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

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**[Comparative effectiveness of 8- and 12-week ledipasvir/sofosbuvir regimens for HCV infection.](#)** Ojha RP1,2, MacDonald BR1, Chu TC1, Fasanmi EO3, Moore JD2, Stewart RA4. Antivir Ther. 2018 Jul 3. doi: 10.3851/IMP3249. [Epub ahead of print]

**BACKGROUND:** Real-world studies have aimed to compare the effects of 8- and 12-week ledipasvir/sofosbuvir regimens on sustained virologic response (SVR) among hepatitis C virus infection genotype 1 (HCV-1) treatment-naïve patients. Nevertheless, real-world comparative effectiveness studies pose unique challenges, such as confounding by indication, that were not adequately addressed in prior studies. We thus aimed to address limitations in prior studies and compare overall- and subgroup-specific effectiveness of 8- and 12-week ledipasvir/sofosbuvir regimens among HCV-1 treatment-naïve patients. **METHODS:** Patients eligible for our study were aged  $\geq 18$  years and initiated 8- or 12-week ledipasvir/sofosbuvir regimens for treatment-naïve HCV-1 at an urban public hospital network. We excluded patients with HIV or cirrhosis. We used marginal structural models to estimate overall and subgroup-specific risk ratios (RRs) and 95% confidence limits (CL) comparing the effect of 8- and 12-week ledipasvir/sofosbuvir regimens on 12-week SVR. **RESULTS:** Our study population comprised 191 patients. Among both regimens, the majority were aged  $>50$  years, non-Hispanic White, and uninsured. The overall risk of SVR was comparable between the 8- and 12-week regimens (RR=1.01, 95% CL: 0.92, 1.11). The risk of SVR did not vary by race/ethnicity (non-Hispanic Black: RR=1.01, 95% CL: 0.84, 1.21; non-Hispanic White: RR=1.01, 95% CL: 0.89, 1.04). **CONCLUSIONS:** Our real-world results suggest that 8- and 12-week ledipasvir/sofosbuvir have comparable effects on SVR among HCV-1 patients without cirrhosis or HIV. In addition, the comparable effectiveness of 8- and 12-week regimens among non-Hispanic Black individuals adds to the growing body of evidence that supports the removal of race-based treatment guidelines.

**[Ledipasvir/Sofosbuvir Effectively Treats Hepatitis C Virus Infections in an Underserved Population.](#)** Stewart RA1, MacDonald BR2, Chu TC2, Moore JD3, Fasanmi EO4, Ojha RP5,6. Dig Dis Sci. 2018 Jul 16. doi: 10.1007/s10620-018-5205-2. [Epub ahead of print]

**BACKGROUND:** Underserved populations have an unequal burden of HCV infections and poor outcomes with interferon-based treatments. Direct-acting antivirals have the potential to reduce these inequalities. **AIMS:** We aimed to estimate sustained virologic response (SVR) following treatment with sofosbuvir-based regimens for HCV infections among underserved

individuals and summarize the frequency of SVR across published studies of underserved populations. **METHODS:** We used data from a clinical cohort of patients aged  $\geq 18$  years who initiated sofosbuvir-based regimens for HCV infection between February 2014 and June 2016 at an urban public hospital network that serves as the healthcare safety-net for Tarrant County, Texas. We estimated SVR with corresponding 95% confidence limits (CL). In addition, we systematically reviewed the evidence to identify other studies of direct-acting antivirals among underserved populations. **RESULTS:** Our study population comprised 435 patients. The majority of patients were aged  $\geq 50$  years (76%), male (52%), non-Hispanic White (54%), HCV genotype 1 (79%) and treated with ledipasvir/sofosbuvir (69%). Overall SVR was 89% (95% CL 86, 92%) and highest for ledipasvir/sofosbuvir (SVR = 95%, 95% CL 92, 97%). The reported SVR following direct-acting antivirals among 837 underserved patients from three other studies ranged between 90 and 99%. **CONCLUSIONS:** Our results suggest that direct-acting antivirals, particularly ledipasvir/sofosbuvir, are generally effective for achieving SVR among underserved patients with HCV infections and may help reduce inequalities in HCV prevalence and outcomes for this vulnerable population.

[Treatment of hepatitis C with direct-acting antivirals significantly reduces liver-related hospitalizations in patients with cirrhosis.](#) Hill LA1, Delmonte RJ1, Andrews B2, Richards L2, Soto R2, Collier S2, Kuo A3, Cachay E4. Eur J Gastroenterol Hepatol. 2018 Jul 2. doi: 10.1097/MEG.0000000000001195. [Epub ahead of print]

**BACKGROUND:** The availability of direct-acting antivirals (DAA) for the treatment of hepatitis C (HCV) has resulted in the ability to safely and effectively treat patients with cirrhosis and end-stage liver disease. However, information is limited with regard to the impact of DAA treatment on inpatient health-related resource utilization in patients with advanced HCV-related cirrhosis. We aimed to ascertain the impact of DAA treatment on the frequency of liver-related hospitalizations and associated costs in patients with cirrhosis. **PATIENTS AND METHODS:** Retrospective cohort analysis carried out at a single US reference center that compared patients with HCV cirrhosis according to treatment status: the untreated group (January 2011 to December 2013) and the DAA-treated group (January 2014 to March 2017). The primary outcome was the difference in the incidence rate of liver-related hospitalizations. Secondary outcomes included differences in the incidence of hepatocellular carcinoma, liver transplant, and all-cause mortality. We calculated the projected savings per-patient treated per-year on the basis of calculated hospitalization rate stratified by Child-Turquotte-Pugh (CTP) score. **RESULTS:** Baseline characteristics were similar between the untreated (n=182) and DAA-treated (n=196) cohorts. Mean follow-up time in the untreated and treated cohort was 20.4 and 17.7 months, respectively. The incidence rates of liver-related hospitalizations were 29.1/100 and 10.4/100 person-years of follow-up ( $P \leq 0.0001$ ) in the untreated and treated cohorts, respectively. This was accounted for by a decreased incidence of hospitalizations in patients with CTP-A (75.8%) and CTP-B (64.5%), but not CTP-C. **CONCLUSION:** Successful DAA treatment reduces hospitalization rate and resource utilization costs in patients with CTP-A and CTP-B, but not in those with CTP-C.

[Significance of mutations in the region coding for NS3/4 protease in patients infected with HCV genotype 1b.](#)

Łapiński TW1, Rogalska-Płońska M1, Kowalczyk O2, Kiśluk J2, Zurnowska J2, Nikliński J2, Flisiak R1. Adv Clin Exp Med. 2018 Jul 26. doi: 10.17219/acem/75511. [Epub ahead of print]

**BACKGROUND:** Fast hepatitis C virus (HCV) replication is one of the reasons for frequent changes in viral genome. **OBJECTIVES:** The objective of this study was to evaluate the frequency and type of mutation in NS3/4 protease in patients with HCV genotype 1b and to determine the effect of the mutation on viral load, fibrosis stage, alanine aminotransferase (ALT) activity, and alpha-fetoprotein (AFP) level. **MATERIAL AND METHODS:** The study included 46 treatment-naïve patients, infected with HCV genotype 1b. Mutations were analyzed after isolating HCV RNA, and then evaluating the compliance of the amino acid sequence, using 3500 Genetic Analyzer (Applied Biosystems, Foster City, USA). RNA fragment from nucleotide 1-181 encoding NS3/4 protease was subjected to analysis. **RESULTS:** Mutations were demonstrated in 65% of subjects. Changes in the protease region affecting resistance to treatment (T54, Q80, V158, M175, D186) were detected in 10.8% of patients. Substitution mutation at T72 was found most frequently - in 49.9% of cases. In 13% of patients, mutation at G86 was demonstrated, including G86P in 5 patients and G86S in 1 patient. In the group of patients with T72 mutation, viral load was significantly higher ( $1.3 \times 10^6$  IU/mL vs  $1.0 \times 10^5$  IU/mL;  $p = 0.01$ ), AFP level was higher and fibrosis level was lower (1.26 vs 2.17;  $p = 0.008$ ) compared to the patients without the mutation. Cryoglobulinemia was observed in 74% of patients with mutation at position T72. **CONCLUSIONS:** Natural mutations of the region coding for NS3/4 protease are found frequently in patients infected with genotype 1b, but they may cause resistance to antiviral agents only in 11% of patients. Changes were most frequently found at position T72. Mutations at position T72 are correlated with the cryoglobulinemia occurrence. This is a substitution mutation, accompanied by a high viral load, high ALT activity and AFP level, which may point to a more unfavorable influence of such a modified virus, compared to wild-type virus, onto pathological processes in the liver.

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

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#### [Hepatitis C virus serologic relapse after treatment with direct-acting antivirals is dependent on viral RNA levels in peripheral blood mononuclear cells and the grade of liver cirrhosis.](#)

Abd Alla MDA1, El Awady MK2, Dawood RM2, Elhawary MA3, Al-Azhari SS3, Galal AGM4. Arch Virol. 2018 Jul 3. doi: 10.1007/s00705-018-3922-7. [Epub ahead of print] The disappearance of hepatitis C virus (HCV) from serum and tissues for 12 weeks after the end of treatment (EOT) with direct-acting antivirals (DAAs) is known as a "sustained virologic response" (SVR) and occurs more frequently in non-cirrhotic patients than in cirrhotic patients. In this study, we evaluated the outcome of HCV treatment with sofosbuvir (SOF) plus ledipasvir (LDV) at both EOT and 12 weeks after EOT in patients with and without hepatic cirrhosis to address the relationship of serologic relapse to persistent infection of PBMCs and the frequency of hepatic encephalopathy and hepatocellular carcinoma (HCC) after treatment. Seventy-five patients with post-HCV liver cirrhosis were assigned to one of three groups (A, B, and C), each of which included 25 patients and corresponded to the patients' Child-Turcotte-Pugh (CTP) classification. All of the patients received a daily dose of SOF (400 mg) plus LDV (90 mg) for 24 weeks and were tested using HCV single-strand reverse transcription (SRT) and PCR analysis of PBMCs at both EOT and 12 weeks after EOT. Fourteen (18.7%) out of 75 patients (all study populations) had intra-PBMC HCV RNA, but only nine of them (64.3%) developed HCV RNA serum relapse (seroconversion) 12 weeks after EOT ( $P < 0.001$ ). Encephalopathy was significantly higher in group C at EOT and 12 weeks after EOT ( $P < 0.05$ ). Development of HCC was observed in decompensated patients of group C (2 out of 5 = 40.0%) 12 weeks post-EOT

( $P = 0.03$ ). In conclusion, detection of HCV RNA within PBMCs at the EOT provides an indication of potential relapse after 12 weeks. Moreover, development of encephalopathy and HCC after HCV eradication by SOF plus LDV therapy is perhaps a future warning for post-treatment hepatic decompensation in cirrhotic patients.

[IL-1 \$\alpha\$  correlates with severity of hepatitis C virus-related liver diseases.](#) Tawfik AK1, Amin AM2, Yousef M1, El-Sayd NM1, Elashry H1, Elkadeem M1, Abd-Elsalam S1. *J Inflamm Res.* 2018 Jul 10;11:289-295. doi: 10.2147/JIR.S166564. eCollection 2018.

**BACKGROUND AND AIMS:** Immunoregulatory cytokines influence the persistence of hepatitis C virus (HCV) chronic infection and the extent of liver damage. Interleukin-1 (IL-1) plays an important role in the inflammatory process. Some studies have demonstrated that IL-1 $\alpha$  production was impaired in patients with chronic infections of HCV, implying that IL-1 $\alpha$  may play a role in viral clearance. The aim of this study was to evaluate the serum level of proinflammatory cytokine IL-1 $\alpha$  in patients with chronic hepatitis C (CHC). **METHODS:** This study was performed on 20 CHC patients with cirrhosis in (Group I), 20 CHC patients without cirrhosis in (Group II), 20 hepatocellular carcinoma (HCC) patients with positive anti-HCV in (Group III), and 10 healthy subjects as a control group. Serum levels of IL-1 $\alpha$  were measured by enzyme-linked immunoassay technique. **RESULTS:** IL-1 $\alpha$  had the highest mean concentration in the HCC group and then in the group of CHC with cirrhosis compared to the group of CHC without cirrhosis. Also, it was higher in all studied groups than in the control group ( $P < 0.001$ ). Statistical analysis showed that IL-1 $\alpha$  was positively correlated with bilirubin ( $P \leq 0.001$ ), alanine aminotransferase ( $P = 0.006$ ), aspartate aminotransferase ( $P = 0.001$ ), and viral load ( $P = 0.001$ ) but it was negatively correlated with albumin ( $P \leq 0.001$ ) and Hb ( $P \leq 0.001$ ), and was not significantly correlated with other parameters (age, international normalized ratio, urea, creatinine, white blood cells, and platelet count). **CONCLUSION:** Serum level of IL-1 $\alpha$  was elevated in patients with CHC and its related liver diseases (liver cirrhosis and HCC) and can be used as an important parameter of inflammatory activity and for fibrosis evaluation in patients with chronic liver disease.

[Unexpected Replication Boost by Simeprevir for Simeprevir-Resistant Variants in Genotype 1a Hepatitis C Virus.](#) Murai K1, Shimakami T2, Welsch C3, et al. *Antimicrob Agents Chemother.* 2018 Jun 26;62(7). pii: e02601-17. doi: 10.1128/AAC.02601-17. Print 2018 Jul.

Simeprevir is a novel NS3/4A protease inhibitor (PI) of hepatitis C virus (HCV). The baseline polymorphism NS3-Q80K is frequently observed in genotype (GT) 1a HCV and often associated with treatment failure in simeprevir-containing regimens. We aimed to elucidate mechanisms of treatment failure due to NS3-Q80K. We included a Q80R mutation in our study and generated a series of Huh-7.5 cell lines, each of which harbored either wild-type GT 1a strain H77S.3 or the Q80K or Q80R variant. The cells were cultured with increasing concentrations of simeprevir, and NS3 domain sequences were determined. The mutations identified by sequence analyses were subsequently introduced into H77S.3. The sensitivity of each mutant to the NS3/4A PIs simeprevir, asunaprevir, grazoprevir, and paritaprevir was analyzed. We introduced the mutations into GT 1b strain N.2 and compared the sensitivity to simeprevir with that of GT 1a strain H77S.3. While simeprevir treatment selected mutations at residue D168, such as D168A/V in the wild-type virus, an additional mutation at residue R155, R155K, was selected in Q80K/R variants at simeprevir concentrations of  $< 2.5 \mu\text{M}$ . Sensitivity analyses showed that simeprevir

concentrations of <1  $\mu\text{M}$  significantly boosted the replication of Q80K/R R155K variants. Interestingly, this boost was not observed with the other NS3/4A PIs or in Q80R R155Q/G/T/W variants or GT 1b isolates. The boosted replication of the Q80K+R155K variant by simeprevir could be related to treatment failure in simeprevir-containing antiviral treatments in GT 1a HCV-infected patients with the NS3-Q80K polymorphism. This result provides new insight into how resistance-associated variants can cause treatment failure.

### **Osteopontin Regulates Hepatitis C Virus (HCV) Replication and Assembly by Interacting with HCV Proteins and Lipid Droplets and by Binding to Receptors $\alpha\text{V}\beta\text{3}$ and CD44.**

Iqbal J1, Sarkar-Dutta M1, McRae S1, Ramachandran A1, Kumar B1, Waris G2. J Virol. 2018 Jun 13;92(13). pii: e02116-17. doi: 10.1128/JVI.02116-17. Print 2018 Jul 1.

Hepatitis C virus (HCV) replication and assembly occur at the specialized site of endoplasmic reticulum (ER) membranes and lipid droplets (LDs), respectively. Recently, several host proteins have been shown to be involved in HCV replication and assembly. In the present study, we demonstrated the important relationship among osteopontin (OPN), the ER, and LDs. OPN is a secreted phosphoprotein, and overexpression of OPN in hepatocellular carcinoma (HCC) tissue can lead to invasion and metastasis. OPN expression is also enhanced in HCV-associated HCC. Our recent studies have demonstrated the induction, proteolytic cleavage, and secretion of OPN in response to HCV infection. We also defined the critical role of secreted OPN in human hepatoma cell migration and invasion through binding to receptors integrin  $\alpha\text{V}\beta\text{3}$  and CD44. However, the role of HCV-induced OPN in the HCV life cycle has not been elucidated. In this study, we showed a significant reduction in HCV replication, assembly, and infectivity in HCV-infected cells transfected with small interfering RNA (siRNA) against OPN,  $\alpha\text{V}\beta\text{3}$ , and CD44. We also observed the association of endogenous OPN with HCV proteins (NS3, NS5A, NS4A/B, NS5B, and core). Confocal microscopy revealed the colocalization of OPN with HCV NS5A and core in the ER and LDs, indicating a possible role for OPN in HCV replication and assembly. Interestingly, the secreted OPN activated HCV replication, infectivity, and assembly through binding to  $\alpha\text{V}\beta\text{3}$  and CD44. Collectively, these observations provide evidence that HCV-induced OPN is critical for HCV replication and assembly. **IMPORTANCE** Recently, our studies uncovered the critical role of HCV-induced endogenous and secreted OPN in migration and invasion of hepatocytes. However, the role of OPN in the HCV life cycle has not been elucidated. In this study, we investigated the importance of OPN in HCV replication and assembly. We demonstrated that endogenous OPN associates with HCV NS3, NS5A, NS5B, and core proteins, which are in close proximity to the ER and LDs. Moreover, we showed that the interactions of secreted OPN with cell surface receptors  $\alpha\text{V}\beta\text{3}$  and CD44 are critical for HCV replication and assembly. These observations provide evidence that HCV-induced endogenous and secreted OPN play pivotal roles in HCV replication and assembly in HCV-infected cells. Taken together, our findings clearly demonstrate that targeting OPN may provide opportunities for therapeutic intervention of HCV pathogenesis.

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## **HIV/HCV COINFECTION**

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### **Markers of Tissue Repair and Cellular Aging Are Increased in the Liver Tissue of Patients With HIV Infection Regardless of Presence of HCV Coinfection.**

Naggie S1,2, Swiderska-Syn M3, Choi S1,4, Lusk S2, Lan A5, Ferrari G1, Syn WK3,6, Guy CD1, Diehl AM1. *Open Forum Infect Dis.* 2018 Jun 11;5(7):ofy138. doi: 10.1093/ofid/ofy138. eCollection 2018 Jul.

Liver disease is a leading cause of HIV-related mortality. Hepatitis C virus (HCV)-related fibrogenesis is accelerated in the setting of HIV coinfection, yet the mechanisms underlying this aggressive pathogenesis are unclear. We identified formalin-fixed paraffin-embedded liver tissue for HIV-infected patients, HCV-infected patients, HIV/HCV-coinfected patients, and controls at Duke University Medical Center. De-identified sections were stained for markers against the wound repair Hedgehog (Hh) pathway, resident T-lymphocytes, and immune activation and cellular aging. HIV infection was independently associated with Hh activation and markers of immune dysregulation in the liver tissue.

[Using Stepwise Pharmacogenomics and Proteomics to Predict Hepatitis C Treatment Response in Difficult to Treat Patient Populations.](#) Naggie S1, Clement M1, Lusk S1, et al. *Proteomics Clin Appl.* 2018 Jul 30:e1800006. doi: 10.1002/prca.201800006. [Epub ahead of print]

**PURPOSE:** In the interferon era of hepatitis C virus (HCV) therapies, genotype/subtype, cirrhosis, prior treatment failure, sex, and race predicted relapse. Our objective was to validate a targeted proteomics platform of 17 peptides to predict sustained virologic response (SVR). **EXPERIMENTAL DESIGN:** Stored plasma from three, open-label, trials of HIV/HCV co-infected subjects receiving interferon-containing regimens was identified. LC-MS/MS was used to quantitate the peptides directly from plasma, and IL28B genotyping was completed using stored PBMC. A logistic regression model was built to analyze the probability of SVR using responders and non-responders to interferon-based regimens. **RESULTS:** The cohort (N = 35) was predominantly black (51.4%), male (86%), with median age 48 years. Most patients achieved SVR (54%). Using multivariable models, we verified that three human corticosteroid binding globulin (CBG) peptides were predictive of SVR in patients with the unfavorable IL28B genotypes (CT/TT). The model performed better than IL28B alone, with an AUC of 0.870. **CONCLUSIONS AND CLINICAL RELEVANCE:** In HIV/HCV co-infected patients, we identified three human CBG peptides that accurately predict treatment response with interferon-based therapy. This study suggests that a stepwise approach combining a genetic predictor followed by targeted proteomics can improve the accuracy of clinical decision-making. This article is protected by copyright. All rights reserved.

[Timing of treatment initiation of direct-acting antivirals for HIV/HCV coinfecting and HCV mono-infected patients.](#) Rice DP1, Ordoveza MA1, Palmer AM1, Wu GY2, Chirch LM2. *AIDS Care.* 2018 Jul 18:1-5. doi: 10.1080/09540121.2018.1499857. [Epub ahead of print]

Direct-acting antiviral therapy is safe and cost-effective for the treatment of hepatitis C virus (HCV) infection. However, variability in drug payment rules represents a barrier to treatment that may disproportionately affect certain populations. We conducted a retrospective cohort study among HIV/HCV coinfecting and HCV mono-infected patients using Kaplan-Meier and Fisher's exact test to analyze the time from the prescription of a direct-acting antiviral agent to delivery to the patient. Variables with significance  $p < .20$  in univariate analysis were included in a Cox regression model. Factors associated with faster treatment were Infectious Diseases office setting ( $p = .01$ ), public insurance payer ( $p = .01$ ), and initial approval of requested regimen ( $p = .01$ ). The presence of other liver disease was associated with delay in treatment ( $p = .05$ ).

Unrestrictive Medicare and Medicaid regulations resulted in more rapid delivery of medication compared to private payers. Fibrosis level, Child-Pugh class and HIV status did not significantly change time to treatment.

**Eradication of Hepatitis C Virus (HCV) Reduces Immune Activation, Microbial Translocation, and the HIV DNA Level in HIV/HCV-Coinfected Patients.** López-Cortés LF1, Trujillo-Rodríguez M1, Báez-Palomo A1, et al. Infect Dis. 2018 Jul 13;218(4):624-632. doi: 10.1093/infdis/jiy136.

**BACKGROUND:** There are contradictory data about the influence that hepatitis C virus (HCV) has on immune activation and inflammation in patients coinfecting with human immunodeficiency virus (HIV) and HCV. **METHODS:** HIV/HCV-coinfecting patients receiving antiretroviral treatment who achieved a sustained virological response with interferon-free regimens were consecutively enrolled in a prospective study. The following factors were assessed before, immediately after the end of, and 1 month after the end of therapy: expression of HLA-DR/CD38, PD-1, and CD57 on CD4+ and CD8+ T-cells; measurement of the total HIV DNA load in peripheral blood mononuclear cells; and determination of plasma levels of soluble CD14 (sCD14), lipopolysaccharide (LPS), 16S ribosomal DNA (rDNA), interleukin 6 (IL-6), D-dimers, and high-sensitivity C-reactive protein (hsCRP). **RESULTS:** Ninety-seven patients were consecutively included. At the end of therapy and 1 month later, there were significant reductions in the expression of HLA-DR and CD38 in CD4+ and CD8+ T cells, as well as levels of proviral HIV DNA, sCD14, LPS, 16S rDNA, and D-dimer ( $P < .001$ ). By contrast, the expression of PD-1 and CD57 in CD4+ and CD8+ T cells and levels of IL-6 and hsCRP did not change. The improvement in levels of immune activation markers, proviral HIV DNA, and microbial translocation markers did not translate into an increased CD4+ T-cell count or increased ratio of the CD4+ T-cell count to the CD8+ T-cell count. **CONCLUSIONS:** HCV eradication in HIV/HCV-coinfecting patients results in significant decreases in levels of immune activation markers, proviral HIV DNA load, microbial translocation markers, and D-dimers. These findings support the use of HCV treatment for all HIV/HCV-coinfecting patients, even those with low-grade fibrosis.

**Hepatocellular carcinoma after sustained virological response with interferon-free regimens in HIV/hepatitis C virus-coinfecting patients.** Merchante N1, Rodríguez-Arondo F2, Revollo B3, Merino E4, et al. AIDS. 2018 Jul 17;32(11):1423-1430. doi: 10.1097/QAD.0000000000001809.

**OBJECTIVE:** To assess the possible association between the use of direct antiviral agents (DAA) and the risk of hepatocellular carcinoma (HCC) in HIV/hepatitis C virus (HCV)-coinfecting patients. **METHODS:** The GEHEP-002 cohort recruits HCC cases in HIV-infected patients from 32 centers from Spain. Three analyses were performed: the proportion of HCC cases after sustained virological response (SVR) and the evolution of this proportion over time, the frequency of HCC after SVR in HIV/HCV-coinfecting patients with cirrhosis, and the probability of HCC recurrence after curative therapies among those undergoing HCV therapy. **RESULTS:** Forty-two (13%) out of 322 HCC cases in HIV/HCV-coinfecting patients occurred after SVR. Twenty-eight (10%) out of 279 HCC cases diagnosed during the years of use of IFN-based regimens occurred after SVR whereas this occurred in 14 (32.6%) out of the 43 HCC cases diagnosed in the all-oral DAA period ( $P < 0.0001$ ). One thousand, three hundred and thirty-seven HIV/HCV-coinfecting patients with cirrhosis achieved SVR in the cohort. The frequency of HCC

after SVR declined from 15% among those cured with pegylated-IFN with ribavirin to 1.62 and 0.87% among those cured with DAA with and without IFN, respectively. In patients with previous HCC treated with curative therapies, HCC recurrence occurred in two (25%) out of eight patients treated with IFN-based regimens and four (21%) out of 19 treated with DAA-IFN-free regimens (P=1.0). **CONCLUSION:** The frequency of HCC emergence after SVR has not increased after widespread use of DAA in HIV/HCV-coinfected patients. DAA do not seem to impact on HCC recurrence in the short-term among those with previously treated HCC.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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[Disparities in hepatitis C virus infection screening among Baby Boomers in the United States.](#) Nili M1, Luo L1, Feng X1, Chang J2, Tan X3. Am J Infect Control. 2018 Jul 13. pii: S0196-6553(18)30699-0. doi: 10.1016/j.ajic.2018.06.008. [Epub ahead of print]

**BACKGROUND:** The study objective was to identify potential sociodemographic disparities in hepatitis C virus (HCV) infection screening among Baby Boomers in the United States.

**METHODS:** We analyzed cross-sectional data from the 2013-2016 National Health Interview Survey. The outcome was whether a person had an HCV infection screening (yes/no). Key independent variables were race/ethnicity, geographic region, poverty level, education level, and health insurance status. Multivariate logistic regression was performed to examine the factors associated with the receipt of HCV screening. **RESULTS:** The study sample included a total of 41,914 United States Baby Boomers, who represented a population size of 69,554,339. In 2016, the HCV screening rate among Baby Boomers was 13.9%. In the multivariate logistic regression, we found that Asians had 27% lower odds of receiving an HCV screening compared to Blacks (odds ratio [OR] = 0.74, P = .02). People who lived in the Northeast, South, and West had a higher likelihood of having an HCV screening than those who lived in the Midwest (OR = 1.33, 1.39, and 1.69, respectively; all P values <.001). Additionally, people with less education, lower income, and private health insurance were significantly less likely to have an HCV screening.

**CONCLUSION:** Future studies or interventions are needed to target these disadvantaged populations to improve HCV screening in Baby Boomers.

[Knowledge of Hepatitis C Risk Factors is Lower in High Incidence Regions.](#) Knick T1, Sherbuk JE2, Dillingham R3. J Community Health. 2018 Jul 7. doi: 10.1007/s10900-018-0545-6. [Epub ahead of print]

Despite ambitious goals to eliminate hepatitis C virus (HCV) in the United States by 2030, the majority of those infected are not aware of their diagnosis, and only a small minority have been cured. A lack of knowledge regarding risk factors and treatment may contribute to low cure rates. We aimed to evaluate HCV knowledge and the association of risk factor knowledge with HCV incidence. In fall 2017, a survey regarding HCV knowledge was disseminated through social media, web link, and in person throughout the state of Virginia. The survey was completed by 613 individuals. Residents of high-incidence counties identified fewer risk factors (5.6 vs 6.1 of 9, p = 0.04), a difference that remained significant when controlling for education and age (p = 0.03). Fewer participants in the high-incidence group recognized snorting drugs to be a risk factor (25% vs 36%, p = 0.01). Only 38% of all respondents correctly identified HCV to be



curable. Knowledge of HCV risk factors is lower in high incidence regions. These results identify a critical knowledge gap in the general population at a time of ongoing HCV transmission. Public health interventions must target these gaps in high-incidence regions as part of comprehensive disease prevention programs.

[Hepatitis C Management Simplification From Test to Cure: A Framework for Primary Care Providers.](#) Kapadia SN1, Marks KM2. Clin Ther. 2018 Jul 5. pii: S0149-2918(18)30237-6. doi: 10.1016/j.clinthera.2018.05.010. [Epub ahead of print]

This article proposes a strategy for primary care providers to begin treating patients with hepatitis C virus (HCV). We are motivated by the need to expand HCV treatment and by developments that have simplified treatment for most patients. This article presents 5 steps to achieving quality HCV treatment in the primary care setting: (1) accurate diagnosis via reflex testing; (2) risk stratification and identifying comorbidities via pretreatment evaluation; (3) simple, once-daily, pan-genotypic HCV treatment regimens; (4) minimized on-treatment monitoring; and (5) posttreatment monitoring and high-quality care for comorbidities such as cirrhosis and injection drug use. We provide indications for referral to specialists: notably children, patients with genotype 3 and cirrhosis, advanced liver or kidney disease, previous treatment failures, drug interactions with recommended regimens, and hepatitis B co-infection. Finally, potential barriers for providers are discussed, as well as further research findings and policy interventions that can promote HCV treatment in the primary care setting. We believe that a substantial portion of patients with HCV can be treated safely and effectively by nonspecialists and that the engagement of primary care providers is critical to efforts to end the HCV epidemic.

[Underutilization of Hepatitis C Virus Seropositive Donor Kidneys in the United States in the Current Opioid Epidemic and Direct-Acting Antiviral Era.](#) Li AA1, Cholankeril G2, Cheng XS3, Tan JC4, Kim D5, Toll AE6, Nair S7, Ahmed A8. Diseases. 2018 Jul 10;6(3). pii: E62. doi: 10.3390/diseases6030062.

In recent years, the opioid epidemic and new hepatitis C virus (HCV) treatments have changed the landscape of organ procurement and allocation. We studied national trends in solid organ transplantation (2000-2016), focusing on graft utilization from HCV seropositive deceased donors in the pre-2014 (2000-2013) versus current (2014-2016) eras with a retrospective analysis of the United Network for Organ Sharing database. During the study period, HCV seropositive donors increased from 181 to 661 donors/year. The rate of HCV seropositive donor transplants doubled from 2014 to 2016. Heart and lung transplantation data were too few to analyze. A higher number of HCV seropositive livers were transplanted into HCV seropositive recipients during the current era: 374 versus 124 liver transplants/year. Utilization rates for liver transplantation reached parity between HCV seropositive and non-HCV donors. While the number of HCV seropositive kidneys transplanted to HCV seropositive recipients increased from 165.4 to 334.7 kidneys/year from the pre-2014 era to the current era, utilization rates for kidneys remained lower in HCV seropositive than in non-HCV donors. In conclusion, relative underutilization of kidneys from HCV seropositive versus non-HCV donors has persisted, in contrast to trends in liver transplantation.

[Has Access to HCV Therapy Changed for Patients with Mental Health or Substance Use Disorders in the DAA Period?](#) Jain MK1,2, Thamer M3, Therapondos G4, Shiffman ML5,

Kshirsagar O3, Clark C2, Wong RJ6. Hepatology. 2018 Jul 17. doi: 10.1002/hep.30171. [Epub ahead of print]

**BACKGROUND:** Direct-acting antivirals (DAA) for hepatitis C virus (HCV) became available in 2014, but the role of mental health or substance use disorders (MH/SUD) on access to treatment is unknown. **OBJECTIVE:** To examine extent and predictors of HCV treatment in the pre-DAA and post-DAA periods in 4 large, diverse health care settings in the United States (US). **METHODS:** Retrospective analysis of 29,544 adults with chronic HCV who did or did not receive treatment from 1/1/11-2/28/17. Kaplan Meier curve was used to examine cumulative risk for receiving HCV treatment stratified by MH/SUD. Predictors of HCV treatment in the pre-DAA (1/1/11-12/31/13) and post-DAA (1/1/14-2/28/17) cohorts were analyzed using multivariate generalized estimating equations (GEE) and a modified Poisson models. **RESULTS:** Overall 21.7% (2,879/13,240) of those with chronic HCV post-DAA were treated compared to 3.5% (574/16,304) in the pre-DAA period. Compared to non-Hispanic Whites, Hispanic Whites (AOR 0.36, 95% CI: 0.25, 0.52) were less likely to be treated in the post-DAA period. Those with concurrent nonalcoholic fatty liver disease (AOR 1.39, 95% CI: 1.05, 1.83), cirrhosis (AOR 2.00, 95% CI: 1.74, 2.31), and liver transplant (AOR 2.72, 95% CI: 1.87, 3.94) were more likely to be treated post-DAA. Those with MH/SUD were less likely to be treated both before (AOR 0.46, 95% CI: 0.36, 0.60) and after (AOR 0.63, 95% CI: 0.55, 0.71) DAA therapy was available. Overall, the cumulative risk for receiving HCV treatment from 2011-17 among those with vs. without MH/SUD was 13.6% vs. 21.6%, respectively, (P <0.001). **CONCLUSIONS:** The volume of patients treated for HCV has increased in the post-DAA period especially among those with liver-related co-morbidities, but disparities in access to treatment continue among those with MH/SUD. This article is protected by copyright. All rights reserved.

[The Micro-Elimination Approach to Eliminating Hepatitis C: Strategic and Operational Considerations.](#) Lazarus JV1, Safreed-Harmon K1, Thursz MR2, et al. Semin Liver Dis. 2018 Aug;38(3):181-192. doi: 10.1055/s-0038-1666841. Epub 2018 Jul 9.

The introduction of efficacious new hepatitis C virus (HCV) treatments galvanized the World Health Organization to define ambitious targets for eliminating HCV as a public health threat by 2030. Formidable obstacles to reaching this goal can best be overcome through a micro-elimination approach, which entails pursuing elimination goals in discrete populations through multi-stakeholder initiatives that tailor interventions to the needs of these populations. Micro-elimination is less daunting, less complex, and less costly than full-scale, country-level initiatives to eliminate HCV, and it can build momentum by producing small victories that inspire more ambitious efforts. The micro-elimination approach encourages stakeholders who are most knowledgeable about specific populations to engage with each other and also promotes the uptake of new models of care. Examples of micro-elimination target populations include medical patients, people who inject drugs, migrants, and prisoners, although candidate populations can be expected to vary greatly in different countries and subnational areas.

[Cirrhosis affects maximal oxygen consumption, functional capacity, quality of life in patients with hepatitis C.](#) Casales da Silva Vieira R1, Álvares-da-Silva MR2, de Oliveira ÁR3, et al. Physiother Res Int. 2018 Jul 2:e1727. doi: 10.1002/pri.1727. [Epub ahead of print]

**OBJECTIVE:** The aim is assess, compare, and correlate maximal oxygen consumption (VO<sub>2</sub>max.), functional capacity and quality of life in cirrhotic patients with hepatitis C virus

(HCV) and in healthy individuals. **METHODS:** This case-control study included 36 participants (18 patients with HCV cirrhosis and 18 healthy individuals) matched for sex and age. VO<sub>2</sub>max was assessed using ergospirometry with an incremental load test on a cycloergometer. Functional capacity was measured by a 6-min walk test (6WT), and quality of life was assessed using the 36-Item Short-Form Health Survey (SF-36). **RESULTS:** Both the cirrhotic group and the control group had similar results for sex (44.4% male) and age (55.6 ± 8.31 and 55.2 ± 8.85 years, respectively). The cirrhotic group scored lower in all domains of the SF-36, on the VO<sub>2</sub>max test (cirrhotic group 16.2 [11.6-18.6] ml/kg/min; control group 19.9 [16.28-26.9]; p = 0.007) and on the 6WT (cirrhotic group 521.5 [476.25-544.75] m; control group 618.0 [570.75-643.75] m; p = 0.0001). Correlations were found between the 6WT and the VO<sub>2</sub>max (r = 0.801, p < 0.0001) and between the 6WT and quality of life (SF-361-functional capacity domain; r = 0.552, p = 0.018) only in the cirrhotic group. **CONCLUSION:** Patients with cirrhosis due to HCV show changes in VO<sub>2</sub>max and in functional capacity, which have a significant impact on their quality of life.

[A Cost Reimbursement Model for Hepatitis C Treatment Care Coordination.](#) Behrends CN1, Eggman AA, Gutkind S, et al. J Public Health Manag Pract. 2018 Jul 2. doi: 10.1097/PHH.0000000000000806. [Epub ahead of print]

**OBJECTIVE:** To estimate the cost of delivering a hepatitis C virus care coordination program at 2 New York City health care provider organizations and describe a potential payment model for these currently nonreimbursed services. **DESIGN:** An economic evaluation of a hepatitis C care coordination program was conducted using micro-costing methods compared with macro-costing methods. A potential payment model was calculated for 3 phases: enrollment to treatment initiation, treatment initiation to treatment completion, and a bonus payment for laboratory evidence of successful treatment outcome (sustained viral response). **SETTING:** Two New York City health care provider organizations. **PARTICIPANTS:** Care coordinators and peer educators delivering care coordination services were interviewed about time spent on service provision. De-identified individual-level data on study participant utilization of services were also used. **INTERVENTION:** Project INSPIRE is an innovative hepatitis C care coordination program developed by the New York City Department of Health and Mental Hygiene. **MAIN OUTCOME MEASURES:** Average cost per participant per episode of care for 2 provider organizations and a proposed payment model. **RESULTS:** The average cost per participant at 1 provider organization was \$787 (\$522 nonoverhead cost, \$264 overhead) per episode of care (5.6 months) and \$656 (\$429 nonoverhead cost, \$227 overhead, 5.7 months) at the other one. The first organization had a lower macro-costing estimate (\$561 vs \$787) whereas the other one had a higher macro-costing estimate (\$775 vs \$656). In the 3-phased payment model, phase 1 reimbursement would vary between the provider organizations from approximately \$280 to \$400, but reimbursement for both organizations would be approximately \$220 for phase 2 and approximately \$185 for phase 3. **CONCLUSIONS:** The cost of this 5.6-month care coordination intervention was less than \$800 including overhead or less than \$95 per month. A 3-phase payment model is proposed and requires further evaluation for implementation feasibility. Project INSPIRE's HCV care coordination program provides good value for a cost of less than \$95 per participant per month. The payment model provides an incentive for successful cure of hepatitis C with a bonus payment; using the bonus payment to support HCV tele-mentoring expands HCV treatment capacity and empowers more primary care providers to treat their own patients with HCV.

[Sofosbuvir and Ledipasvir is Associated with High Sustained Virologic Response and Improvement of Health-Related Quality of Life in East Asian Patients with Hepatitis C Virus Infection.](#) Younossi ZM<sup>1,2</sup>, Stepanova M<sup>3</sup>, Henry L<sup>3</sup>, et al. J Viral Hepat. 2018 Jul 4. doi: 10.1111/jvh.12965. [Epub ahead of print]

Although HCV infection is highly prevalent in East Asia, these patients have been underrepresented in HRQL studies. Here we assess HRQL in East Asian HCV patients treated with different anti-HCV regimens. Patients completed Short Form-36 (SF-36) before, during and after treatment. A total of 989 HCV patients were enrolled in two phase 3 clinical trials [China: 60.2%, South Korea: 22.4%, Taiwan: 17.4%; genotype 1: 55.3%, treatment-naïve: 57.5%; cirrhosis: 14.0%]. Patients received pegylated interferon, sofosbuvir, and ribavirin (Peg-IFN+SOF+RBV; n=130, genotypes 1, 6) or SOF+RBV (n=475, all genotypes) or SOF and ledipasvir (LDV/SOF; n=384, genotype 1). The SVR-12 rates were 94.6%, 96.2%, and 99.2%, respectively (p=0.005). During treatment, Peg-IFN+SOF+RBV-treated group experienced significant declines in most HRQL scores (by the end of treatment, mean decline up to -12.0 points, all p<0.05). Patients on SOF+RBV had milder HRQL impairment (up to -5.8 points, p<0.05 for 5/8 HRQL domains). In contrast, patients receiving IFN- and RBV-free regimen with LDV/SOF had their HRQL scores improve (mean up to +4.3 points, p<0.0001 for 3/8 scales). In multivariate analysis, receiving Peg-IFN+SOF+RBV was consistently independently associated with HRQL impairment during treatment ( $\beta$ : -10.3 to -16.4) and after achieving SVR-12 ( $\beta$ : -4.4 to -9.1) (all p<0.01). The results were reproduced in a subgroup of patients enrolled in China. We conclude that in East Asian patients with HCV, HRQL improved from baseline after treatment with LDV/SOF but not with Peg-IFN+RBV-containing or Peg-IFN-free RBV-containing regimens. The HRQL impairment associated with the use of Peg-IFN persists even after achieving sustained virologic clearance. This article is protected by copyright. All rights reserved.

[Health risk and health seeking behaviours among people who inject performance and image enhancing drugs who access needle syringe programs in Australia.](#) Van de Ven K1, Maher L2, Wand H2, Memedovic S1,2, Jackson E3, Iversen J2. Drug Alcohol Rev. 2018 Jul 2. doi: 10.1111/dar.12831. [Epub ahead of print]

**INTRODUCTION AND AIMS:** People who use performance and image enhancing drugs (PIED) are a growing population in needle syringe programs (NSP) in Australia. Previous international research has identified heterogeneity among the PIED-using population. This study investigated health behaviours among NSP attendees who had recently (last 12 months) injected PIEDs and examined differences among this group according to recent psychoactive drug use. **DESIGN AND METHODS:** The Australian Needle and Syringe Program Survey is an annually repeated cross-sectional survey conducted at approximately 50 NSPs nationally. In 2015, respondents provided information on their demographic characteristics, health risk and health monitoring behaviours, and provided a capillary dried blood spot for HIV and hepatitis C virus antibody testing. Univariable and multivariable logistic regressions assessed factors associated with recent (last 12 months) use (all routes of administration) of psychoactive drugs. **RESULTS:** Among recent PIED injectors (n = 156), 59% had recently used psychoactive substances. Those who had recently used psychoactive drugs were significantly younger, less educated and more likely to have experienced redness at an injection site in the previous 12 months but were more likely to report recent HIV/hepatitis C virus testing. **DISCUSSION AND CONCLUSIONS:**

This study identified significant differences in demographic characteristics, risk and health seeking behaviour among PIED users who did and did not also use psychoactive substances. There is a need to enhance and tailor harm reduction efforts and to build the capacity of NSP staff to better meet the needs of this diverse group.

[Enhanced identification of maternal hepatitis C virus infection using existing public health surveillance systems.](#) Gowda C1,2,3, Kennedy S1, Glover C4, Prasad MR5, Wang L3, Honegger JR1,4. Paediatr Perinat Epidemiol. 2018 Jul 4. doi: 10.1111/ppe.12481. [Epub ahead of print]

**BACKGROUND:** Hepatitis C virus (HCV) infection is under-recognized among US adults and children. Prenatal HCV screening may help close the diagnosis gap among women while also identifying at-risk infants. Current surveillance efforts for maternal HCV rely primarily on birth certificate data. We sought a more accurate assessment of HCV prevalence among pregnant women in Ohio by combining existing public health surveillance data. **METHODS:** Vital Statistics (VS) birth certificate data and Ohio Disease Reporting System (ODRS) HCV case data, both available through the Ohio Department of Health, were linked to determine rates of past or present HCV infection among women giving birth from 2012 to 2015 in Ohio, overall and by county. Among women with available test results, the proportion with present HCV infection indicated by detectable viraemia during pregnancy was calculated. **RESULTS:** Birth certificate data identified 4695 deliveries to women with past/present HCV infection during the study period. Linkage to ODRS revealed an additional 1778 deliveries to women with past/present infection, including 355 with confirmed viraemia during pregnancy. The prevalence of past/present HCV among pregnant women in Ohio rose from 0.82% in 2012 to 1.54% in 2015. **CONCLUSIONS:** Maternal HCV infection is under-recognized and increasing in prevalence. Current case identification processes are inadequate in pregnancy, even among women with prior positive HCV testing. Alternative approaches, including enhanced risk factor-based screening or universal prenatal screening in high prevalence settings, are needed to improve rates of HCV recognition among reproductive-aged women and newborns at risk of vertical transmission.

[Sustained Virologic Response and Costs Associated with Direct-Acting Antivirals for Chronic Hepatitis C Infection in Oklahoma Medicaid.](#) Pham TT1, Keast SL1, Farmer KC1, et al. J Manag Care Spec Pharm. 2018 Jul;24(7):664-676. doi: 10.18553/jmcp.2018.24.7.664.

**BACKGROUND:** Outcomes involving newer direct-acting antiviral (DAA) hepatitis C virus (HCV) regimens have not been studied extensively among the Medicaid population. **OBJECTIVE:** To assess clinical (treatment failure) and economic outcomes for chronic HCV-infected Oklahoma Medicaid members following treatment with DAAs and to measure associations with patient, treatment, and clinical characteristics. **METHODS:** This cross-sectional study used Oklahoma Medicaid pharmacy and medical claims data for adult members who used a newer DAA agent and had reported a successful or failed sustained virological response rate 12 weeks after therapy completion (SVR12) from January 1, 2014, to June 30, 2016. Multivariable logistic and gamma regressions assessed predictors of SVR12 failure and costs controlling for member demographics (i.e., age, sex, race, rural residence); type of DAA and adherence; clinical characteristics (e.g., comorbid conditions, advanced liver disease); and the implementation of changes to a prior authorization program. **RESULTS:** Of 934 Medicaid members eligible for treatment with DAAs between January 1, 2014, and June 30, 2016, 906 received DAA treatment, 40.6% (368/906) had reported SVR12 outcomes, and 59.4% (n = 538)

did not have a reported SVR recorded. Of those with reported SVR12 outcomes, patients were  $53.1 \pm 9.7$  years of age, 51.1% were male, 8.4% had SVR12 failure, and each member had mean costs of  $\$140,283 \pm \$52,779$ . Multivariable analyses indicated higher odds of SVR12 failure was independently associated with cirrhosis (OR [decompensated] = 6.69 and OR [compensated] = 3.52,  $P < 0.001$ ), while males had higher odds of failure than females (OR = 3.34,  $P < 0.010$ ). No significant difference in SVR12 failure was noted, according to DAA type or a medication adherence threshold of  $> 95\%$ . Ledipasvir/sofosbuvir was independently associated with lower costs ( $\exp[b] = 0.81$ ;  $P < 0.001$ ) compared with sofosbuvir, while higher costs were associated with decompensated cirrhosis ( $\exp[b] = 1.22$ ;  $P < 0.001$ ) and treatment failure ( $\exp[b] = 1.18$ ,  $P < 0.010$ ). In an analysis including members without reported SVR12 outcomes, decompensated and compensated cirrhosis had lower odds ( $P < 0.001$ ) of no reported SVR12 from ambulatory clinic settings. **CONCLUSIONS:** Almost 60% of Medicaid members receiving DAA treatment did not have a final reported SVR12 outcome. Among those with viral load measurements, treatment success was high and both decompensated and compensated cirrhosis were independently associated with significantly higher odds of treatment failure. Addressing a loss to follow-up among HCV patients and curtailing the development of cirrhosis to improve treatment success may warrant interventions that improve access to care and remove barriers that impede treatment initiation and completion. **DISCLOSURES:** No outside funding supported this study. Pham, Keast, Holderread, Nesser, and Skrepnek disclose either employment by the Oklahoma Health Care Authority or contractual work for this employer. Pham discloses fellowship funding from Purdue Pharma unrelated to this study. Keast and Skrepnek disclose research grant funding from Gilead Sciences and Abbvie. Holderread also reports grant funding from Gilead Sciences and fees from PRIME Education. Thompson, Farmer, and Rathbun have nothing to disclose.

### [Effectiveness of Ledipasvir/Sofosbuvir and Predictors of Treatment Failure in Members with Hepatitis C Genotype 1 Infection: A Retrospective Cohort Study in a Medicaid](#)

[Population](#). Kouris G1, Hyderey T1, Greenwood BC1, Lavitas P1, Price M1, Clements K2, Alper CJ1, Lenz K2, Jeffrey PL2. *J Manag Care Spec Pharm*. 2018 Jul;24(7):591-597. doi: 10.18553/jmcp.2018.24.7.591.

**BACKGROUND:** The primary goal of therapy for patients with chronic hepatitis C virus (HCV) infection is eradication of HCV ribonucleic acid, which is predicted by achievement of sustained virologic response at 12 weeks (SVR12). Ledipasvir/sofosbuvir was approved by the FDA in 2014 and 2015 as a once-daily regimen for the treatment of HCV genotype 1 and HCV genotypes 4, 5, and 6, respectively. Although its efficacy has been demonstrated in randomized controlled trials, there is an unmet need for real-world effectiveness data and studies that assess the association of rates of SVR12 with specific clinical and demographic factors in the Medicaid population. **OBJECTIVES:** To (a) evaluate the effectiveness of HCV genotype 1 treatment with ledipasvir/sofosbuvir as measured by the rate of SVR12 overall and within the subgroups of 8-, 12-, and 24-week regimens and (b) identify predictors of treatment failure in the Massachusetts Medicaid (MassHealth) population. **METHODS:** This retrospective cohort study evaluated the rate of SVR12 among 796 MassHealth Primary Care Clinician and fee-for-service plan members who completed treatment with at least one 8-, 12-, or 24-week treatment with ledipasvir/sofosbuvir for HCV genotype 1 infection between October 10, 2014, and November 1, 2016. The following variables were evaluated to identify predictors of treatment failure: sex, history of treatment failure, cirrhosis, substance use disorder, human immunodeficiency virus coinfection, and concomitant use of interacting medications. The proportion of members who achieved

SVR12 was calculated for the entire study population and stratified by treatment regimen. Chi-square tests were used to compare the proportion of members who achieved SVR12, stratified by clinical and demographic variables. **RESULTS:** SVR12 was achieved in 95% (756/796) of members. High proportions of members who received 8 weeks of treatment or 12 weeks of treatment without concomitant ribavirin achieved SVR12 (96.0% [285/297] and 95.7% [382/399], respectively). A slightly lower proportion of members who received 12 weeks of treatment with concomitant ribavirin or 24 weeks of treatment achieved SVR12 (89.9% [62/69] and 87.1% [27/31], respectively). The proportion of members who achieved SVR12 with each treatment regimen was consistent when stratified by clinical and demographic variables. None of the included variables were found to be associated with statistically significant differences in odds of treatment failure. **CONCLUSIONS:** In the Medicaid population of 1 state, treatment of HCV genotype 1 infection with ledipasvir/sofosbuvir was associated with a high rate of SVR12. The outcomes of treatment of HCV genotype 1 infection with ledipasvir/sofosbuvir in the Medicaid population are comparable with outcomes observed in other patient populations. **DISCLOSURES:** No outside funding supported this study. The authors have no financial disclosures. A poster of this manuscript was presented at the Academy of Managed Care Pharmacy 2017 Annual Meeting, March 27-30, 2017, in Denver, Colorado.

[Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs.](#) Grebely J1, Larney S2, Peacock A1, et al. *Addiction*. 2018 Jul 23. doi: 10.1111/add.14393. [Epub ahead of print]

**BACKGROUND AND AIMS:** People who have recently injected drugs are a priority population in efforts to achieve hepatitis C virus (HCV) elimination. This study estimated the prevalence and number of people with recent injecting drug use living with HCV, and the proportion of people with recent injecting drug use among all people living with HCV infection at global, regional, and country-levels. **METHODS:** Data from a global systematic review of injecting drug use and HCV antibody prevalence among people with recent (previous year) injecting drug use were used to estimate the prevalence and number of people with recent injecting drug use living with HCV. These data were combined with a systematic review of global HCV prevalence to estimate the proportion of people with recent injecting drug use among all people living with HCV. **RESULTS:** There are an estimated 6.1 million [95% uncertainty interval (UI) 3.4-9.2] people with recent injecting drug use aged 15-64 years living with HCV globally (39.2% viraemic prevalence; UI 31.6-47.0), with the greatest numbers in East and Southeast Asia (1.5 million, UI 1.0-2.1), Eastern Europe (1.5 million, UI 0.7-2.4), and North America (1.0 million, UI 0.4-1.7). People with recent injecting drug use comprise an estimated 8.5% (UI 4.6-13.1) of all HCV infections globally, with the greatest proportions in North America (30.5%, UI 11.7-56.7), Latin America (22.0%, UI 15.3-30.4), and Eastern Europe (17.9%, UI 8.2-30.9). **CONCLUSIONS:** Although globally about forty percent of people with recent injecting drug use are living with hepatitis C virus (HCV) and almost nine percent of all HCV infections globally occur among people with recent injecting drug use, there is wide variation among countries and regions. **FUNDING:** National Drug and Alcohol Research Centre, UNSW Sydney; Australian National Health and Medical Research Council; John C Martin Foundation.

[Assessment of the effect of an enhanced prior authorization and management program in a United States Medicaid program on chronic hepatitis C treatment adherence and cost.](#)

Keast SL, Holderread B, Cothran T, Skrepnek GH. J Am Pharm Assoc (2003). 2018 Jul 19. pii: S1544-3191(18)30250-4. doi: 10.1016/j.japh.2018.06.013. [Epub ahead of print]

**OBJECTIVES:** The market for chronic hepatitis C (HCV) treatment has changed rapidly. New treatments offer high cure rates, fewer adverse effects, and shorter treatments-but also increased costs per therapy. The objective of this study was to compare adherence and cost between HCV patients included in an enhanced prior authorization and management program (PAMP) versus no intervention in Medicaid members undergoing treatment. **DESIGN:** A retrospective study using longitudinal panel data assessed differences in adherence and costs associated with implementation of the PAMP from the payer perspective. The PAMP included case management, patient education, pharmacy counseling, and medication adherence. Multivariable generalized estimating equations were used to assess associations between program and outcomes. **SETTING AND PARTICIPANTS:** Patients with HCV enrolled in a state Medicaid program receiving or requesting HCV treatment from January 2014 to November 2015. **OUTCOME MEASURES:** Outcomes included medication adherence, treatment gaps, and pharmacy and total direct costs after controlling for demographic and clinical factors between those in the PAMP and those in the preintervention period. **RESULTS:** There were 384 Medicaid members included (156 pre-PAMP, 228 post-PAMP). Overall adherence was high regardless of PAMP intervention, although an adjusted 1.086-fold increase in medication possession ratio (MPR) was observed with the program and a 2.732-fold higher odds of adherence above 80% ( $P < 0.05$ ). Members in the program had 0.358 times lower adjusted odds of a greater than 3-day treatment gap, and pharmacy-related costs were 0.940 times lower ( $P < 0.05$ ); no difference was observed in total medical costs ( $P = 0.333$ ). **CONCLUSION:** This enhanced Medicaid program was associated with increased adherence to HCV therapy, decreased treatment gaps, and decreased pharmacy-related costs compared with the preintervention period. Because challenges exist if patients fail HCV treatment or if viral resistance emerges, ensuring high adherence and persistence remains key. Continued work is needed to develop and assess enhanced management programs for this population.

**[The Burden of Untreated HCV Infection in Hospitalized Inmates: a Hospital Utilization and Cost Analysis.](#)** Wurcel AG<sup>1,2</sup>, Burke DJ<sup>3</sup>, Wang JJ<sup>4</sup>, Engle B<sup>5</sup>, Noonan K<sup>6</sup>, Knox TA<sup>5</sup>, Kim AY<sup>7</sup>, Linas BP<sup>4</sup>. J Urban Health. 2018 Jul 19. doi: 10.1007/s11524-018-0277-z. [Epub ahead of print]

Hepatitis C virus (HCV) is highly prevalent in incarcerated populations. The high cost of HCV therapy places a major burden on correctional system healthcare budgets, but the burden of untreated HCV is not known. We investigated the economic impact of HCV through comparison of length of stay (LOS), frequency of 30-day readmission, and costs of hospitalizations in inmates with and without HCV using a 2004-2014 administrative claims database. Inmates with HCV had longer LOS, higher frequency of 30-day readmission, and increased cost of hospitalizations. Costs were higher in inmates with HCV even without advanced liver disease and in inmates with HIV/HCV compared to HCV alone. We conclude that although HCV treatment may not avert all of the observed increases in hospitalization, modest reductions in hospital utilization with HCV cure could help offset treatment costs. Policy discussions on HCV treatment in corrections should be informed by the costs of untreated HCV infection.

**[Take Charge, Get Cured: The development and user testing of a culturally targeted mHealth decision tool on HCV treatment initiation for methadone patients.](#)** Bauerle Bass



S1, Jessop A2, Gashat M2, Maurer L3, Alhajji M3, Forry J3. Patient Educ Couns. 2018 Jul 20. pii: S0738-3991(18)30350-1. doi: 10.1016/j.pec.2018.07.007. [Epub ahead of print]

**OBJECTIVE:** This paper describes the development of a mobile health tool to facilitate Hepatitis C (HCV) treatment decision making in methadone patients. **METHODS:** Using an iterative, formative evaluation framework, we used commercial marketing techniques to create 3D maps of survey data to develop culturally relevant messaging that was concept tested. The resulting tool was then user tested and results were used to modify the tool. **RESULTS:** The "Take Charge, Get Cured" tool was developed with surveys (n = 100), perceptual mapping analysis, concept testing (n = 5), and user testing (n = 10). "Think aloud" sessions were audio recorded and surveys given. Patients thought the goal of the tool was to encourage treatment and it was aimed to the needs of methadone patients. Means of 6.7-7 (on a 7 point scale) were observed for survey items related to ease of use, content, and satisfaction. **CONCLUSION:** The iterative development was essential to ensuring a culturally targeted tool, specific to the needs of HCV + methadone patients. There was a high level of acceptance for the tool. **PRACTICE IMPLICATIONS:** Our study indicates that using a formative evaluation strategy is essential for development of highly targeted patient communication, especially in hard-to-reach populations.

[Prevalence and mapping of hepatitis C infections among men who have sex with men in New York City.](#) Tieu HV1,2, Laeyendecker O3,4, Nandi V5, et al. PLoS One. 2018 Jul 18;13(7):e0200269. doi: 10.1371/journal.pone.0200269. eCollection 2018.

Emerging sexually transmitted hepatitis C virus (HCV) epidemics among men who have sex with men (MSM) have been reported worldwide, with higher HCV infection rates among those who are HIV-infected. This study aims to determine prevalence of recent and chronic HCV infections among community-recruited MSM in New York City (NYC), map HCV infections by home, social, and sexual neighborhoods, and identify clusters of genetically linked HCV variants using phylogenetic analysis. The NYC M2M study recruited MSM via modified time-space, venue-based sampling and internet/mobile app-based recruitment during 2010-13. Participants completed a Google Earth map on neighborhoods of where they lived, socialized, and had sex in the last 3 months, an ACASI questionnaire, and a sexual network inventory about their sex partners. The men received HIV testing and provided serum samples. Testing on stored serum samples included HCV antibody and RNA viral load, HCV antibody avidity assay (avidity index <30% with positive viral load is considered recently infected), and HCV RNA extraction and amplification to generate a 432 base-pair region of Core/E1 for sequencing and phylogenetic analysis. Historic local controls were included in the phylogenetic analysis. Of 1,028 MSM, 79.7% were HIV-negative and 20.3% HIV-positive. Twenty nine MSM (2.8%) were HCV antibody-positive. MSM who were HCV antibody-positive reported a median of 2 male sex partners in last 3 months, with 6.9% aged 18-24, 17.2% 25-29, 13.8% 30-39, and 62.1% 40 and over. 8.1% of HIV-positive MSM were HCV antibody-positive vs. 1.5% of HIV-negative men (p<0.0001). Of 29 HCV-antibody positive MSM, 12 (41%) were HCV RNA-positive (11 subtype 1a and 1 subtype 1b). Two of 12 HCV RNA-positive participants had low antibody avidity values, suggesting recent HCV infection. HCV antibody seropositivity was significantly associated with older age >40 years, adjusted odds ratio (aOR) 3.56 (95% CI 1.57, 8.08), HIV-positive serostatus, aOR 3.18 (95% CI 1.40, 7.22), any sexually transmitted infection (STI) in the last 3 months, aOR 2.81 (95% CI 1.11, 7.13), and injection drug use (IDU) ever, aOR 4.34 (95% CI 1.69, 11.17). Mapping of HCV infections differed slightly by home, social, and sexual

neighborhoods. Based on phylogenetic analysis from 12 HCV RNA-positive samples, no evidence of a clustered HCV epidemic was found. Overall HCV seroprevalence was 2.8% among community-recruited MSM in NYC, with higher prevalence among HIV-positive MSM compared to HIV-negative MSM. Only two participants were found to have recent HCV infection, with no evidence of a clustered HCV epidemic based on phylogenetic analysis. Our results support testing of HCV infection among HIV-negative MSM if they report having a recent STI and IDU in the past rather than universal HCV testing in all HIV-negative MSM.

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## HEPATOCELLULAR (LIVER) CANCER

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**[Oncoprotein Stathmin Modulates Sensitivity to Apoptosis in Hepatocellular Carcinoma Cells During Hepatitis C Viral Replication.](#)** Lu NT1,2, Liu NM1, Patel D1, et al. *J Cell Death.* 2018 Jul 4;11:1179066018785141. doi: 10.1177/1179066018785141. eCollection 2018. Patients with chronic hepatitis C virus (HCV) infection risk complications of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Previously, our proteomic examination of hepatocytes carrying a HCV-replicon revealed that deregulation of cytoskeletal dynamics may be a potential mechanism of viral-induced HCC growth. Here, we demonstrate the effect of HCV replication on the microtubule regulator stathmin (STMN1) in HCC cells. We further explore how the altered activity or synthesis of stathmin affects cellular proliferation and sensitivity to apoptosis in control HCC cells (Huh7.5) and experimental HCV-replicon harboring HCC cells (R-Huh7.5). The HCV-replicon harboring HCC cells (R-Huh 7.5) lack viral structural genes/proteins for acute infectivity and thus is the standard model for in vitro chronic infection study. Knockdown of endogenous stathmin reduced sensitivity to apoptosis in replicon cells. Meanwhile, constitutively active stathmin increased sensitivity to apoptosis in replicon cells. In addition, overexpression of constitutively active stathmin reduced cell proliferation in both control and replicon cells. These findings implicate, for the first time, a novel role for stathmin in viral replication-related apoptosis. Stathmin's potential role in HCV replication and HCC make it a candidate for the future study of viral-induced malignancies.

**[Changing Trends in Etiology- and Ethnicity-Based Annual Mortality Rates of Cirrhosis and Hepatocellular Carcinoma in the United States.](#)** Kim D1, Li AA2, Perumpail BJ3, et al. *Hepatology.* 2018 Jul 16. doi: 10.1002/hep.30161. [Epub ahead of print] With recent improvements in the treatment of end-stage liver disease (ESLD), a better understanding of the burden of cirrhosis and hepatocellular carcinoma (HCC) is needed in the United States (US). A population-based study using the US Census and national mortality database was performed. We identified the age-standardized etiology-specific mortality rates for cirrhosis and HCC among US adults aged  $\geq 20$  years from 2007 to 2016. We determined temporal mortality rate patterns by joinpoint analysis with estimates of annual percentage change (APC). Age-standardized cirrhosis-related mortality rates increased from 19.77/100,000 persons in 2007 to 23.67 in 2016 with an annual increase of 2.3% (95% CI 2.0-2.7). The APC in mortality rates for hepatitis C virus (HCV)-cirrhosis shifted from a 2.9% increase per year during 2007-2014 to a 6.5% decline per year during 2014-2016. Meanwhile, mortality for cirrhosis from alcoholic liver disease (ALD, APC 4.5%) and nonalcoholic fatty liver disease (NAFLD, APC 15.4%) increased over the same period, while mortality for hepatitis B virus (HBV)-cirrhosis decreased with an average APC of -1.1%. HCC-related mortality increased from 3.48/100,000 persons in 2007 to 4.41 in 2016 at an annual rate of 2.0% (95% CI 1.3-2.6). Etiology-specific

mortality rates of HCC were largely consistent with cirrhosis-related mortality. Minority populations had a higher burden of HCC-related mortality. **CONCLUSION:** Cirrhosis- and HCC-related mortality rates increased between 2007 and 2016 in the US. However, mortality rates in HCV-cirrhosis demonstrated a significant decline from 2014-2016, during the direct-acting antiviral era. Mortality rates for ALD/NAFLD-cirrhosis and HCC have continued to increase, while HBV-cirrhosis-related mortality declined during the 10-year period. Importantly, minorities had a disproportionately higher burden of ESLD-related mortality. This article is protected by copyright. All rights reserved.

**[Antiviral Therapy in Patients With Chronic Hepatitis C-related Hepatocellular Carcinoma Responding to Palliative Treatment.](#)** Yu JH1, Kim JK, Lee KS, Lee JI. *J Clin Gastroenterol.* 2018 Jul;52(6):557-562. doi: 10.1097/MCG.0000000000000923.

2018 Jul;52(6):557-562. doi: 10.1097/MCG.0000000000000923.

**BACKGROUND/AIM:** Advances in hepatitis C virus (HCV) treatment offer high sustained virologic response rates with minimal side-effects. However, benefits of eradicating HCV in hepatocellular carcinoma (HCC) patients whose life expectancies are hard to be determined after palliative therapy still needs to be assessed. This study sought to evaluate prognostic factors for survival in HCV-related HCC patients that responded to the palliative HCC treatment to speculate whether treating HCV would be beneficial in these patients. **MATERIALS AND METHODS:** In this retrospective cohort study, the medical records of 97 patients that showed complete or partial response to the initial HCC treatment were included. **RESULTS:** Receiving HCV treatment [hazard ratio (HR), 0.244; 95% confidence interval (CI), 0.075-0.788; P=0.018] increased the survival, whereas partial response to the initial HCC treatment (HR, 1.795; 95% CI, 1.071-3.008; P=0.026) and increased Child-Turcotte-Pugh score (HR, 2.017; 95% CI, 1.196-3.403; P=0.009) reduced the survival. From 97 patients, 16 patients were eventually treated for HCV. The mean time from the last HCC therapy to HCV treatment was 16.9±13.9 months. The median time of follow-up after HCV treatment was 10.0 months (range, 3 to 47 mo). Among the HCV-treated patients 3 patients had HCC recurred. The time to progression in HCV-treated patients were significantly longer than those untreated for HCV (P=0.032). **CONCLUSIONS:** Although treating HCV in HCC patient that undergo noncurative HCC treatment is still debatable, this study results carefully suggest that HCV-related HCC patients that responded to the initial HCC palliative treatment might benefit from HCV treatment.

**[Impact of immigration in presentation and outcomes of hepatocellular carcinoma in the USA.](#)** Ashhab AA1, Rodin H2, Powell J1, Debes JD1,3. *Eur J Gastroenterol Hepatol.* 2018 Jul 18. doi: 10.1097/MEG.0000000000001212. [Epub ahead of print]

**BACKGROUND AND AIMS:** Hepatocellular carcinoma's (HCC) epidemiology and prognosis differs among regions across the globe, largely because of environmental factors and underlying liver disease. Little is known about the changes led by immigration and the effect on HCC outcome. We aimed to understand the effect of immigration on HCC. **PATIENTS AND METHODS:** A retrospective cohort study of patients diagnosed with HCC was carried out in a tertiary center in the USA between 2005 and 2016. We characterized individuals as US born or having immigrated there after being born elsewhere. Variables related to clinical presentation, surveillance, therapy, and survival were evaluated. **RESULTS:** A total of 232 HCC cases were included, 169 US born (73%) and 63 immigrants (27%). Both groups were diagnosed with HCC at similar ages (60 vs. 62 years, P=0.13). Hepatitis C was the most common underlying liver

disease in the US-born population compared with the immigrant population (83 vs. 52%,  $P < 0.001$ ), whereas hepatitis B was more common in the latter (4 vs. 29%,  $P < 0.001$ ). Interestingly, hepatitis B virus-related HCC was diagnosed at similar ages in US-born and immigrant individuals (59 and 57 years). At the time of diagnosis, both populations had similar tumor sizes, rates of metastasis, and diagnosis during surveillance. One-year survival was similar in both groups (65 vs. 63%). **CONCLUSION:** Immigrants that develop HCC have different underlying liver disease than those born in the USA, but similar HCC characteristics and outcomes, even when including hepatitis B virus-related HCCs. Our study, albeit small, suggests that changes in the environment by immigration leads to clinical adaptation of HCC.

### **Serum biomarkers for diagnosis and monitoring viral hepatitis and hepatocellular**

**carcinoma.** Kotha S1, Neong S1, Patel K1. *Expert Rev Mol Diagn.* 2018 Jul 18;1-10. doi: 10.1080/14737159.2018.1496020. [Epub ahead of print]

Chronic liver disease due to viral hepatitis continues to be a major global health concern. Timely diagnosis and treatment will prevent cirrhosis, risk of hepatocellular carcinoma (HCC), and requirement for liver transplantation. Numerous serum biomarkers are available for viral hepatitis that are helpful in diagnosis, measuring severity, progression of disease, evaluating the best therapeutic options, and monitoring antiviral treatment response. Determining the clinical use of available diagnostic tests can be challenging for the health care provider. Areas covered: This review article attempts to summarize the established and emerging serological markers for diagnosis and managing viral hepatitis. The literature search was performed in February 2018 and included MEDLINE and Embase databases for recent relevant literature on biomarkers for viral hepatitis. Expert Commentary: Despite the discovery of several candidate biomarkers, translating these to clinical practice in viral hepatitis and HCC remains challenging. While limited availability of the new biomarkers in prevalent geographic areas and significant cost remain major obstacles, there have been exciting developments in this field. Understanding the detection limits and sensitivity of these markers and translating them into clinical use is important in management of viral hepatitis and complications of liver disease such as cirrhosis and hepatocellular cancer.

### **Obesity and recurrence-free survival in patients with hepatocellular carcinoma after achieving sustained virological response to interferon therapy for chronic hepatitis C.**

Shinkawa H1, Tanaka S1, Takemura S1, Ito T1, Aota T1, Koda M1, Miyazaki T1, Yamamoto T2, Kubo S1. *Ann Gastroenterol Surg.* 2018 Jun 22;2(4):319-326. doi: 10.1002/ags3.12183. eCollection 2018 Jul.

**AIM:** Some patients who achieve a sustained virological response (SVR) to interferon (IFN) treatment for chronic hepatitis C prior to hepatic resection for hepatocellular carcinoma (HCC) experience postoperative recurrence. This study investigated the relationship between obesity and postoperative HCC recurrence in SVR patients. **METHODS:** Fifty-nine patients who had achieved SVR before hepatic resection were evaluated. Patients had a solitary tumor  $\leq 5$  cm in diameter or  $\leq 3$  lesions each  $\leq 3$  cm in size with no macroscopic vascular invasion (Milan criteria). Patient characteristics potentially associated with recurrence risk were investigated. **RESULTS:** Three-, 5-, and 7-year recurrence-free survival after surgery were 65%, 44%, and 41%, respectively. Univariate analysis showed that obesity ( $P < .01$ ), hypertension ( $P = .038$ ), and non-anatomical resection ( $P = .022$ ) were significantly associated with a lower recurrence-free survival rate. In a multivariate analysis, obesity (hazard ratio, 2.8; 95% confidence interval

[CI] 1.3-6.1;  $P < .01$ ) and non-anatomical resection (hazard ratio, 2.7; 95% CI 1.1-6.2;  $P = .025$ ) were independently associated with postoperative recurrence. Three-, 5-, and 7-year overall survival rates after surgery were 100%, 80%, and 64% in obese patients and 100%, 92%, and 82% in non-obese patients, respectively ( $P = .014$ ). However, other variables showed no significant difference in the overall survival rate. **CONCLUSIONS:** Obesity and non-anatomical resection were independent risk factors for HCC recurrence after hepatic resection and successful IFN therapy. Obesity is an important clinical problem to consider to improve postoperative outcomes in such patients.

[Effect of Hepatocellular Carcinoma on Mortality Among Individuals With Hepatitis B or Hepatitis C Infection in New York City, 2001-2012.](#) Moore MS1, Bocour A1, Tran OC2, Qiao B3, Schymura MJ3, Laraque F4, Winters A4. Open Forum Infect Dis. 2018 Jun 16;5(7):ofy144. doi: 10.1093/ofid/ofy144. eCollection 2018 Jul.

**BACKGROUND:** Hepatocellular carcinoma (HCC) is a complication of chronic hepatitis B and C virus (HBV and HCV) infection. New York City (NYC) has a high prevalence of HBV and HCV, and infected persons likely face increased mortality from HCC and other causes. We describe the mortality profile of NYC residents with HBV or HCV, emphasizing the contributions of HCC and HIV coinfection. **METHODS:** Two existing data sets were combined to examine all individuals diagnosed with HBV or HCV in NYC first reported to the Health Department during 2001-2012 and their HCC, HIV, and vital status. Logistic regression was used to calculate the odds of HCC diagnosis by viral hepatitis status, whereas Cox proportional hazard regression was used to estimate the hazard of death by HCC/HIV status. **RESULTS:** In total, 120 952 and 127 933 individuals were diagnosed with HBV or HCV, respectively. HCV-infected individuals had 17% higher odds of HCC diagnosis than HBV-infected individuals and 3.2 times higher odds of HIV coinfection. Those with HCV were twice as likely to die during the study period (adjusted hazard ratio, 2.04; 95% confidence interval, 1.96-2.12). The risk of death increased for those with HIV or HCC and was highest for those with both conditions. **CONCLUSIONS:** HCC and HIV represent substantial risks to survival for both HBV- and HCV-infected individuals. Individuals with HBV need close monitoring and treatment, when indicated, and routine HCC screening. Those with HCV need increased, timely access to curative medications before developing liver disease.

[Estimating the impact of early hepatitis C virus clearance on hepatocellular carcinoma risk.](#) Darvishian M1,2, Janjua NZ1,2, Chong M1, et al. J Viral Hepat. 2018 Jul 26. doi: 10.1111/jvh.12977. [Epub ahead of print]

Although achieving sustained virological response (SVR) through anti-viral therapy could reduce the risk of hepatocellular carcinoma (HCC) attributable to hepatitis C virus (HCV) infection, the impact of early viral clearance on HCC is not well defined. In this study we compared the risk of HCC among individuals who spontaneously cleared HCV (SC), the referent population, with the risk in untreated chronic HCV (UCHC), those achieved SVR, and those who failed interferon-based treatment (TF). The BC Hepatitis Testers Cohort (BC-HTC) includes individuals tested for HCV between 1990-2013, integrated with medical visits, hospitalizations, cancers, prescription drugs and mortality data. This analysis included all HCV positive patients with at least one valid HCV RNA by PCR on or after HCV diagnosis. Of 46,666 HCV infected individuals, there were 12,527 (26.8%) SC; 24,794 (53.1%) UCHC; 5,355 (11.5%) SVR and 3,990 (8.5%) TF. HCC incidence was lowest (0.3/1000 person-years (PY)) in the SC group and highest in the TF group

(7.7/1000 PY). In a multivariable model, compared to SC, TF had the highest HCC risk (hazard ratio (HR):14.52, 95% confidence interval (CI): 9.83-21.47), followed by UCHC (HR: 5.85; 95% CI: 4.07-8.41). Earlier treatment-based viral clearance similar to SC, could decrease HCC incidence by 69.4% (95%CI: 57.5-78.0), 30% (95%CI: 10.8-45.1), and 77.5% (95% CI: 69.4-83.5) among UCHC, SVR, and TF patients, respectively. In conclusion, using SC as a real-world comparator group, it showed that substantial reduction in HCC risk could be achieved with earlier treatment initiation. These data should be replicated among treated patients with direct acting antiviral therapies. This article is protected by copyright. All rights reserved.

### **Past history of hepatocellular carcinoma is an independent risk factor of treatment failure in patients with chronic hepatitis C virus infection receiving direct-acting antivirals.**

Sugiura A1, Joshita S1,2, Umemura T1,2, et al. J Viral Hepat. 2018 Jul 25. doi: 10.1111/jvh.12973. [Epub ahead of print]

Direct-acting antiviral (DAA) treatment can achieve a high sustained virological response (SVR) rate in patients with hepatitis C virus (HCV) infection regardless of a history of hepatocellular carcinoma (HCC [+]). We examined 838 patients (370 men, median age: 69 years) who were treated with DAAs for comparisons of clinical findings between 79 HCC (+) (9.4%) and 759 HCC (-) (90.6%) patients and associations with treatment outcome. Male frequency was significantly higher in the HCC (+) group (60.8% vs. 42.4%,  $p = 0.006$ ). There were significant differences between the HCC (+) and HCC (-) groups for platelet count (115 vs. 152  $\times 10^9$  /L,  $p < 0.001$ ), baseline AFP (9.9 vs. 4.5 ng/ml,  $p < 0.001$ ), and the established fibrosis markers of FIB-4 index (4.7 vs. 3.0,  $p < 0.001$ ), APRI (1.1 vs. 0.7,  $p = 0.009$ ), M2BPGi (3.80 vs. 1.78 COI,  $p < 0.001$ ), and autotaxin (1.91 vs. 1.50 mg/L,  $p < 0.001$ ). The overall SVR rate was 94.7% and significantly lower in the HCC (+) group (87.3 vs. 95.5%,  $p = 0.001$ ). Multivariate analysis revealed that a history of HCC was independently associated with DAA treatment failure (odds ratio: 3.56, 95% confidence interval: 1.32-9.57,  $p = 0.01$ ). In conclusion, patients with chronic HCV infection and prior HCC tended to exhibit more advanced disease progression at DAA commencement. HCC (+) status at the initiation of DAAs was significantly associated with adverse therapeutic outcomes. DAA treatment for HCV should therefore be started as early as possible, especially before complicating HCC. This article is protected by copyright. All rights reserved.

### **Impact of Anatomical Resection for Hepatocellular Carcinoma With Microportal Invasion (vp1): A Multi-institutional Study by the Kyushu Study Group of Liver Surgery.**

Hidaka M1,2, Eguchi S1,2, Okuda K1, et al. Ann Surg. 2018 Jul 24. doi: 10.1097/SLA.0000000000002981. [Epub ahead of print]

**OBJECTIVE:** The aim of the present study was to evaluate the value of anatomical resection for hepatocellular carcinoma (HCC) with microportal vascular invasion (vp1) between 2000 and 2010. **BACKGROUND:** Vascular invasion has been reported as a prognostic factor of liver resection for HCC. Anatomical resection for HCC has resulted in optimum outcomes of eradicating intrahepatic micrometastases through the portal vein, but opposite results have also been reported. **METHODS:** A clinical chart review was performed for 546 patients with HCC with vp1. We retrospectively evaluated the recurrence-free survival (RFS) between anatomical (AR) and nonanatomical resection (NAR). The site of recurrence was also compared between these groups. The influence of AR on the overall survival (OS) and RFS rates was analyzed in patients selected by propensity score matching, and the prognostic factors were identified.

**RESULTS:** A total of 546 patients were enrolled, including 422 in the AR group and 124 in the NAR group. There was no difference in the 5-year OS and RFS rates between the 2 groups. Local recurrence was significantly more frequent in the NAR group than in the AR group. In a multivariate analysis, hepatitis C virus, serum protein induced by vitamin K absence II of 380mAU/mL or more, tumor diameter of 5 cm or more, and age of 70 years or older were significant predictors of a poor RFS after liver resection. There were no significant differences in the OS or RFS between the AR and NAR groups by a propensity score-matched analysis.

**CONCLUSIONS:** Although local recurrence around the resection site was suppressed by AR, AR for HCC with vp1 did not influence the RFS or OS rates after hepatectomy in the modern era.