitis C is an important public health concern. Recently launched drugs to treat hepatitis C virus (HCV) infection are effective but costly. Uptake of innovative and expensive prescription drugs may not be even across patient groups. We examined racial-ethnic disparities in uptake of new HCV drugs in the first year of their use (year 2014) in Medicare.

**METHODS:** The study population was Medicare beneficiaries who had chronic hepatitis C in 2013 or 2014 and who were continuously enrolled in Part D stand-alone Prescription Drug Plans in 2014. We examined trends in monthly uptake of new HCV drugs and adjusted annual uptake rates by race. We used logistic regressions to obtain adjusted odds ratios and adjusted differences in annual uptake rates.

**RESULTS:** Monthly uptake of new HCV drugs was lower among Black Medicare patients than Whites or Hispanics in 2014. The racial gap in monthly uptake became narrower toward the end of the year. Adjusted odds of using new HCV drugs were 11% lower for Blacks with cirrhosis than Whites (odds ratio (OR) = 0.89; 95% confidence interval (CI), 0.84-0.95), and 16% lower for Blacks with HCV/HIV coinfection than Whites (OR = 0.81; 95% CI, 0.72-0.92). Annual uptake rates were not significantly different for Whites and Hispanics.

**CONCLUSIONS:** Black Medicare patients with cirrhosis or HCV/HIV coinfection had lower uptake rates than Whites in 2014. As utilization of new HCV drugs increases, continuing efforts will be necessary to ensure equal delivery of the drugs.

[From Care to Cure: Demonstrating a Model of Clinical Patient Navigation for Hepatitis C Care and Treatment in High-Need Patients.](#) Ford MM1, Johnson N2, Desai P2, Rude E2, Laraque F2. Clin Infect Dis. 2016 Dec 10. pii: ciw806. [Epub ahead of print]

The NYC Department of Health implemented a patient navigation program, Check Hep C, to address patient and provider barriers to HCV care and potentially lifesaving treatment. Services were delivered at two clinical care sites and two sites that linked patients to off-site care.

Working with a multidisciplinary care team, patient navigators provided risk assessment, health education, treatment readiness and medication adherence counseling, and medication coordination. Between March 2014 and January 2015, 388 participants enrolled in Check Hep C, 129 (33%) initiated treatment, and 119 (91% of initiators) had sustained virologic response (SVR). Participants receiving on-site clinical care had higher odds of initiating treatment than those linked to off-site care. Check Hep C successfully supported high-need participants through HCV care and treatment, and SVR rates demonstrate the real-world ability of achieving high cure rates using patient navigation care models.

[Correlates of Hepatitis C Virus Infection in the Targeted Testing Program of the New York City Jail System.](#) Akiyama MJ1, Kaba F2, Rosner Z2, Alper H3, Kopolow A2, Litwin AH1,

Venters H2, MacDonald R2. Public Health Rep. 2017 Jan/Feb;132(1):41-47. doi: 10.1177/0033354916679367. Epub 2016 Dec 14.

**OBJECTIVE:** The objective of this study was to understand predictors of hepatitis C virus (HCV) antibody positivity in a large urban jail system in New York City. **METHODS:** We examined demographic characteristics, risk behaviors, and HCV antibody prevalence among 10 790 jail inmates aged 16 to 86 who were screened from June 13, 2013, to June 13, 2014, based on birth cohort or conventional high-risk criteria. We used logistic regression analysis to determine predictors of HCV antibody positivity. **RESULTS:** Of the 10 790 inmates screened, 2221 (20.6%) were HCV antibody positive. In the multivariate analysis, HCV antibody positivity was associated most strongly with injection drug use (IDU; adjusted odds ratio [aOR] = 35.0; 95% confidence interval [CI], 28.5-43.0). Women were more likely than men to be infected with HCV (aOR = 1.3; 95% CI, 1.1-1.5). Compared with non-Hispanic black people, Hispanic (aOR = 2.1; 95% CI, 1.8-2.4) and non-Hispanic white (aOR = 1.7; 95% CI, 1.5-2.1) people were more likely to be infected with HCV. Non-IDU, recidivism, HIV infection, homelessness, mental illness, and lower education level were all significantly associated with HCV infection. The prevalence rate of HCV infection among a subset of inmates born after 1965 who denied IDU and were not infected with HIV was 5.6% (198 of 3529). Predictors of HCV infection among this group included non-IDU as well as being non-Hispanic white, Hispanic, recidivist, and homeless. **CONCLUSION:** These data reveal differences in HCV infection by sex, race/ethnicity, and socioeconomics in a large jail population, suggesting that a focused public health intervention is required and that universal screening may be warranted. Further sensitivity and cost-benefit analyses are needed to make this determination.

[Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents.](#) Tsui JI1, Williams EC2, Green PK3, Berry K3, Su F4, Ioannou GN5. Drug Alcohol Depend. 2016 Dec 1;169:101-109. doi: 10.1016/j.drugalcdep.2016.10.021. Epub 2016 Oct 22.

**BACKGROUND:** It is unclear whether alcohol use negatively impacts HCV treatment outcomes in the era of direct antiviral agents (DAAs). We aimed to evaluate the associations between current levels of drinking and treatment response among persons treated for HCV with DAAs in the national Veterans Affairs (VA) healthcare system. **METHODS:** We identified patients who initiated HCV DAAs over 18 months (1/1/14-6/30/15) and had documented alcohol screening with the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questionnaire within one year prior to initiating therapy. DAAs included: sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF) or ombitasvir-paritaprevir-ritonavir, and dasabuvir (PrOD). AUDIT-C scores were categorized as 0 (abstinence), 1-3 (low-level drinking) and 4-12 (unhealthy drinking) in men or 0, 1-2 and 3-12 in women. **RESULTS:** Among 17,487 patients who initiated DAAs, 15,151 (87%) completed AUDIT-C screening: 10,387 (68.5%) were categorized as abstinent, 3422 (22.6%) as low-level drinking and 1342 (8.9%) as unhealthy drinking. There were no significant differences in sustained virologic response (SVR) rates between abstinent (SVR 91%; 95% CI: 91-92%), low-level drinking (SVR 93%; 95% CI 92-94%) or unhealthy drinking (SVR 91%; 95% 89-92) categories in univariable analysis or in multivariable logistic regression models. However, after imputing missing SVR data, unhealthy drinkers were less likely to achieve SVR in multivariable analysis (AOR 0.75, 95% CI 0.60-0.92). **CONCLUSION:** Absolute SVR rates were uniformly high among all persons regardless

of alcohol use, with only minor differences in those who report unhealthy drinking, which supports clinical guidelines that do not recommend excluding persons with alcohol use.

### **Drug-Drug Interactions Between Direct-Acting Antivirals and Psychoactive Medications.**

Smolders EJ1, de Kanter CT2, de Knegt RJ3, van der Valk M4, Drenth JP5, Burger DM6. Clin Pharmacokinet. 2016 Dec;55(12):1471-1494.

Treatment options for chronic hepatitis C virus (HCV) infection have drastically changed since the development and licensing of new potent direct-acting antivirals (DAAs). The majority of DAAs are extensively metabolized by liver enzymes and have the ability to influence cytochrome P450 (CYP) enzymes. Additionally, these DAAs are both substrates and inhibitors of drug transporters, which makes the DAAs both possible victims or perpetrators of drug-drug interactions (DDIs). There is a high prevalence of mental illnesses such as depression or psychosis in HCV-infected patients; therefore, psychoactive medications are frequently co-administered with DAAs. The majority of these psychoactive medications are also metabolized by CYP enzymes but remarkably little information is available on DDIs between psychoactive medications and DAAs. Hence, the aim of this review is to provide an overview of the interaction mechanisms between DAAs and psychoactive agents. In addition, we describe evidenced-based interactions between DAAs and psychoactive drugs and identify safe options for the simultaneous treatment of mental illnesses and chronic HCV infection.

### **Vital Signs: Trends in HIV Diagnoses, Risk Behaviors, and Prevention Among Persons Who Inject Drugs - United States.**

Wejnert C1, Hess KL1, Hall HI1, Van Handel M1, Hayes D1, Fulton P Jr1, An Q1, Koenig LJ1, Prejean J1, Valleroy LA1. MMWR Morb Mortal Wkly Rep. 2016 Dec 2;65(47):1336-1342. doi: 10.15585/mmwr.mm6547e1.

**BACKGROUND:** Persons who inject drugs (PWID) are at increased risk for poor health outcomes and bloodborne infections, including human immunodeficiency virus (HIV), hepatitis C virus and hepatitis B virus infections. Although substantial progress has been made in reducing HIV infections among PWID, recent changes in drug use could challenge this success.

**METHODS:** CDC used National HIV Surveillance System data to analyze trends in HIV diagnoses. Further, National HIV Behavioral Surveillance interviews of PWID in 22 cities were analyzed to describe risk behaviors and use of prevention services among all PWID and among PWID who first injected drugs during the 5 years before their interview (new PWID).

**RESULTS:** During 2008-2014, HIV diagnoses among PWID declined in urban and nonurban areas, but have leveled off in recent years. Among PWID in 22 cities, during 2005-2015, syringe sharing decreased by 34% among blacks/African Americans (blacks) and by 12% among Hispanics/Latinos (Hispanics), but remained unchanged among whites. The racial composition of new PWID changed during 2005-2015: the percentage who were black decreased from 38% to 19%, the percentage who were white increased from 38% to 54%, and the percentage who were Hispanic remained stable. Among new PWID interviewed in 2015, whites engaged in riskier injection behaviors than blacks. **CONCLUSIONS:** Decreases in HIV diagnoses among PWID indicate success in HIV prevention. However, emerging behavioral and demographic trends could reverse this success. **IMPLICATIONS FOR PUBLIC HEALTH PRACTICE:** Access to comprehensive prevention services is essential for all PWID. Syringe services programs reduce syringe sharing and can help PWID access prevention and treatment services for HIV and other bloodborne diseases, such as hepatitis C and hepatitis B.

**Racial Differences in HIV and HCV Risk Behaviors, Transmission, and Prevention Knowledge among Non-Treatment-Seeking Individuals with Opioid Use Disorder.**

Metz VE1, Sullivan MA2, Jones JD3, Evans E4, Luba R5, Vogelman J5, Comer SD5. J Psychoactive Drugs. 2016 Dec 5:1-10. [Epub ahead of print]

In light of New York's recently reinforced strategy to end the AIDS epidemic by expanding testing, treatment, and access to pre-exposure prophylaxis (PrEP), we assessed drug use and sexual risk behaviors, along with HIV/Hepatitis C virus (HCV) transmission and prevention knowledge among non-treatment-seeking adults with opioid use disorder (OUD) in New York City. Over the course of 18 months, volunteers screening for research studies in the Opioid Laboratory at the New York State Psychiatric Institute completed a locally developed self-assessment questionnaire. A total of 138 adults with OUD (24 female, 114 male) with a mean age of 46.5 years (SD = 9.5 yrs) were assessed. Significant differences among the four racial/ethnic subgroups (n = 65 African-Americans, n = 34 Hispanics, n = 31 Caucasians or Whites, n = 8 Multiracial) were found. Whites were the youngest (p = 0.001), most frequently injecting drugs (p < 0.001), and engaged more often in risky drug use and sexual behaviors, although their virus transmission knowledge was comparable to that of the other subgroups. Few participants had heard about PrEP. White opioid users showed the most risk behaviors among races/ethnicities, despite comparable prevention knowledge. Better HIV/HCV prevention interventions targeting individuals with opioid use disorders who are not currently in treatment would be desirable, given their large health burden.

**A systematic model improves hepatitis C virus birth cohort screening in hospital-based primary care.**

Goel A1, Sanchez J1, Paulino L1, Feuille C2, Arend J2, Shah B3, Dieterich D1, Perumalswami PV1. J Viral Hepat. 2016 Dec 31. doi: 10.1111/jvh.12669. [Epub ahead of print]

Despite national and local governing board recommendations in the United States of America to perform an HCV screening test in baby boomers, screening rates remain low. Our goal was to study the impact of an HCV screening and link to care program with patient navigation in two New York City primary care practices. This was a two-year prospective study of patients born between 1945-1965 ("baby boomers") with encounters at two primary care practices at the Mount Sinai Hospital between November 1, 2013 and November 30, 2015. Baseline HCV screening rates were collected for four months. A multifaceted intervention was sequentially implemented involving electronic alerts, housestaff education, data feedback and patient navigation. HCV screening rates and link to care, defined as attending an appointment with a viral hepatitis specialist, were compared before and after these interventions. There were 14,642 primary care baby boomer patients of which 4,419 (30.2%) were newly screened during the study. There was a significant increase in HCV screening rates from 55% to 75% (p<0.01) and the HCV seropositive rate was 3.3%. Factors associated with being HCV seropositive included older age (p<0.01), male sex (p<0.01), African American race (p<0.01) and receiving care in the housestaff practice (p<0.01). With patient navigation, 78 of 84 (93%) newly diagnosed HCV infected persons were referred to a specialist and 60 (77%) attended their first appointment. A structured, multifaceted HCV screening program using well-studied principles identifies a large number of undiagnosed baby boomers within hospital-based primary care and improves access to specialty providers in a timely manner. This article is protected by copyright. All rights reserved.

**Awareness of Hepatitis C Virus Seropositivity and Chronic Infection in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).**

Kuniholm MH1, Jung M2, Del

Amo J3, Talavera GA4, Thyagarajan B5, Hershow RC6, Damas OM7, Kaplan RC2. *J Immigr Minor Health*. 2016 Dec;18(6):1257-1265.

Few population-based studies have assessed awareness of hepatitis C virus (HCV) seropositivity and chronic infection. We report awareness of HCV seropositivity and chronic infection and correlates of awareness in a multi-city (Bronx, Miami, Chicago, and San Diego) community-dwelling population sample of United States (US) Hispanics/Latinos recruited during 2008-2011. Included were 260 HCV-seropositive participants, among whom 190 had chronic HCV. Among those with chronic HCV, 46 % had been told by a doctor that they had liver disease and 32 % had been told that they had HCV-related liver disease. Among those with chronic HCV who also lacked health insurance (37 % of those with chronic HCV), only 8 % had been told that they had HCV-related liver disease. As compared with the uninsured, those with insurance were over five times more likely to be aware of having HCV-related liver disease (44 %). Sex, age, education, city of residence, and birthplace were not associated with HCV awareness. Less than half of Hispanics/Latinos were aware of their HCV chronic infection. Lack of health insurance may be an important barrier to HCV awareness in this population.

**Real-World Drug Costs of Treating Hepatitis C Genotypes 1-4 with Direct-Acting Antivirals: Initiating Treatment at Fibrosis 0-2 and 3-4.** Bach TA1, Zaiken K1. *J Manag Care Spec Pharm*. 2016 Dec;22(12):1437-1445.

**BACKGROUND:** Direct-acting antivirals (DAA) for the treatment of hepatitis C virus (HCV) have drastically improved outcomes but are also very costly. For this reason, priority for treatment is often given to patients with a higher fibrosis score at baseline by payers and providers rather than treating all eligible patients. Simulation studies have suggested that waiting to treat patients until fibrosis 3-4 may be more costly and result in worse outcomes; however, real-world implications are unknown. **OBJECTIVE:** To determine drug costs and outcomes for treating hepatitis C in patients with fibrosis scores of 0-2 and 3-4 at baseline in a real-world ambulatory care setting. **METHODS:** A total of 322 patients at 36 clinical sites in Massachusetts with HCV genotype 1-4 and a prescription for at least 1 DAA medication between May 2011 and October 2015 were included. Retrospective and prospective chart reviews were completed by the primary investigator. Data were collected through April 2016. The primary outcome for the study was to determine the mean drug cost per sustained virologic response (SVR) achieved for patients with fibrosis scores of 0-2 and 3-4. Drug costs were calculated using average wholesale price and only included the cost of HCV medications, not for adjunctive medications, blood work, hospitalizations, anticipated complications, or any other projected medical costs. **RESULTS:** The mean  $\pm$  SD (median) drug cost per patient was \$130,391  $\pm$  46,787 (113,400) and completed treatment duration was 15.0  $\pm$  8.9 (12) weeks. The mean drug cost per SVR was \$155,662 for all patients with a mean drug cost per SVR of \$122,452 and \$178,401 for patients with fibrosis scores of 0-2 and 3-4, respectively. SVR rates were 83.5% (269/322) for all patients and 92.2% (107/116) and 78.6% (162/206) for patients with fibrosis scores of 0-2 and 3-4, respectively. Ledipasvir/ sofosbuvir; sofosbuvir + ribavirin; ledipasvir/sofosbuvir + ribavirin; sofosbuvir + interferon + ribavirin; boceprevir + interferon + ribavirin; sofosbuvir + simeprevir; and telaprevir + interferon + ribavirin had a mean drug cost per SVR of \$123,559; \$153,347; \$157,969; \$184,800; \$248,640; \$251,550; and \$373,333; respectively. **CONCLUSIONS:** Real-world knowledge about outcomes and drug costs may influence future decisions. Further studies are needed to evaluate emerging treatment options and to reflect changes in treatment guidelines.



**DISCLOSURES:** No outside funding supported this study. The authors report no conflicts of interest. Data in this study were presented as a poster at the ASHP Midyear Clinical Meeting; New Orleans, Louisiana; December 9, 2015; at the Massachusetts Society of Health-System Pharmacists Annual Meeting; Newton, Massachusetts; April 12, 2016; and at Eastern States Conference for Pharmacy Residents and Preceptors; Hershey, Pennsylvania; May 2, 2016. Study concept and design was primarily contributed by Bach, along with Zaiken. Bach took the lead in data collection, data interpretation, and preparation of the manuscript, along with Zaiken.

**[Racial disparity in all-cause mortality among hepatitis C virus-infected individuals in a general US population, NHANES III.](#)** Emmanuel B1, Shardell MD2, Tracy L3,4, Kottlilil S1, El-Kamary SS3. *J Viral Hepat.* 2016 Dec 1. doi: 10.1111/jvh.12656. [Epub ahead of print]

There are few long-term nationally representative studies of all-cause mortality among those infected with hepatitis C virus (HCV). When an additional 5 years of data were made publicly available in 2015, the Third National Health and Nutrition Examination Survey Linked Mortality File became the longest nationally representative study in the United States. Our objective was to update the estimated HCV-associated all-cause mortality in the general US population and determine any differences by sex, age and race/ethnicity. HCV status was assessed in 9117 nationally representative adults aged 18-59 years from 1988 to 1994, and mortality follow-up of the same individuals was completed through 2011 and made publicly available in 2015. There were 930 deaths over a median follow-up of 19.8 years. After adjusting for all covariate risk factors, chronic HCV had 2.63 times (95% CI: 1.59-4.37; P=.0002) higher all-cause mortality rate ratio (MRR) compared with being HCV negative. All-cause MRR was stratified by sex, age and race/ethnicity. Only race/ethnicity was a significant effect modifier of MRR (P<.0001) as the highest MRR of chronic HCV compared to HCV negative was 7.48 (95% CI: 2.15-26.10, P=.001) among Mexican Americans, 2.67 (95% CI: 2.67-5.56, P=.009) among non-Hispanic Whites and 2.02 (95% CI: 1.20-3.40, P=.007) among non-Hispanic Blacks. Racial disparity was seen in the all-cause mortality as Mexican Americans with chronic HCV had approximately seven times higher mortality rate than HCV-negative individuals. This suggests that these at-risk individuals should be targeted for HCV screening and treatment, given the availability of new highly effective HCV therapies.

**[The Safety and Effectiveness of Ledipasvir-Sofosbuvir in Adolescents 12 to 17 Years Old With Hepatitis C Virus Genotype 1 Infection.](#)** Balistreri WF1, Murray KF2, Rosenthal P3, et al. *Hepatology.* 2016 Dec 20. doi: 10.1002/hep.28995. [Epub ahead of print]

No all-oral, direct-acting antiviral regimens have been approved for children with chronic hepatitis C virus (HCV) infection. We conducted a Phase 2, multi-center, open-label study to evaluate the efficacy and safety of ledipasvir-sofosbuvir in adolescents with chronic HCV genotype 1 infection. One hundred patients ages 12 to 17 years received a combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 weeks. On the 10th day following initiation of dosing, 10 patients underwent an intensive pharmacokinetic evaluation of the concentrations of sofosbuvir, ledipasvir, and the sofosbuvir metabolite GS-331007. The primary efficacy endpoint was the percentage of patients with a sustained virologic response 12 weeks posttreatment (SVR12). Median age of patients was 15 years (range, 12-17 years). A majority (80%) were HCV treatment naïve, and 84% were infected through perinatal transmission. One patient had cirrhosis and 42 did not; in 57 patients the degree of fibrosis was unknown. Overall, 98% (98/100; 95% CI, 93% to 100%) of patients reached SVR12. No patient had virologic

failure. The 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment. The 3 most commonly reported adverse events were headache (27% of patients), diarrhea (14%), and fatigue (13%). No serious adverse events were reported. AUC<sub>tau</sub> and C<sub>max</sub> values for sofosbuvir, ledipasvir, and GS-331007 were within the predefined pharmacokinetic equivalence boundaries of 50% to 200% when compared with adults from Phase 2 and 3 studies of ledipasvir and sofosbuvir.

[Telemedicine specialty support promotes hepatitis c treatment by primary care providers in the Department of Veterans Affairs.](#) Beste LA1, Glorioso TJ2, Ho PM3, et al. Am J Med. 2016 Dec 17. pii: S0002-9343(16)31227-X. doi: 10.1016/j.amjmed.2016.11.019. [Epub ahead of print]

**BACKGROUND & AIMS:** The Department of Veterans Affairs (VA) is the largest US provider of hepatitis c treatment. Although antiviral regimens are becoming simpler, hepatitis c antivirals are not typically prescribed by primary care providers (PCPs). The VA-Extension for Community Health Outcomes (VA-ECHO) program was launched to promote primary care-based hepatitis C treatment using videoconferencing-based specialist support. We aimed to assess whether PCP participation in VA-ECHO was associated with hepatitis C treatment and sustained virologic response. **METHODS:** We identified 4,173 PCPs (n=152 sites) responsible for 38,753 patients with chronic hepatitis C infection. 6,431 patients had a PCP participating in VA-ECHO; 32,322 patients had an unexposed PCP. Exposure was modeled as a patient-level time-varying covariate. Patients became exposed after PCP participation in >1 VA-ECHO session. Multivariable Cox proportional hazards frailty modeling assessed the association between VA-ECHO exposure and hepatitis C treatment. Among treated patients, modified Poisson regression assessed the relationship between exposure and sustained virologic response. **RESULTS:** After adjustment, exposed patients received significantly higher rates of antiviral treatment compared to unexposed (AHR 1.20 [95% CI 1.10, 1.32], P < 0.01). The rate of PCP-initiated antiviral medication was 21.4% among treated patients reviewed on VA-ECHO teleconferences, compared to 2.5% in unexposed (p<.01). No difference in adjusted rates of sustained virologic response was observed for patients with exposed PCPs (p=0.32), with similar crude rates for PCPs versus specialists. **CONCLUSIONS:** National implementation of VA-ECHO was positively associated with hepatitis C treatment initiation by PCPs, without differences in sustained virologic response.

[Determinants of Treatment Eligibility in Veterans With Hepatitis C Viral Infection.](#) Taylor J1, Carr-Lopez S2, Robinson A3, Malmstrom R4, Duncan K5, Maniar A6, Re AC7, Carmichael JM8. Clin Ther. 2016 Dec 15. pii: S0149-2918(16)30857-8. doi: 10.1016/j.clinthera.2016.11.019. [Epub ahead of print]

**PURPOSES:** The objective of this study was to determine the percentage of veterans with active hepatitis C virus (HCV) infection who were deemed to be candidates for treatment and to identify factors associated with treatment ineligibility. **METHODS:** This was a multisite, retrospective cohort analysis of veterans with HCV infection within the Veteran Integrated Service Network 21. Patients evaluated between August and November 2015 who were viremic and not receiving HCV treatment were included in the analysis. Reasons for treatment exclusion were determined by an experienced clinician and recorded into a regional population management dashboard. Descriptive statistics were used to describe the population. The t test for normally distributed data, the Mann-Whitney rank sum test for data that failed normality testing,

or the  $\chi^2$  test were used to examine differences between the treatment eligible and ineligible cohorts. Generalized linear mixed-effects models were conducted to estimate patient outcomes relevant to various disease states and characteristics while controlling for interfacility variability. **FINDINGS:** The cohort included 1,003 veterans within 5 medical centers; 988 (98.5%) were male, and 625 (62%) had a fibrosis 4 score  $>3.25$ , indicating the presence of ALD. According to clinician classification, 478 (48%) were considered HCV treatment candidates, whereas 525 (52%) were determined to be treatment ineligible. The most common reasons documented by clinicians for treatment ineligibility included unstable or uncontrolled comorbidities ( $n = 118$  [22.4%]), excessive alcohol use ( $n = 116$  [22.1%]), and treatment refusal by the patient ( $n = 69$  [13%]). On the basis of statistical modeling and reporting odds ratios (ORs) and 95% CIs, diagnoses of active alcohol use disorder (OR = 0.68; 95% CI, 0.47-0.98;  $P = 0.038$ ), hepatocellular carcinoma (OR = 0.24; 95% CI, 0.13-0.47;  $P < 0.001$ ), and palliative care status (OR = 0.21; 95% CI, 0.05-0.99;  $P = 0.049$ ) were statistically associated with treatment ineligibility, whereas posttraumatic stress disorder (OR = 1.48; 95% CI, 1.01-2.18;  $P = 0.046$ ) was associated with treatment eligibility. There were no statistically significant differences found for other psychiatric diagnoses or an encounter for homelessness. **IMPLICATIONS:** Results of this study indicate that a high percentage of patients may not be considered treatment eligible at initial clinical review. Within this veteran population, the presence of uncontrolled comorbidities and excessive alcohol use were the most commonly reported reasons for treatment ineligibility. On the basis of this analysis, processes could be established to address modifiable barriers to treatment, thus expanding the number of individuals receiving potentially curative therapy for HCV infection.

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## HEPATOCELLULAR (LIVER) CANCER

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[Single-Nucleotide Resolution Mapping of Hepatitis B Virus Promoters in Infected Human Livers and Hepatocellular Carcinoma.](#) Altinel K1, Hashimoto K2, Wei Y3, et al. J Virol. 2016 Nov 14;90(23):10811-10822. Print 2016 Dec 1.

Hepatitis B virus (HBV) is a major cause of liver diseases, including hepatocellular carcinoma (HCC), and more than 650,000 people die annually due to HBV-associated liver failure. Extensive studies of individual promoters have revealed that heterogeneous RNA 5' ends contribute to the complexity of HBV transcriptome and proteome. Here, we provide a comprehensive map of HBV transcription start sites (TSSs) in human liver, HCC, and blood, as well as several experimental replication systems, at a single-nucleotide resolution. Using CAGE (cap analysis of gene expression) analysis of 16 HCC/nontumor liver pairs, we identify 17 robust TSSs, including a novel promoter for the X gene located in the middle of the gene body, which potentially produces a shorter X protein translated from the conserved second start codon, and two minor antisense transcripts that might represent viral noncoding RNAs. Interestingly, transcription profiles were similar in HCC and nontumor livers, although quantitative analysis revealed highly variable patterns of TSS usage among clinical samples, reflecting precise regulation of HBV transcription initiation at each promoter. Unlike the variety of TSSs found in liver and HCC, the vast majority of transcripts detected in HBV-positive blood samples are pregenomic RNA, most likely generated and released from liver. Our quantitative TSS mapping using the CAGE technology will allow better understanding of HBV transcriptional responses in further studies aimed at eradicating HBV in chronic carriers. **IMPORTANCE:** Despite the availability of a safe and effective vaccine, HBV infection remains a global health problem, and

current antiviral protocols are not able to eliminate the virus in chronic carriers. Previous studies of the regulation of HBV transcription have described four major promoters and two enhancers, but little is known about their activity in human livers and HCC. We deeply sequenced the HBV RNA 5' ends in clinical human samples and experimental models by using a new, sensitive and quantitative method termed cap analysis of gene expression (CAGE). Our data provide the first comprehensive map of global TSS distribution over the entire HBV genome in the human liver, validating already known promoters and identifying novel locations. Better knowledge of HBV transcriptional activity in the clinical setting has critical implications in the evaluation of therapeutic approaches that target HBV replication.

### [Genetics Variants and Serum Levels of MHC Class I Chain-related A in Predicting Hepatocellular Carcinoma Development in Chronic Hepatitis C Patients Post Antiviral Treatment.](#)

Huang CF1, Huang CY2, Yeh ML3, et al. EBioMedicine. 2016 Dec 1. pii: S2352-3964(16)30549-7. doi: 10.1016/j.ebiom.2016.11.031. [Epub ahead of print]

**BACKGROUND/AIMS:** The genome-wide association study has shown that MHC class I chain-related A (MICA) genetic variants were associated with hepatitis C virus (HCC) related hepatocellular carcinoma. The impact of the genetic variants and its serum levels on post-treatment cohort is elusive. **METHODS:** MICA rs2596542 genotype and serum MICA (sMICA) levels were evaluated in 705 patients receiving antiviral therapy. **RESULTS:** Fifty-eight (8.2%) patients developed HCC, with a median follow-up period of 48.2 months (range: 6-129 months). The MICA A allele was associated with a significantly increased risk of HCC development in cirrhotic non-SVR patients but not in patients of non-cirrhotic and/or with SVR. For cirrhotic non-SVR patients, high sMICA levels (HR/CI: 5.93/1.86-26.38.61, P=0.002) and the MICA rs2596542 A allele (HR/CI: 4.37/1.52-12.07, P=0.002) were independently associated with HCC development. The risk A allele or GG genotype with sMICA >175 ng/mL provided the best accuracy (79%) and a negative predictive value of 100% in predicting HCC. **CONCLUSIONS:** Cirrhotic patients who carry MICA risk alleles and those without risk alleles but with high sMICA levels possessed the highest risk of HCC development once they failed antiviral therapy.

### [Cost-Effectiveness of Direct-Acting Anti-viral Treatment in Hepatitis C-infected Liver Transplant Candidates with Compensated Cirrhosis and Hepatocellular Carcinoma.](#)

Salazar J1, Saxena V, Kahn JG, Roberts JP, Mehta N, Volk M, Lai JC. Transplantation. 2016 Dec 6. [Epub ahead of print]

**BACKGROUND:** HCV(+) donors represent an effective strategy to increase liver donor availability to HCV-infected recipients. However, many HCV(+) transplant candidates are now receiving treatment with direct acting anti-virals (DAA) that lower the risk of posttransplant HCV recurrence but could make the patient ineligible for HCV(+) livers. **METHODS:** We compared pretransplant DAA treatment versus deferred DAA treatment using a cost-effectiveness decision analysis model to estimate incremental cost-effectiveness ratios (ICERs; cost per quality-adjusted life year [QALY] gained) from the societal perspective across a range of HCV(+) liver availability rates. For practical considerations, the population modelled was restricted to well-compensated HCV(+) cirrhotics listed for liver transplantation with HCC MELD exception points. **RESULTS:** Under base case conditions, the deferred DAA treatment strategy was found to be the "dominant" strategy. That is, it provided superior health outcomes at cost savings compared to the pretransplant DAA treatment strategy. The pretransplant DAA treatment strategy trended towards cost-effectiveness as HCV(+) donor liver availability

declined. However, only in 1 scenario that was highly optimized for favorable outcomes in the pretransplant DAA treatment arm (low availability of HCV(+) organs, low cost of DAA treatment, high cost of HCV recurrence) was the ICER associated with HCV DAA treatment before transplant <\$150,000/QALY gained. **CONCLUSIONS:** Deferring HCV treatment until after liver transplant and maintaining access to the expanded pool of HCV(+) donors appears to be the most cost-effective strategy for well-compensated HCV-infected cirrhotics listed for liver transplantation with HCC, even in geographic areas of relatively low HCV(+) donor availability.

**[Hepatocellular carcinoma as an emerging morbidity in the thalassemia syndromes: A comprehensive review.](#)** Moukhadder HM1, Halawi R2, Cappellini MD3,4, Taher AT1. *Cancer*. 2016 Dec 1. doi: 10.1002/cncr.30462. [Epub ahead of print]

The incidence of hepatocellular carcinoma (HCC) in patients with thalassemia is on the rise. The 2 well recognized HCC risk factors in thalassemia are iron overload and chronic viral infection with hepatitis C. The carcinogenicity of iron is related to its induction of oxidative damage, which results in genotoxicity, and to immunologic dysregulation, which attenuates cancer immune surveillance. Chronic hepatitis B and C infections lead to necroinflammation, which can prompt progression to HCC, but an independent role of hepatitis B virus in hepatic carcinogenesis among patients with thalassemia has not been demonstrated. Screening patients who have thalassemia using magnetic resonance imaging-based liver iron concentration measurement and liver ultrasound is recommended for early detection of iron overload and HCC, respectively. Prevention primarily resides in hepatitis B vaccination, donor blood screening, hepatitis treatment, and iron chelation. Although solid data is lacking on the outcomes of HCC treatment in patients with thalassemia, a personalized approach tailored to the individual patient's comorbidities remains necessary for treatment success. Treatment modalities for HCC include surgical resection, chemoembolization, and liver transplantation, among others. Multicenter studies are needed to better explore therapeutic targets that can improve the prognosis of these patients. *Cancer* 2016. © 2016 American Cancer Society.  
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**[Action and function of Wnt/ \$\beta\$ -catenin signaling in the progression from chronic hepatitis C to hepatocellular carcinoma.](#)** Wang W1, Pan Q2, Fuhler GM2, Smits R2, Peppelenbosch MP2. *J Gastroenterol*. 2016 Dec 29. doi: 10.1007/s00535-016-1299-5. [Epub ahead of print]

Hepatitis C virus (HCV) infection is one of the leading causes of hepatocellular carcinoma (HCC) worldwide but the mechanistic basis as to how chronic HCV infection furthers the HCC process remains only poorly understood. Accumulating evidence indicates that HCV core and nonstructural proteins provoke activation of the Wnt/ $\beta$ -catenin signaling pathway, and the evidence supporting a role of Wnt/ $\beta$ -catenin signaling in the onset and progression of HCC is compelling. Convincing molecular explanations as to how expression of viral effectors translates into increased activity of the Wnt/ $\beta$ -catenin signaling machinery are still largely lacking, hampering the design of rational strategies aimed at preventing HCC. Furthermore, how such increased signaling is especially associated with HCC oncogenesis in the context of HCV infection remains obscure as well. Here we review the body of contemporary biomedical knowledge on the role of the Wnt/ $\beta$ -catenin pathway in the progression from chronic hepatitis C to cirrhosis and HCC and explore potential hypotheses as to the mechanisms involved.  
PMID: 28035485 [PubMed - as supplied by publisher]



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[Hepatocellular Carcinoma is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States.](#) Yang JD1, Larson JJ2, Watt KD1, Allen AM1, Wiesner RH1, Gores GJ1, Roberts LR1, Heimbach JA3, Leise MD4. Clin Gastroenterol Hepatol. 2016 Dec 21. pii: S1542-3565(16)31226-5. doi: 10.1016/j.cgh.2016.11.034. [Epub ahead of print]

**BACKGROUND & AIMS:** Management strategies for patients with hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC) have changed, along with liver allocation policies based on model for end-stage liver disease (MELD) score. We investigated etiologic-specific trends in liver transplantation in the United States (US) during different time periods.

**METHODS:** We performed a retrospective study, using the United Network for Organ Sharing/Organ Procurement and Transplantation Network registry data to identify all adult patients registered for liver transplantation in the US from January 1, 2004 through December 31, 2015. For subjects listed with multiple diagnoses, HCC was considered the primary listing diagnosis. To determine whether availability of direct-acting antiviral agents, which began in 2011, affected pre-transplant (death or dropout) and post-transplant outcomes for patients with HCV infection, we compared data from the time periods of 2004-2010 and 2011-2014. We used competing risk analysis to compare differences in endpoints between these periods. Differences between periods in pre- and post-transplantation outcomes were estimated using Kaplan-Maier analysis and compared using the log-rank test. Associations between year of listing and pre-liver transplant outcome, and year of liver transplant and survival following transplant, were examined using the log-rank test. Proportional hazard regression was used to evaluate the reliability of the time period effect with potential confounders. **RESULTS:** Among 109,018 registrants, 18.5% were registered for liver transplantation due to HCC. In 2015, HCC was the leading diagnosis among registrants (23.9% of registrations) and recipients (27.2% of recipients). Between 2004 and 2015, the ratio of registrants with vs without HCC increased 5.6-fold for patients with HCV infection, 1.9-fold for patients with HBV infection, 2.7-fold for patients with alcohol abuse, and 10.2-fold for patients with nonalcoholic steatohepatitis. After adjusting for covariates, we associated the period of 2011-2014 with a decreased probability that HCC registrants would undergo liver transplantation (hazard ratio [HR], 0.62;  $P < .0001$ ). The period of 2011-2014 was also associated with decreased probability of dropout due to deterioration or death from HCV-induced (HR, 0.90;  $P = .0003$ ), HBV-induced (HR, 0.71;  $P = .002$ ), or alcohol-induced (HR, 0.90;  $P = .01$ ) liver disease, and an increased probability of delisting due to clinical improvement in patients with HCV infection (HR, 3.4;  $P < .0001$ ), HBV infection (HR, 2.3;  $P = .004$ ), or alcohol abuse (HR, 2.2;  $P < .0001$ ). The period of 2011-2014 was associated with a decreased risk of graft loss or death, with the largest effect seen in HCV-infected recipients (HR, 0.76;  $P < .0001$ ). **CONCLUSION:** HCC was the leading indication for liver transplantation in the US in 2015. Despite this, the probability of liver transplantation decreased the most in registrants with HCC. Pre- and post-transplantation outcomes have improved, particularly in patients with HCV infection.