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

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**[Increasing Access to Hepatitis C Virus Medications: A Program Model Using Patient Navigators and Specialty Pharmacy to Obtain Prior Authorization Approval.](#)** Vu TM1, Toribio W1, Riazi F1, et al. J Manag Care Spec Pharm. 2018 Apr;24(4):329-333. doi: 10.18553/jmcp.2018.24.4.329.

**BACKGROUND:** Obtaining prior authorization (PA) approval for the new direct-acting antiviral (DAA) hepatitis C medications is time consuming and requires specific expertise. Our primary care-based program treats hepatitis C virus (HCV)-infected patients at an urban academic medical center and employs patient navigators trained in the PA process who collaborate with a nurse and specialty pharmacy to manage the PA process. **OBJECTIVE:** To demonstrate the rate of PA approvals for our programmatic model and determine potential predictors of PA approval. **METHODS:** We conducted a review of program databases and medical records of patients for whom DAA hepatitis C medications were ordered between November 1, 2014, and October 31, 2015 (n = 197). We first evaluated patient characteristics associated with the number of steps to approval. Then we used a multivariable ordinal regression to determine independent predictors of fewer steps to approval. Using Kaplan-Meier methods, we assessed patient characteristics associated with approval time and then fit a multivariable Cox regression model to determine independent predictors of time to approval. **RESULTS:** Of the 197 patients, 69% (n = 136) had Medicaid; 12% (n = 24) had Medicare; 10% (n = 19) had both Medicaid and Medicare; 5% (n = 10) had private insurance; and 4% (n = 8) were uninsured. Ninety-three percent of the patients were eventually approved for HCV treatment. The steps in the PA cascade were approval on first submission (37%; mean days = 30.7; SD = 29.9); approval after internal appeal (45%; mean days = 66.8; SD = 70.5); approval after external appeal (11%; mean days = 124.7; SD = 60.2); and no approval obtained (7%). Unadjusted factors found to have a P value < 0.200 in relation to fewer steps in the PA cascade were older age, female gender, non-Medicaid insurance, comorbid hypertension, comorbid diabetes, being domiciled, and being nongenotype 2. After adjustment, non-Medicaid insurance and nongenotype 2 remained significant. In survival analysis, non-Medicaid insurance and mid-range fibrosis were associated with fewer days to PA approval. **CONCLUSIONS:** Our program obtained 93% of PA approvals for hepatitis C medications. Patient navigators collaborating with a nurse and specialty pharmacy as a program may improve the PA approval process, although further research with a control group is necessary.

**Results of a Hepatitis C Virus Screening Program of the 1945-1965 Birth Cohort in a Large Emergency Department in New Jersey.**

Cornett JK1, Bodiwala V1, Razuk V1, Shukla D1, Narayanan N1,2. Open Forum Infect Dis. 2018 Mar 26;5(4):ofy065. doi: 10.1093/ofid/ofy065. eCollection 2018 Apr.

**BACKGROUND:** Persons born between 1945 and 1965 account for an estimated 81% of those infected with hepatitis C virus (HCV) in the United States. However, up to 60% remain undiagnosed. Prior studies have reported HCV screening results from large urban emergency departments. **METHODS:** This is a retrospective cohort study of patients in the 1945-1965 birth cohort tested for HCV in a large emergency department (ED) in New Jersey from June 1, 2016, through December 31, 2016. The purpose was to report HCV antibody and viral load results of this testing program located in a small urban/suburban area and to analyze specific characteristics associated with positive results, such as race/ethnicity and insurance status. Descriptive statistics were performed, and, using a multivariate logistic regression model, adjusted odds ratios and 95% confidence intervals were calculated. **RESULTS:** A total of 3046 patients were screened: 55.8% were white, and 17.9% were black; 52.1% had private insurance, 33.4% Medicare, 3.9% Medicaid. One hundred ninety-two were antibody positive (6.3%). Of 167 with HCV viral load testing results, 43% had a positive viral load. On multivariate analysis, black race and Medicaid were independently associated with a positive HCV viral load. **CONCLUSIONS:** HCV antibody seropositivity was above 6% and twice as high as the Centers for Disease Control and Prevention estimated prevalence in this birth cohort. These results indicate that EDs outside of large urban cities are also important sites for routine HCV screening. Other findings of interest include 43% with chronic HCV infection and the persistent association between black race and positive HCV viral load even when adjusted for insurance status.

**Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection.**

Martinello M1,2, Bhagani S3, Gane E4, et al. J Viral Hepat. 2018 Apr 16. doi: 10.1111/jvh.12917. [Epub ahead of print] Paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for 12 weeks is approved for treatment of chronic HCV genotype 1 infection. This study assessed the efficacy of shortened duration paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for eight weeks among people with recent HCV infection. In this open-label single-arm trial conducted in Australia, England and New Zealand, adults with recent HCV (duration of infection <12 months) received paritaprevir/ritonavir/ombitasvir and dasabuvir (with weight-based ribavirin for genotype 1a and 1, no subtype) for eight weeks. The primary endpoint was sustained virologic response at 12 weeks post-treatment (SVR12) in the intention-to treat (ITT) population. Thirty people (median age 38 years, male 93%) commenced treatment (with ribavirin, 97%), of whom 77% (n=23) were HIV-positive, 93% (n=28) had genotype 1a infection and 53% (n=16) had ever injected drugs. Median maximum ALT in the preceding 12 months was 433 IU/L (IQR 321, 1012). Acute clinical hepatitis with ALT>10xULN was documented in 83% (n=25); one participant (3%) had jaundice. At baseline, median estimated duration of infection was 30 weeks (range 11, 51) and median HCV RNA was 5.7 log<sub>10</sub> IU/mL (range 2.7, 7.3). SVR12 was achieved in 97% (29/30; early discontinuation at week 2, n=1; per-protocol 100%, 29/29). No relapse or reinfection was observed. In conclusion, Paritaprevir/ritonavir/ombitasvir and dasabuvir (with ribavirin) for eight weeks was highly effective among HIV-positive and HIV-negative individuals with recent HCV infection. This

data supports the use of this shortened duration direct-acting antiviral regimen in this population. This article is protected by copyright. All rights reserved.

**Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir Regimen in the Treatment of Genotype 1 Chronic Hepatitis C Infection in Patients with Severe Renal Impairment and End-Stage Renal Disease: a Real-Life Cohort.**

Sperl J1, Kreidlova M2, Merta D3, Chmelova K1, Senkerikova R1, Frankova S1. *Kidney Blood Press Res.* 2018 Apr 13;43(2):594-605. doi: 10.1159/000488965. [Epub ahead of print]

**BACKGROUND/AIMS:** Chronic hepatitis C (HCV) virus infection reactivates under immunosuppressive drugs and therefore has a negative impact on long-term survival of kidney transplant recipients. Treatment-induced clearance of hepatitis C virus (HCV) in kidney transplant candidates prevents virus reactivation after transplantation.

Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir (PrOD) represents a highly effective treatment regimen for HCV genotype 1 (GT1), also suitable for patients with end-stage renal disease (ESRD). Serious drug-drug interactions may represent a limiting factor of this regimen. The aim of this retrospective study was to evaluate safety, efficacy and drug-drug interactions management associated with PrOD treatment in the Czech real-world cohort. **METHODS:**

Emphasizing concomitant medication adjustment, we described the treatment course with PrOD regimen in 23 patients (4 with CKD4 and 19 on maintenance haemodialysis) infected with HCV GT1 (21 GT1b, 2 GT1a), 18 males and 5 females with an average age of 53.7 years. Six patients had compensated liver cirrhosis and 3 of them were liver transplant recipients. **RESULTS:** All 23 patients completed the 12-week treatment and achieved sustained virological response 12 weeks after the treatment (SVR12 rate 100%). None of the patients presented with a significant decrease in haemoglobin level, white blood cell and platelet count during the treatment period. The most frequent adverse events were nausea, hypotension, diarrhoea, and hyperkalemia. Four patients presented with a serious adverse event unrelated to the antiviral drugs (salmonellosis, non-functional kidney graft rejection, early gastric cancer, renal cyst infection, initiation of haemodialysis). Concomitant medication had to be modified with the treatment initiation in 10 out of 23 (43.5%) patients (calcium channel blockers, ACE inhibitors, statins, diuretics, tacrolimus); four patients required further adjustment of antihypertensive drugs or tacrolimus dosage on-treatment. **CONCLUSION:** PrOD regimen demonstrated an excellent efficacy and good tolerability. Both prospective adjustment of concomitant medication and further on-treatment adjustment allowed for a safe treatment course.

**Elbasvir/grazoprevir in black adults with hepatitis C virus infection: a pooled analysis of phase 2/3 clinical trials.** Zamor PJ1, Vierling J2, Ghalib R3, et al. *Am J Gastroenterol.* 2018 Apr 26. doi: 10.1038/s41395-018-0053-4. [Epub ahead of print]

**OBJECTIVES:** Although direct-acting antiviral regimens have dramatically improved the treatment of hepatitis C virus (HCV) infection, there is some evidence that black race may be an independent predictor of treatment failure. We report a retrospective analysis of black participants receiving elbasvir/grazoprevir (EBR/GZR) in nine phase 2/3 clinical trials.

**METHODS:** Black participants with chronic HCV genotype 1 or 4 (GT1 or GT4) infection who received EBR 50 mg/GZR 100 mg once daily for 12 weeks, or in combination with ribavirin for 16 weeks, were included. The primary end point was sustained virologic response 12 weeks after completion of therapy (SVR12, HCV RNA < 15 IU/mL). **RESULTS:** Compared with nonblack participants (n = 1310), black participants (n = 332) were more likely to have chronic kidney

disease stage 4/5 (9.2% vs. 31.0%, respectively), while other comorbidities were similar between the groups. In black and nonblack participants receiving EBR/GZR for 12 weeks, SVR12 rates were 93.7% (282/301) and 94.2% (1072/1138) in those with GT1 infection, and 93.8% (15/16) and 94.6% (88/93) in those with GT4 infection. SVR12 was 100.0% (15/15) in black participants and 97.5% (77/79) in nonblack participants with GT1 infection receiving EBR/GZR plus ribavirin for 16 weeks. Rates of drug-related adverse events (AEs) were 30% vs. 36.6%, and serious AEs were 7.6% vs. 3.4% in black and nonblack participants, respectively.

**CONCLUSION:** EBR/GZR showed high efficacy in black participants with HCV GT1 or GT4 infection and was generally well tolerated, with a safety profile similar to that reported overall in phase 2/3 clinical trials. **DISCLOSURES:** The Respectful & Equitable Access to Comprehensive Healthcare (REACH) program receives funding from the Robin Hood Foundation and the New York State Department of Health AIDS Institute. Weiss receives grant support from Gilead Sciences and has served as a consultant for AbbVie and Gilead Sciences. Vu reports speaker fees from Peer View Institute. All other authors report no conflict of interest. Study design and concept were contributed by Chasan, Sigel, Vu, and Weiss. Riazi, Ciprian, Giardina, and Gibbs collected the data, which were interpreted by Toribio, Amory, Chasan, and Sigel. The manuscript was written by Vu and Weiss and revised by Parrella, Cambe, Camacho, and Vu. Research from this study was presented as an abstract poster on November 14, 2016, at the AASLD Liver Meeting in Boston, Massachusetts.

[Mental and physical health-related quality of life in patients with hepatitis C is related to baseline comorbidities and improves only marginally with hepatitis C cure.](#) Thuluvath PJ1,2, Savva Y3. Clin Transl Gastroenterol. 2018 Apr 25;9(4):149. doi: 10.1038/s41424-018-0016-5.

The objective of the study was to analyze the relationship between patient characteristics and the health-related quality of life (HRQoL) among patients with hepatitis C at the start of treatment, 2-12 weeks of treatment and  $\geq 3$  months post treatment using Short-Form 36 (SF-36). The eight domains and two composite scores of SF-36 were analyzed using 236 individuals. Compared to US general population norms, on average, the physical health scores were significantly lower for the studied hepatitis C population, while the differences related to mental health were between zero and small. For a physical health composite score, the treatment effect was between medium and large (0.70, 0.66, and 0.64 at the baseline and follow-ups), and for a mental health composite score it was close to zero. After controlling for demographic factors, the mixed-effects models demonstrated that HRQoL significantly improved only for general health during the treatment and vitality during post treatment. The strongest predictor of HRQoL at the two follow-up periods was HRQoL at baseline of the same domain. The ordinal logistic regressions showed that at the baseline, the strongest negative predictors of HRQoL in most of the domains were hypertension, diabetes, high BMI, high number of comorbidities including pulmonary comorbidities, low hemoglobin, and public health insurance. Considering that the improvement in HRQoL sustained after treatment only for a mental (vitality) domain, the main determinants of quality of life of the patients with hepatitis C were comorbidities.

[A pilot single arm observational study of sofosbuvir/ledipasvir \(200 + 45 mg\) in 6- to 12-year old children.](#) El-Shabrawi MHF1, Kamal NM1, El-Khayat HR2, Kamal EM3, AbdElgawad MMAH4, Yakoot M5. Aliment Pharmacol Ther. 2018 Apr 25. doi: 10.1111/apt.14677. [Epub ahead of print]

**BACKGROUND:** No available data on the use of sofosbuvir/ledipasvir combination in treatment of hepatitis C virus (HCV) infection in children 6- to 12- year old. **AIM:** To assess the safety and efficacy of sofosbuvir plus ledipasvir in children 6- to 12- year old with chronic HCV genotype 4 infection. **METHODS:** This is a pilot prospective single arm observational open-label multicentre study. A total of 20 consecutive eligible chronic HCV infected children, aged from 6- to 12- years were included in this study and treated with a fixed sofosbuvir/ledipasvir combination in half the adult dose (200/45 mg) once daily for 12 weeks. Laboratory tests including virological markers were measured at baseline, 2, 4, 8 and 12 weeks (end of treatment [EOT]), and 12 weeks after end of treatment for sustained virological response 12 (SVR12). **RESULTS:** The intention-to-treat (ITT) SVR12 rate was 19/20 (95%; 95% CI: 76.4%-99.1%). SVR12 was not assessed in one patient who was lost to follow-up after showing viral negativity at the EOT12. All the remaining 19 patients (100%, 95% CI: 83.18%-100%) who completed the full protocol and follow-up visits achieved SVR12 with normal liver, haematological, and renal function tests and no side effects or fatalities. **CONCLUSIONS:** This pilot study demonstrated that the fixed dose sofosbuvir/ledipasvir combination could be safe and effective treatment in children 6- to 12- years with chronic hepatitis C genotype 4 infection. Our pilot results might encourage larger and multicentre studies in this age group.  
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**[Baseline Intrahepatic and Peripheral Innate Immunity are Associated with Hepatitis C Virus Clearance During DAA Therapy.](#)** Alao H1, Cam M2, Keembiyehetty C3, et al.

Hepatology. 2018 Apr 27. doi: 10.1002/hep.29921. [Epub ahead of print]

**OBJECTIVE:** Hepatitis C virus (HCV) infection induces interferon-stimulated genes (ISGs) and downstream innate immune responses. This study investigated whether baseline and on-treatment differences in these responses predict response versus virological breakthrough during therapy with direct-acting antivirals (DAA). **METHODS:** Thirteen HCV genotype 1b-infected patients who had previously failed a course of peginterferon/ribavirin were re-treated with asunaprevir/daclatasvir for 24 weeks. After pre-treatment biopsy, patients were randomized to undergo a second biopsy at week 2 or 4 on-therapy. Microarray and NanoString analyses were performed on paired liver biopsies and analyzed using linear mixed models. As biomarkers for peripheral IFN responses, peripheral blood natural killer cells were assessed for pSTAT1 and TRAIL expression and degranulation. **RESULTS:** Nine (9/13, 69%) patients achieved sustained virological responses (SVR12) and four experienced virological breakthroughs between weeks 4-12. Patients who achieved SVR12 displayed higher ISG expression levels in baseline liver biopsies and a higher frequency of pSTAT1 and TRAIL-expressing, degranulating NK cells in baseline blood samples than those who experienced virological breakthrough. Comparing gene expression levels from baseline and on-therapy biopsies, 408 genes ( $\pm 1.2$  fold,  $p < 0.01$ ) were differentially expressed. Genes downregulated on treatment were predominantly ISGs. Downregulation of ISGs was rapid and correlated with HCV RNA suppression. **CONCLUSIONS:** An enhanced interferon signature is observed at baseline in liver and blood of patients who achieve SVR12 as compared to those who experience a virological breakthrough. The findings suggest innate immunity may contribute to clearance of HCV during DAA therapy by preventing the emergence of resistance-associated substitutions that lead to viral breakthrough during DAA therapy. This article is protected by copyright. All rights reserved.



**Antiviral Activity, Safety, and Tolerability of Multiple Ascending Doses of Elbasvir or Grazoprevir in Participants Infected With Hepatitis C Virus Genotype-1 or -3.**

Yeh WW1, Fraser IP2, Jumes P2, et al. Clin Ther. 2018 Apr 24. pii: S0149-2918(18)30094-8. doi: 10.1016/j.clinthera.2018.03.002. [Epub ahead of print]

**PURPOSE:** Elbasvir (MK-8742) and grazoprevir (MK-5172; Merck & Co, Inc, Kenilworth, New Jersey) are hepatitis C virus (HCV)-specific inhibitors of the nonstructural protein 5A phosphoprotein and the nonstructural protein 3/4A protease, respectively. The aims of these studies were to evaluate the antiviral activity and safety of different doses of elbasvir or grazoprevir each administered as monotherapy to participants infected with either HCV genotype (GT) 1 or GT3. **METHODS:** These 2 double-blind, randomized, placebo-controlled, sequential-panel, multiple ascending dose studies were conducted to assess the safety and pharmacodynamics of 5 days of once-daily elbasvir or 7 days of once-daily grazoprevir in adult male participants chronically infected with either HCV GT1 or GT3. **FINDINGS:** Oral administration of elbasvir or grazoprevir once daily exhibited potent antiviral activity in participants with chronic GT1 or GT3 HCV infections. HCV RNA levels declined rapidly (within 1 day for elbasvir and 2 days for grazoprevir). At 50 mg of elbasvir once daily, the mean maximum reductions in HCV RNA from baseline were 5.21, 4.17, and 3.12 log<sub>10</sub> IU/mL for GT1b-, GT1a-, and GT3-infected participants, respectively. At 100 mg of grazoprevir once daily, the mean maximum reductions in HCV RNA from baseline were 4.74 and 2.64 log<sub>10</sub> IU/mL for GT1- and GT3-infected participants. **IMPLICATIONS:** The results in the elbasvir monotherapy study showed that 10 to 50 mg of elbasvir was associated with a rapid decline in HCV viral load; the results in the grazoprevir monotherapy study suggest that doses of 50 mg of grazoprevir and higher are on the maximum response plateau of the dose-response curve for GT1-infected participants. The results of these proof-of-concept studies provided preliminary data for the selection of the dosages of elbasvir and grazoprevir to test in Phase II and III clinical studies. ClinicalTrials.gov identifiers: NCT00998985 (Protocol 5172-004) and NCT01532973 (Protocol 8742-002).

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

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**Insufficiency of DNA repair enzyme ATM promotes naive CD4 T-cell loss in chronic hepatitis C virus infection.** Zhao J1,2, Dang X1,2, Zhang P3, et al. Cell Discov. 2018 Apr 10;4:16. doi: 10.1038/s41421-018-0015-4. eCollection 2018.

T cells have a crucial role in viral clearance and vaccine response; however, the mechanisms regulating their responses to viral infections or vaccinations remain elusive. In this study, we investigated T-cell homeostasis, apoptosis, DNA damage, and repair machineries in a large cohort of subjects with hepatitis C virus (HCV) infection. We found that naive CD4 T cells in chronically HCV-infected individuals (HCV T cells) were significantly reduced compared with age-matched healthy subjects. In addition, HCV T cells were prone to apoptosis and DNA damage, as evidenced by increased 8-oxoguanine expression and  $\gamma$ H2AX/53BP1-formed DNA damage foci-hallmarks of DNA damage responses. Mechanistically, the activation of DNA repair enzyme ataxia telangiectasia mutated (ATM) was dampened in HCV T cells. ATM activation was also diminished in healthy T cells exposed to ATM inhibitor or to HCV (core protein) that inhibits the phosphoinositide 3 kinase pathway, mimicking the biological effects in HCV T cells. Importantly, ectopic expression of ATM was sufficient to repair the DNA damage, survival deficit, and cell dysfunctions in HCV T cells. Our results demonstrate that insufficient

DNA repair enzyme ATM leads to increased DNA damage and renders HCV T cells prone to apoptotic death, which contribute to the loss of naive T cells in HCV infection. Our study reveals a novel mechanism for T-cell dysregulation and viral persistence, providing a new strategy to improve immunotherapy and vaccine responses against human viral diseases.

**[Interleukin-7 Regulates T Follicular Helper Cell Function in Patients with Chronic Hepatitis C.](#)** Zhang ZH1, Jiang BC1, Liu XH2, Zhang MX3, Li ZS4, Zhu GZ1. *Viral Immunol.* 2018 Apr 19. doi: 10.1089/vim.2018.0010. [Epub ahead of print]

Signaling through interleukin (IL)-7 is essential and required for development, differentiation, proliferation, and homeostasis of T cells. However, the role of IL-7 in regulation of CD4<sup>+</sup> T cells in chronic viral infections was not fully elucidated. Thus, the aim of the current study was to investigate the immunomodulatory activity of IL-7 to T follicular helper (Tfh) cells and its contribution to pathogenesis of chronic HCV, hepatitis C virus (HCV) infection. A total of 47 patients with chronic hepatitis C and 19 normal controls were enrolled. Serum IL-7 and proportion of Tfh cells was measured. The regulatory function of IL-7 to Tfh cells was also investigated in CD4<sup>+</sup> T cells and CD4<sup>+</sup> T/HCVcc-infected Huh7.5 cell cocultured system. Serum IL-7 concentration was significantly downregulated in patients with chronic hepatitis C, and was negatively correlated with HCV RNA level. Tfh frequency and Tfh-associated cytokines (IL-21 and IL-6) were also reduced in chronic HCV-infected patients. Moreover, recombinant IL-7 stimulation elevated proportion of Tfh cells and IL-21/IL-6 secretion in both HCV-specific and nonspecific manners. Furthermore, IL-7-treated CD4<sup>+</sup> T cells exhibited elevated antiviral activities without killing infected hepatocytes, which presented as inhibition of HCV RNA, induction of antiviral proteins, and promotion of cytokine production (especially IL-21) in cocultured system. This process might be dependent on IL-6 secretion. The current data revealed that IL-7 regulated HCV-specific and nonspecific activated Tfh cells, which might contribute to viral clearance. IL-7 could be a potential therapeutic agent for the treatment of chronic hepatitis C.

**[Sofosbuvir and Ribavirin Liver Pharmacokinetics in Patients Infected with Hepatitis C Virus.](#)** Babusis D1, Curry MP2, Kirby B1, et al. *Antimicrob Agents Chemother.* 2018 Apr 26;62(5). pii: e02587-17. doi: 10.1128/AAC.02587-17. Print 2018 May.

Sofosbuvir and ribavirin exert their anti-hepatitis C virus (anti-HCV) activity following metabolic activation in the liver. However, intrahepatic concentrations of the pharmacologically active nucleotide metabolites in humans are poorly characterized due to the inaccessibility of tissue and technical challenges with measuring nucleotide levels. A clinical study assessing the efficacy of sofosbuvir and ribavirin administered prior to liver transplantation to prevent HCV recurrence provided a unique opportunity to quantify nucleotide concentrations in human liver. We analyzed nucleotides using high-performance liquid chromatography coupled to tandem mass spectrometry in liver tissue from 30 HCV-infected patients with hepatocellular carcinoma who were administered sofosbuvir (400 mg/day) and ribavirin (1,000 to 1,200 mg/day) for 3 to 52 weeks prior to liver transplantation. Median total hepatic metabolite concentrations (the sum of nucleoside and mono-, di-, and triphosphates) were 77.1  $\mu$ M for sofosbuvir and 361  $\mu$ M for ribavirin in patients on therapy at the time of transplantation. Ribavirin and sofosbuvir efficiently loaded the liver, with total hepatic metabolite concentrations exceeding maximal levels in plasma by approximately 30-fold. Ribavirin metabolite levels suggest that its monophosphate is in great excess of its inhibition constant for IMP dehydrogenase and that its triphosphate is approaching

the binding constant for incorporation by the HCV NS5B RNA-dependent RNA polymerase. In accordance with the potent antiviral activity of sofosbuvir, these results demonstrate that the liver triphosphate levels achieved following sofosbuvir administration greatly exceed the inhibition constant for HCV NS5B. In conclusion, this study expands the quantitative understanding of the pharmacology of sofosbuvir and ribavirin by establishing efficient hepatic delivery in the clinic. (This study has been registered at ClinicalTrials.gov under identifier

### **Induction of Genotype Cross-Reactive, Hepatitis C Virus-Specific, Cell-Mediated**

**Immunity in DNA-Vaccinated Mice.** Wijesundara DK#1, Gummow J#1, Li Y1, et al. J Virol. 2018 Mar 28;92(8). pii: e02133-17. doi: 10.1128/JVI.02133-17. Print 2018 Apr 15.

A universal hepatitis C virus (HCV) vaccine should elicit multiantigenic, multigenotypic responses, which are more likely to protect against challenge with the range of genotypes and subtypes circulating in the community. A vaccine cocktail and vaccines encoding consensus HCV sequences are attractive approaches to achieve this goal. Consequently, in a series of mouse vaccination studies, we compared the immunogenicity of a DNA vaccine encoding a consensus HCV nonstructural 5B (NS5B) protein to that of a cocktail of DNA plasmids encoding the genotype 1b (Gt1b) and Gt3a NS5B proteins. To complement this study, we assessed responses to a multiantigenic cocktail regimen by comparing a DNA vaccine cocktail encoding Gt1b and Gt3a NS3, NS4, and NS5B proteins to a single-genotype NS3/4/5B DNA vaccine. To thoroughly evaluate in vivo cytotoxic T lymphocyte (CTL) and T helper (Th) cell responses against Gt1b and Gt3a HCV peptide-pulsed target cells, we exploited a novel fluorescent-target array (FTA). FTA and enzyme-linked immunosorbent spot (ELISpot) analyses collectively indicated that the cocktail regimens elicited higher responses to Gt1b and Gt3a NS5B proteins than those with the consensus vaccine, while the multiantigenic DNA cocktail significantly increased the responses to NS3 and NS5B compared to those elicited by the single-genotype vaccines. Thus, a DNA cocktail vaccination regimen is more effective than a consensus vaccine or a monovalent vaccine at increasing the breadth of multigenotypic T cell responses, which has implications for the development of vaccines for communities where multiple HCV genotypes circulate. **IMPORTANCE:** Despite the development of highly effective direct-acting antivirals (DAA), infections with hepatitis C virus (HCV) continue, particularly in countries where the supply of DAA is limited. Furthermore, patients who eliminate the virus as a result of DAA therapy can still be reinfected. Thus, a vaccine for HCV is urgently required, but the heterogeneity of HCV strains makes the development of a universal vaccine difficult. To address this, we developed a novel cytolytic DNA vaccine which elicits robust cell-mediated immunity (CMI) to the nonstructural (NS) proteins in vaccinated animals. We compared the immune responses against genotypes 1 and 3 that were elicited by a consensus DNA vaccine or a DNA vaccine cocktail and showed that the cocktail induced higher levels of CMI to the NS proteins of both genotypes. This study suggests that a universal HCV vaccine can most readily be achieved by use of a DNA vaccine cocktail.

### **Genetic variants in chemokine CC subfamily genes influence hepatitis C virus viral**

**clearance.** Yao Y1, Yue M2, Zang F1, et al. J Hum Genet. 2018 Apr 27. doi: 10.1038/s10038-018-0452-9. [Epub ahead of print]

Chemokine genes may influence both hepatitis C virus (HCV) spontaneous clearance in acute infection and treatment response in chronic infection. We conducted this study to evaluate whether the genetic variants in several CC family genes influence HCV spontaneous clearance



and treatment response. The current research genotyped eight SNPs, including CCR1 rs3733096, rs13096371, CCR5 rs746492, rs1800874, CCL3 rs1130371, CCL5 rs3817656, CCL8 rs1133763, CCL14 rs854625, to explore their associations with HCV spontaneous clearance and response to treatment in two populations. We identified that the CCR1 rs3733096 (dominant model: adjusted OR = 2.29, 95% CI = 1.49-3.53, additive model: adjusted OR = 2.21, 95% CI = 1.50-3.25) and CCL5 rs3817656 (dominant model: OR = 1.37, 95% CI = 1.10-1.70, additive model: OR = 1.33, 95% CI = 1.12-1.58) were associated with HCV spontaneous clearance in Chinese Han population, while we found no association with treatment response. Moreover, the expression quantitative trait loci (eQTL) analysis showed that the risk alleles of rs3817656 were significantly associated with downregulated expression of CCL5 in whole blood ( $P < 0.001$ ). The polymorphism of CCR1 rs3733096 and CCL5 rs3817656 are associated with spontaneous clearance of HCV in Chinese Han population.

#### **Early and late changes in natural killer cells in response to ledipasvir/sofosbuvir treatment.**

Golden-Mason L1, McMahan RH1, Kriss MS1, Kilgore AL2,3, Cheng L1, Dran RJ1, Wieland A1, Rosen HR1,4. *Hepatol Commun*. 2018 Mar 1;2(4):364-375. doi: 10.1002/hep4.1166. eCollection 2018 Apr.

Chronic hepatitis C virus (HCV) infection is characterized by dysregulated natural killer (NK) cell responses. NKs play a critical role in achieving sustained responses to interferon (IFN)- $\alpha$ -based therapy. Rapid sustained HCV-RNA clearance is now achieved with direct-acting antivirals (DAAs). Studies of patients receiving first-wave DAAs suggest NK functional restoration. Here, we investigate the effect of mainstream DAA treatment on NKs. We collected a prospective cohort of male HCV genotype 1-infected patients treated with ledipasvir/sofosbuvir ( $n = 22$ ). Peripheral blood was obtained at treatment start, week 2 (W2), W4, W8, and W12 of treatment and 12 weeks posttreatment. Flow cytometry was used to characterize NK responses to therapy. Mean baseline viral load was 1.75 million IU/mL. All subjects rapidly cleared virus and remained HCV RNA-negative posttreatment. No change was seen in total NK levels; however, the frequency of immature NKs (clusters of differentiation [CD]56bright) decreased by W2 and was maintained throughout the study. Phenotypic changes were evident by W2/W4, coincident with rapid viral clearance. At W2, T-cell immunoglobulin and mucin-domain containing-3 and CD161 were significantly increased, returning to pretreatment levels by W12. Some changes were not evident until late (W12 or posttreatment). Down-regulation of several activation markers, including NKp30 and tumor necrosis factor-related apoptosis-inducing ligand, was observed at W12 and sustained posttreatment. No difference was observed in IFN- $\gamma$  production or cytokine-mediated killing of NK-sensitive cell line K562 posttreatment compared to pretreatment. Conclusion: Our phenotype data suggest transient activation followed by dampening of NK cell activity to pretreatment levels. The NK response to ledipasvir/sofosbuvir is not universal in a homogeneous patient cohort. More studies are needed to elucidate the roles of NK cells in IFN-free regimens, which will have implications for protection from re-infection and fibrosis progression. (*Hepatology Communications* 2018;2:364-375).

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## **HIV/HCV COINFECTION**

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### **Rural Incarcerated Women: HIV/HCV Knowledge and Correlates of Risky Behavior.**

Peteet B1, Staton M2, Miller-Roenigk B1, Carle A1,3, Oser C2. Health Educ Behav. 2018 Apr 1;1090198118763879. doi: 10.1177/1090198118763879. [Epub ahead of print]

Rural incarcerated women have an increased risk of acquiring the human immunodeficiency virus (HIV) and the hepatitis C virus (HCV) due to prevalent engagement in drug use and sexual behaviors. Limited research has investigated HIV and HCV knowledge in this high-risk population. Furthermore, the interplay of sociodemographic factors (i.e., education, age, income, and sexual orientation) and risky behavior is understudied in this population. The present study evaluated a sample of adult, predominately White women from rural Kentucky (n = 387) who were recruited from local jails. The sample had high HIV and HCV knowledge but also reported extensive risk behaviors including 44% engaging in sex work and 75.5% reporting a history of drug injection. The results of multiple regression analysis for risky sexual behavior indicated that sexual minority women and those with less HIV knowledge were more likely to engage in high-risk sexual behaviors. The regression model identifying the significant correlates of risky drug behavior indicated that HIV knowledge, age, and income were negative correlates and that sexual minority women were more likely to engage in high-risk drug use. When HCV knowledge was added to the regression models already including HIV knowledge, the interaction was significant for drug risk. Interventions for rural imprisoned women should consider the varied impact of sociodemographic background and prioritize HIV education to more effectively deter risky sexual and drug behaviors.

**HIV and Viral Hepatitis Among Imprisoned Key Populations.** Wirtz AL1, Yeh PT2, Flath NL3,4, Beyrer C1, Dolan K5. Epidemiol Rev. 2018 Apr 21. doi: 10.1093/epirev/mxy003. [Epub ahead of print]

Prisons and other closed facilities create opportunities for transmission of human immunodeficiency virus (HIV) and viral hepatitis during detention and after release. We conducted a systematic review and meta-analysis of peer-reviewed publications (2005-2015) to describe the prevalence of HIV, hepatitis C virus, and hepatitis B virus among key populations in prisons worldwide and to compare estimates of infection with those of other prison populations. Most data were reported for people who inject drugs (PWID; n = 72) and for men who have sex with men (MSM; n = 21); few data were reported on sex workers (SW; n = 6), or transgender women (n = 2). Publications were identified from 29 countries, predominantly middle- and high-income countries. Globally, PWID had 6 times the prevalence of HIV (pooled prevalence ratio (PPR) = 6.0, 95% CI: 3.8, 9.4), 8 times the prevalence of hepatitis C virus (PPR = 8.1, 95% CI: 6.4, 10.4), and 2 times the prevalence of hepatitis B virus (PPR = 2.0, 95% CI: 1.5, 2.7) compared with noninjecting prisoner populations. Among these articles, only those from Iran, Scotland, Spain, and Italy included the availability of methadone therapy; 2 articles included information on access to needle exchange programs by PWID detainees. HIV prevalence was more than 2 times higher among SW (PPR = 2.6, 95% CI: 2.2, 3.1) and 5 times higher among MSM (PPR = 5.3, 95% CI: 3.5, 7.9) compared with other prisoners. None of these articles reported HIV prevention coverage among SW or transgender women; 1 described HIV and sexually transmitted infection screening for MSM in prison. Prevention programs specific to key populations are important, particularly for populations that are criminalized and/or may cycle in and out of prison.

[Cluster of differentiation 4+ T-cell counts and human immunodeficiency virus-1 viral load in patients coinfecting with hepatitis B virus and hepatitis C virus.](#) Gupta S1, Malhotra B1, Tiwari JK1, Khandelwal PD2, Maheshwari RK1. J Lab Physicians. 2018 Apr-Jun;10(2):162-167. doi: 10.4103/JLP.JLP\_37\_17.

**BACKGROUND:** Coinfections of human immunodeficiency virus (HIV) with hepatitis viruses may affect the progress of disease and response to therapy. **OBJECTIVES:** To study the incidence of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfections in HIV-positive patients and their influence on HIV-1 viral load and cluster of differentiation 4+ (CD4+) T-cell counts. **MATERIALS AND METHODS:** This pilot study was done on 179 HIV-positive patients attending antiretroviral therapy (ART) centre. Their blood samples were tested for HIV-1 viral load, CD4+ T-cell counts, hepatitis B surface antigen, anti-HCV antibodies, HBV DNA and HCV RNA polymerase chain reaction. **RESULTS:** Among the 179 patients, 7.82% (14/179) were coinfecting with HBV and 4.46% (8/179) with HCV. Median CD4+ T-cell count of HIV mono-infected patients was 200 cells/ $\mu$ l and viral load was 1.67 log<sub>10</sub> copies/ $\mu$ l. Median CD4+ T-cell counts of 193 cells/ $\mu$ l for HBV (P = 0.230) and 197 cells/ $\mu$ l for HCV (P = 0.610) coinfecting patients were similar to that of HIV mono-infected patients. Viral load was higher in both HBV and HCV infected patients but statistically significant only for HCV (P = 0.017). Increase in CD4+ T-cell counts and decrease in HIV-1 viral load in coinfecting patients on 2 years of ART were lower than that in HIV mono-infected patients. **CONCLUSION:** HBV/HCV coinfecting HIV patients had similar CD4+ T-cell counts as in HIV mono-infected patients, higher HIV viral load both in chemo-naive patients and in those on ART as compared to HIV mono-infected patients. However, this study needs to be done on a large scale to assess the impact of coinfection on CD4 count and HIV viral load with proper follow-up of patients every 6 months till at least 2 years.

[Proteomic fingerprinting in HIV/HCV co-infection reveals serum biomarkers for the diagnosis of fibrosis staging.](#) Golizeh M1, Melendez-Pena CE2, Ward BJ1,2, et al. PLoS One. 2018 Apr 2;13(4):e0195148. doi: 10.1371/journal.pone.0195148. eCollection 2018.

**BACKGROUND:** Hepatic complications of hepatitis C virus (HCV), including fibrosis and cirrhosis are accelerated in human immunodeficiency virus (HIV)-infected individuals. Although, liver biopsy remains the gold standard for staging HCV-associated liver disease, this test can result in serious complications and is subject to sampling errors. These challenges have prompted a search for non-invasive methods for liver fibrosis staging. To this end, we compared serum proteome profiles at different stages of fibrosis in HIV/HCV co- and HCV mono-infected patients using surface-enhanced laser desorption ionization time-of-flight mass spectrometry (SELDI-TOF MS). **METHODS:** Sera from 83 HIV/HCV co- and 68 HCV mono-infected subjects in 4 stages of fibrosis were tested. Sera were fractionated, randomly applied to protein chip arrays (IMAC, CM10 and H50) and spectra were generated at low and high laser intensities. **RESULTS:** Sixteen biomarkers achieved a p value < 0.01 (ROC values > 0.75 or < 0.25) predictive of fibrosis status in co-infected individuals and 14 in mono infected subjects. Five of these candidate biomarkers contributed to both mono- and co-infected subjects. Candidate diagnostic algorithms were created to distinguish between non-fibrotic and fibrotic individuals using a panel of 4 biomarker peaks. **CONCLUSION:** These data suggest that SELDI MS profiling can identify diagnostic serum biomarkers for fibrosis that are both common and distinct in HIV/HCV co-infected and HCV mono-infected individuals.

[Linkage and retention in HCV care for HIV-infected populations: early data from the DAA era.](#) Sacks-Davis R1,2, Doyle JS1,3, Rauch A4, et al. J Int AIDS Soc. 2018 Apr;21 Suppl 2:e25051. doi: 10.1002/jia2.25051.

**INTRODUCTION:** There is currently no published data on the effectiveness of DAA treatment for elimination of HCV infection in HIV-infected populations at a population level. However, a number of relevant studies and initiatives are emerging. This research aims to report cascade of care data for emerging HCV elimination initiatives and studies that are currently being evaluated in HIV/HCV co-infected populations in the context of implementation science theory.

**METHODS:** HCV elimination initiatives and studies in HIV co-infected populations that are currently underway were identified. Context, intervention characteristics and cascade of care data were synthesized in the context of implementation science frameworks. **RESULTS:** Seven HCV elimination initiatives and studies were identified in HIV co-infected populations, mainly operating in high-income countries. Four were focused mainly on HCV elimination in HIV-infected gay and bisexual men (GBM), and three included a combination of people who inject drugs (PWID), GBM and other HIV-infected populations. None were evaluating treatment delivery in incarcerated populations. Overall, HCV RNA was detected in 4894 HIV-infected participants (range within studies: 297 to 994): 48% of these initiated HCV treatment (range: 21% to 85%; within studies from a period where DAAs were broadly available the total is 57%, range: 36% to 74%). Among studies with treatment completion data, 96% of 1109 initiating treatment completed treatment (range: 94% to 99%). Among those who could be assessed for sustained virological response at 12 weeks (SVR12), 1631 of 1757 attained SVR12 (93%, range: 86% to 98%). **CONCLUSIONS:** Early results from emerging research on HCV elimination in HIV-infected populations suggest that HCV treatment uptake is higher than reported levels prior to DAA treatment availability, but approximately half of patients remain untreated. These results are among diagnosed populations and additional effort is required to increase diagnosis rates. Among those who have initiated treatment, completion and SVR rates are promising. More data are required in order to evaluate the effectiveness of these elimination programmes in the long term, assess which intervention components are effective, and whether they need to be tailored to particular population groups.

[High Treatment Uptake in Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients After Unrestricted Access to Direct-Acting Antivirals in the Netherlands.](#)

Boerekamps A1, Newsum AM2,3, Smit C4, et al. Clin Infect Dis. 2018 Apr 17;66(9):1352-1359. doi: 10.1093/cid/cix1004.

**BACKGROUND:** The Netherlands has provided unrestricted access to direct-acting antivirals (DAAs) since November 2015. We analyzed the nationwide hepatitis C virus (HCV) treatment uptake among patients coinfecting with human immunodeficiency virus (HIV) and HCV.

**METHODS:** Data were obtained from the ATHENA HIV observational cohort in which >98% of HIV-infected patients ever registered since 1998 are included. Patients were included if they ever had 1 positive HCV RNA result, did not have spontaneous clearance, and were known to still be in care. Treatment uptake and outcome were assessed. When patients were treated more than once, data were included from only the most recent treatment episode. Data were updated until February 2017. In addition, each treatment center was queried in April 2017 for a data update on DAA treatment and achieved sustained virological response. **RESULTS:** Of 23574 HIV-infected patients ever linked to care, 1471 HCV-coinfected patients (69% men who have sex with men, 15% persons who [formerly] injected drugs, and 15% with another HIV

transmission route) fulfilled the inclusion criteria. Of these, 87% (1284 of 1471) had ever initiated HCV treatment between 2000 and 2017, 76% (1124 of 1471) had their HCV infection cured; DAA treatment results were pending in 6% (92 of 1471). Among men who have sex with men, 83% (844 of 1022) had their HCV infection cured, and DAA treatment results were pending in 6% (66 of 1022). Overall, 187 patients had never initiated treatment, DAAs had failed in 14, and a pegylated interferon-alfa-based regimen had failed in 54. **CONCLUSIONS:** Fifteen months after unrestricted DAA availability the majority of HIV/HCV-coinfected patients in the Netherlands have their HCV infection cured (76%) or are awaiting DAA treatment results (6%). This rapid treatment scale-up may contribute to future HCV elimination among these patients.

**The Differential Effects of Human Immunodeficiency Virus and Hepatitis C Virus on Bone Microarchitecture and Fracture Risk.** Bedimo RJ1, Adams-Huet B2, Poindexter J3, et al. Clin Infect Dis. 2018 Apr 17;66(9):1442-1447. doi: 10.1093/cid/cix1011.

**BACKGROUND:** Human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected individuals have a significantly greater osteoporotic fracture risk than HIV-monoinfected persons, despite the fact that HIV/HCV coinfection has not been associated with lower bone mineral density (BMD) than HIV or HCV alone. To evaluate if changes in bone microarchitecture, measured by trabecular bone score (TBS), could explain these differences, we performed a prospective, cross-sectional cohort study of virologically suppressed HIV-infected subjects, untreated HCV-infected subjects, HIV/HCV-coinfected subjects, and uninfected controls. **METHODS:** We enrolled 532 male subjects: 57 HIV/HCV coinfecting, 174 HIV infected, 123 HCV infected, and 178 controls. We conducted analysis of covariance comparing BMD and TBS between groups, controlling for age, race, body mass index, and smoking. We used linear regression to evaluate predictors of BMD and TBS and evaluated the effects of severity of HCV infection and tenofovir disoproxil fumarate use. **RESULTS:** Despite both infections being associated with decreased BMD, only HCV, but not HIV, was associated with lower TBS score. Also, HIV/HCV-coinfected subjects had lower TBS scores than HIV-monoinfected, HCV-monoinfected, and uninfected subjects. Neither the use of TDF or HCV viremia nor the severity of HCV liver disease was associated with lower TBS. **CONCLUSIONS:** HCV infection is associated with microarchitectural changes at the lumbar spine as assessed by the low TBS score, suggesting that microstructural abnormalities underlie some of the higher fracture risk in HCV infection. TBS might improve fracture risk prediction in HCV infection.

**Generic velpatasvir plus sofosbuvir for hepatitis C virus infection in patients with or without human immunodeficiency virus coinfection.** Liu CH1,2,3, Sun HY1, Liu CJ1,2,4, et al. Aliment Pharmacol Ther. 2018 Apr 17. doi: 10.1111/apt.14647. [Epub ahead of print]

**BACKGROUND:** Data are limited regarding the effectiveness and safety of generic velpatasvir plus sofosbuvir (VEL/SOF) for hepatitis C virus (HCV) in patients with or without human immunodeficiency virus (HIV) coinfection. **AIM:** To evaluate the effectiveness and safety of generic VEL/SOF-based therapy for HCV infection in patients with or without HIV coinfection in Taiwan. **METHODS:** Sixty-nine HIV/HCV-coinfected and 159 HCV-monoinfected patients receiving 12 weeks of generic VEL/SOF with or without ribavirin (RBV) for HCV were prospectively enrolled. The anti-viral responses and the adverse events (AEs) were compared between the two groups. The characteristics potentially related to sustained virological response 12 weeks off therapy (SVR12) were analysed. **RESULTS:** The SVR12 was achieved in 67



HIV/HCV-coinfected patients (97.1%; 95% CI: 90.0%-99.2%) and in 156 HCV-monoinfected patients (98.1%; 95% CI: 94.6%-99.4%) receiving VEL/SOF-based therapy, respectively. The SVR12 rates were comparable between HIV/HCV-coinfected and HCV-monoinfected patients, regardless of pre-specified baseline characteristics. One hundred twenty-two (53.5%) and seven (3.1%) patients had baseline resistance-associated substitutions (RASs) in HCV NS5A and NS5B regions, but the SVR12 rates were not affected by the presence or absence of RASs. One (1.4%) and five (3.1%) patients in the HIV/HCV-coinfected and HCV-monoinfected groups had serious AEs. No patient died or discontinued treatment due to AEs. The eGFR remained stable throughout the course of treatment in HIV/HCV-coinfected patients receiving anti-retroviral therapy containing tenofovir disoproxil fumarate (TDF). **CONCLUSIONS:** Generic VEL/SOF-based therapy is well-tolerated and provides comparably high SVR12 rates for HCV infection in patients with and without HIV coinfection.

**Prognostic value of liver stiffness in HIV/HCV-Coinfected patients with decompensated cirrhosis.** Pérez-Latorre L1,2, Sánchez-Conde M3, Miralles P4,5, et al. BMC Infect Dis. 2018 Apr 11;18(1):170. doi: 10.1186/s12879-018-3067-z.

**BACKGROUND:** Little is known about the utility of transient elastography (TE) for assessing the prognosis of patients with decompensated cirrhosis (DC). **METHODS:** We analyzed HIV/HCV-coinfected patients with DC who underwent TE as part of their routine follow-up between 2006 and 2015. We also calculated the liver stiffness spleen diameter-to-platelet score (LSPS), FIB-4 index, albumin, MELD score, and Child-Pugh score. The primary outcome was death. **RESULTS:** The study population comprised 65 patients. After a median follow-up of 32 months after the first TE, 17 patients had received anti-HCV therapy and 31 patients had died. The highest area under the receiver operating characteristic curve (AUROC) value for prediction of death was observed with albumin (0.695), followed by Child-Pugh score (0.648), both with P values < .05. Lower AUROC values were observed with MELD score (0.633), TE (0.618), LSPS score (0.595), and FIB-4 (0.569), all with P values > .05. In the univariate Cox regression analysis, albumin, FIB-4, Child-Pugh score, and MELD score, but not TE, were associated with death. In the multivariate analysis, albumin and Child-Pugh score were the only baseline variables associated with death. **CONCLUSIONS:** Our results suggest that TE is not useful for assessing the prognosis of HIV-infected patients with decompensated HCV-related cirrhosis. Albumin concentration and Child-Pugh scores were the most consistent predictors of death in this population group.

**HIV and viral hepatitis coinfection analysis using surveillance data from 15 US states and two cities.** Bosh KA1, Coyle JR2, Hansen V3, et al. Epidemiol Infect. 2018 Apr 11:1-11. doi: 10.1017/S0950268818000766. [Epub ahead of print]

Coinfection with human immunodeficiency virus (HIV) and viral hepatitis is associated with high morbidity and mortality in the absence of clinical management, making identification of these cases crucial. We examined characteristics of HIV and viral hepatitis coinfections by using surveillance data from 15 US states and two cities. Each jurisdiction used an automated deterministic matching method to link surveillance data for persons with reported acute and chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, to persons reported with HIV infection. Of the 504 398 persons living with diagnosed HIV infection at the end of 2014, 2.0% were coinfecting with HBV and 6.7% were coinfecting with HCV. Of the 269 884 persons ever reported with HBV, 5.2% were reported with HIV. Of the 1 093 050 persons ever reported

with HCV, 4.3% were reported with HIV. A greater proportion of persons coinfecting with HIV and HBV were males and blacks/African Americans, compared with those with HIV monoinfection. Persons who inject drugs represented a greater proportion of those coinfecting with HIV and HCV, compared with those with HIV monoinfection. Matching HIV and viral hepatitis surveillance data highlights epidemiological characteristics of persons coinfecting and can be used to routinely monitor health status and guide state and national public health interventions.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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### EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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#### [Experiences of liver health related uncertainty and self-reported stress among people who inject drugs living with hepatitis C virus: a qualitative study.](#)

Goutzamanis S1,2, Doyle JS3,4, Thompson A5,6, Dietze P3,7, Hellard M3,7,4, Higgs P3,7,8; TAP study group. BMC Infect Dis. 2018 Apr 2;18(1):151. doi: 10.1186/s12879-018-3057-1.

**BACKGROUND:** People who inject drugs (PWID) are most at risk of hepatitis C virus infection in Australia. The introduction of transient elastography (TE) (measuring hepatitis fibrosis) and direct acting antiviral medications will likely alter the experience of living with hepatitis C. We aimed to explore positive and negative influences on wellbeing and stress among PWID with hepatitis C. **METHODS:** The Treatment and Prevention (TAP) study examines the feasibility of treating hepatitis C mono-infected PWID in community settings. Semi-structured interviews were conducted with 16 purposively recruited TAP participants. Participants were aware of their hepatitis C seropositive status and had received fibrosis assessment (measured by TE) prior to interview. Questions were open-ended, focusing on the impact of health status on wellbeing and self-reported stress. Interviews were voice recorded, transcribed verbatim and thematically analysed, guided by Mishel's (1988) theory of Uncertainty in Illness. **RESULTS:** In line with Mishel's theory of Uncertainty in Illness all participants reported hepatitis C-related uncertainty, particularly mis-information or a lack of knowledge surrounding liver health and the meaning of TE results. Those with greater fibrosis experienced an extra layer of prognostic uncertainty. Experiences of uncertainty were a key motivation to seek treatment, which was seen as a way to regain some stability in life. Treatment completion alleviated hepatitis C-related stress, and promoted feelings of empowerment and confidence in addressing other life challenges. **CONCLUSION:** TE scores seemingly provide some certainty. However, when paired with limited knowledge, particularly among people with severe fibrosis, TE may be a source of uncertainty and increased personal stress. This suggests the need for simple education programs and resources on liver health to minimise stress.

#### [Under one roof: identification, evaluation, and treatment of chronic hepatitis C in](#)

[addiction care.](#) Martin SA1,2,3, Bosse J4, Wilson A5, Losikoff P6,7, Chiodo L5,4. Addict Sci Clin Pract. 2018 Apr 25;13(1):10. doi: 10.1186/s13722-018-0111-7.

For over a decade, the vast majority of new hepatitis C virus (HCV) infections have been among young people who inject drugs (PWID). Well-characterized gaps in chronic HCV diagnosis, evaluation, and treatment have resulted in fewer than 5% of PWID receiving HCV treatment. While interferon-based treatment may have intentionally been foregone during part of this time

in anticipation of improved oral therapies, the overall pattern points to deficiencies and treatment exclusions in the health care system. Treatment for HCV with all-oral, highly effective direct-acting antiviral medication for 12 weeks or less is now the standard of care, putting renewed focus on effective delivery of care. We describe here both the need for and process of chronic HCV care under the roof of addiction medicine.

**[A longitudinal study assessing depression in hepatitis C: does gender play a role in the new-onset depression during interferon-alpha treatment?](#)** Fialho R1,2, Pereira M3, Gillece Y4, Rusted J1, Whale R2,5. *Women Health*. 2018 Apr 9. doi: 10.1080/03630242.2018.1449778. [Epub ahead of print]

In this prospective study conducted from October 2013 to June 2015 in Brighton, England, we examined differences between men and women in new-onset major depressive disorder (MDD) during interferon-alpha-based (IFN- $\alpha$ ) therapy for hepatitis C virus (HCV). We included 155 HCV-infected patients (47 women), eligible to receive HCV therapy, including direct-acting antivirals. The Semi-Structured Clinical Interview (SCID-I) was used to assess MDD. Severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale. Patients were assessed at baseline, during treatment and six months after treatment completion. A significant increase in depressive symptoms was observed in the total sample from baseline to week 4, and a significant decrease was observed from end of treatment (week 24) to the sustained virological response (SVR) endpoint at six months post-treatment. Women were more likely to have a MDD at week 24. In both men and women, neuro-vegetative and mood-cognitive syndromes increased significantly at the early stage of treatment but remitted by the end of HCV therapy. Proportions with SVR was similar among females and males (91.5% vs. 87%). Under an inflammatory condition, boosted by interferon-based treatments, these results suggest that female gender is not associated with increased vulnerability for developing depression during IFN- $\alpha$  therapy.

**[Race affects SVR12 in a large and ethnically diverse hepatitis C-infected patient population following treatment with direct-acting antivirals: Analysis of a single-center Department of Veterans Affairs cohort.](#)** Benhammou JN1,2, Dong TS1,2, May FP1,2, et al. *Pharmacol Res Perspect*. 2018 Feb 22;6(2):e00379. doi: 10.1002/prp2.379. eCollection 2018 Apr.

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. HCV cure has been linked to improved patient outcomes. In the era of direct-acting antivirals (DAAs), HCV cure has become the goal, as defined by sustained virological response 12 weeks (SVR12) after completion of therapy. Historically, African-Americans have had lower SVR12 rates compared to White people in the interferon era, which had been attributed to the high prevalence of non-CC interleukin 28B (IL28B) type. Less is known about the association between race/ethnicity and SVR12 in DAA-treated era. The aim of the study is to evaluate the predictors of SVR12 in a diverse, single-center Veterans Affairs population. We conducted a retrospective study of patients undergoing HCV therapy with DAAs from 2014 to 2016 at the VA Greater Los Angeles Healthcare System. We performed a multivariable logistic regression analysis to determine predictors of SVR12, adjusting for age, HCV genotype, DAA regimen and duration, human immunodeficiency virus (HIV) status, fibrosis, nonalcoholic fatty liver disease (NAFLD) fibrosis score, homelessness, mental health, and adherence. Our cohort included 1068 patients, out of which 401 (37.5%) were White people and 400 (37.5%) were African-American. Genotype 1 was the most common genotype (83.9%, N = 896). In the adjusted models, race/ethnicity and the presence of fibrosis were statistically significant predictors of non-SVR. African-Americans had

57% lower odds for reaching SVR12 (adj.OR = 0.43, 95% CI = 1.5-4.1) compared to White people. Advanced fibrosis (adj.OR = 0.40, 95% CI = 0.26-0.68) was also a significant predictor of non-SVR. In a single-center VA population on DAAs, African-Americans were less likely than White people to reach SVR12 when adjusting for covariates.

**[Estimated hepatitis C prevalence and key population sizes in San Francisco: A foundation for elimination.](#)** Facente SN1,2, Grebe E3, Burk K4, et al. PLoS One. 2018 Apr

11;13(4):e0195575. doi: 10.1371/journal.pone.0195575. eCollection 2018.

**BACKGROUND:** Initiated in 2016, End Hep C SF is a comprehensive initiative to eliminate hepatitis C (HCV) infection in San Francisco. The introduction of direct-acting antivirals to treat and cure HCV provides an opportunity for elimination. To properly measure progress, an estimate of baseline HCV prevalence, and of the number of people in various subpopulations with active HCV infection, is required to target and measure the impact of interventions. Our analysis was designed to incorporate multiple relevant data sources and estimate HCV burden for the San Francisco population as a whole, including specific key populations at higher risk of infection. **METHODS:** Our estimates are based on triangulation of data found in case registries, medical records, observational studies, and published literature from 2010 through 2017. We examined subpopulations based on sex, age and/or HCV risk group. When multiple sources of data were available for subpopulation estimates, we calculated a weighted average using inverse variance weighting. Credible ranges (CRs) were derived from 95% confidence intervals of population size and prevalence estimates. **RESULTS:** We estimate that 21,758 residents of San Francisco are HCV seropositive (CR: 10,274-42,067), representing an overall seroprevalence of 2.5% (CR: 1.2%- 4.9%). Of these, 16,408 are estimated to be viremic (CR: 6,505-37,407), though this estimate includes treated cases; up to 12,257 of these (CR: 2,354-33,256) are people who are untreated and infectious. People who injected drugs in the last year represent 67.9% of viremic HCV infections. **CONCLUSIONS:** We estimated approximately 7,400 (51%) more HCV seropositive cases than are included in San Francisco's HCV surveillance case registry. Our estimate provides a useful baseline against which the impact of End Hep C SF can be measured. Free Article

**[Feasibility of ecological momentary assessment to study mood and risk behavior among young people who inject drugs.](#)** Mackesy-Amiti ME1, Boodram B2. Drug Alcohol Depend. 2018 Apr 16;187:227-235. doi: 10.1016/j.drugalcdep.2018.03.016. [Epub ahead of print]

**AIMS:** To test the acceptability and feasibility of ecological momentary assessment (EMA) of mood and injection risk behavior among young people who inject drugs (PWID), using mobile phones. **METHODS:** Participants were 185 PWID age 18-35 recruited from two sites of a large syringe service program in Chicago. After completing a baseline interview, participants used a mobile phone app to respond to momentary surveys on mood, substance use, and injection risk behavior for 15 days. Participants were assigned to receive surveys 4, 5, or 6 times per day. **RESULTS:** Participants were 68% male, 61% non-Hispanic white, 24% Hispanic, and 5% non-Hispanic Black. Out of 185 participants, 8% (n = 15) failed to complete any EMA assessments. Among 170 EMA responders, the mean number of days reporting was 10 (SD 4.7), the mean proportion of assessments completed was 0.43 (SD 0.27), and 76% (n = 130) completed the follow-up interview. In analyses adjusted for age and race/ethnicity, women were more responsive than men to the EMA surveys in days reporting (IRR = 1.33, 95% CI 1.13-1.56), and total number of surveys completed (IRR = 1.51, 95% CI 1.18-1.93). Homeless participants

responded on fewer days (IRR = 0.76, 95% CI 0.64-0.90) and completed fewer surveys (IRR = 0.70, 95% CI 0.54-0.91), and were less likely to return for follow-up (p = 0.016). EMA responsiveness was not significantly affected by the number of assigned daily assessments.

**CONCLUSIONS:** This study demonstrated high acceptability and feasibility of EMA among young PWID, with up to 6 survey prompts per day. However, homelessness significantly hampered successful participation.

### **Drug-Drug Interaction Profile of the Fixed-Dose Combination Tablet Regimen**

**Ledipasvir/Sofosbuvir.** German P1, Mathias A2, Brainard DM2, Kearney BP2. Clin Pharmacokinet. 2018 Apr 11. doi: 10.1007/s40262-018-0654-5. [Epub ahead of print] Ledipasvir/sofosbuvir (Harvoni®), a fixed-dose combination tablet of an NS5A inhibitor ledipasvir and an NS5B polymerase inhibitor sofosbuvir, is approved for the treatment of chronic hepatitis C virus infection. Ledipasvir/sofosbuvir exhibits a favorable drug-drug interaction profile and can be administered with various medications that may be used by hepatitis C virus-infected patients, including patients with comorbidities, such as co-infection with human immunodeficiency virus or immunosuppression following liver transplantation. Ledipasvir/sofosbuvir is not expected to act as a victim or perpetrator of cytochrome P450- or UDP-glucuronosyltransferase 1A1-mediated drug-drug interactions. With the exception of strong inducers of P-glycoprotein, such as rifampin, ledipasvir/sofosbuvir is not expected to act as a victim of clinically relevant drug-drug interactions. As a perpetrator of pharmacokinetic drug-drug interactions via P-glycoprotein/BCRP, ledipasvir/sofosbuvir should not be used with rosuvastatin and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, whereas its co-administration with amiodarone is not recommended because of a pharmacodynamic interaction. This review summarizes a number of drug interaction studies conducted in support of the clinical development of ledipasvir/sofosbuvir.

### **Vitamin D deficiency in hepatitis C virus infection: what is old? what is new?**

Jin CN1, Chen JD1, Sheng JF2. Eur J Gastroenterol Hepatol. 2018 Apr 16. doi: 10.1097/MEG.0000000000001134. [Epub ahead of print]

In the past few years, a growing body of clinical evidence has highlighted the risk of vitamin D deficiency in patients with chronic hepatitis C and that vitamin D levels are associated with the course of hepatitis C virus (HCV) infection, adverse effects, and treatment response to peginterferon/ribavirin. Recently, studies have found that vitamin D status is related to drug resistance and increased risk of infection in patients with liver cirrhosis. Vitamin D-related gene polymorphisms have been found to explain the interactions between vitamin D deficiency and HCV infection, offering a new perspective toward understanding the current problems such as the development of insulin resistance and racial differences in sustained virological response. Studies have been conducted to determine whether vitamin D supplementation as an adjuvant yields a better result compared with traditional HCV treatment. Here, we provide a brief review of the past and present knowledge of vitamin D in HCV infection.

PMID: 29664746

### **Integrated Care for the Use of Direct-acting Antivirals in Patients With Chronic Hepatitis C and Substance Use Disorder.**

Trabut JB1, Barrault C, Charlot H, et al. J Addict Med. 2018 Apr 26. doi: 10.1097/ADM.0000000000000415. [Epub ahead of print]



**OBJECTIVES:** Since little is currently known about predictors of response to direct-acting antiviral agents (DAAs) in people who inject drugs, we undertook an analysis of patients attending a hepatitis clinic with addiction services (outpatient clinics and inpatient services) to examine the outcomes associated with the treatment of difficult-to-manage patients with substance use. Our experience was based on integrated care. **METHOD:** A retrospective analysis was undertaken of 50 patients with hepatitis C virus (HCV) and a history of addiction who received treatment with DAAs, according to European guidelines. These regimens were sofosbuvir/ledipasvir for 8 weeks (n=3), sofosbuvir/ledipasvir±ribavirin for 12 weeks (n=19), sofosbuvir/daclatasvir for 12 weeks (n=20), sofosbuvir/simeprevir (n=1), or sofosbuvir/daclatasvir for 24 weeks (n=7). Characteristics of patients who did versus did not achieve a sustained virologic response (SVR) 12 weeks after treatment were compared by univariate analysis. **RESULTS:** Forty-two patients (84%) were male; mean age was 46.2±7.3 years. Genotypes were 1 (n=21), 2 (n=4), 3 (n=18), 4 (n=6), or 6 (n=1). Most patients were treatment-naïve (n=38). Five patients had coinfection with human immunodeficiency virus (n=4) or hepatitis B (n=1), 28 (56%) had evidence of cirrhosis on FibroScan (>12.5kPa), and 34 (68%) were receiving opioid substitution therapy. Psychiatric disease, illicit drug use, unemployment, and homelessness/precarious housing were common. Forty-five patients (90%) achieved SVR, 2 were lost to follow-up, and 3 had treatment relapse. **CONCLUSIONS:** SVR was not significantly associated with sociodemographic or virological characteristics, treatment, social environment, alcohol/drug use, and adherence. Although adherence was slightly worse than in "usual" patients, it did not affect the SVR rate. In these difficult-to-manage patients with HCV and substance use disorder, the real-world SVR rate (90%) was similar to that in nonaddicted populations.

[Knowledge of hepatitis C status moderates the relationship between history of drug treatment and sterile syringe use.](#) Fisher KA1, Cahill LM1, Broyles S1,2, Rorke M3, Robinson WT1,4. PLoS One. 2018 Apr 27;13(4):e0196157. doi: 10.1371/journal.pone.0196157. eCollection 2018.

High-risk injection related behavior including use of non-sterile syringes is associated with negative health outcomes among people who inject drugs (PWID). Drug treatment programs have been reported to curb hepatitis C (HCV) transmission. This study aims to assess the role of drug treatment programs and knowledge of HCV status, and how they influence current injection-related risk. Data were collected in 2012 by the New Orleans arm of the CDC funded National HIV Behavioral Surveillance. Respondent driven sampling was used to recruit a sample of PWID. The analytic sample consisted of 473 participants. Univariate, bivariate, and linear regression analyses were performed. Findings indicated that history of drug treatment is associated with sterile syringe use among PWID. Further, knowledge of HCV status modifies the relationship between history of drug treatment and sterile syringe use in this sample. These findings highlight the importance of scaling up prevention efforts by expanding testing, counselling, and treatment for HCV among PWID who enter drug treatment facilities.

[Hepatitis C in Pregnancy.](#) Dibba P1, Cholankeril R2, Li AA3, et al. Diseases. 2018 Apr 27;6(2). pii: E31. doi: 10.3390/diseases6020031.

The prevalence of hepatitis C in pregnancy is as high as 3.6% in large cohorts. The prevalence of hepatitis C acquired by vertical transmission is 0.2% to 0.4% in the United States and Europe. Although screening is not recommended in the absence of certain risk factors, the importance of

understanding hepatitis C in pregnancy lies in its association with adverse maternal and neonatal outcomes. There is potential for those infants infected by vertical transmission to develop chronic hepatitis C, cirrhosis or hepatocellular carcinoma. The risk of vertical transmission is increased when mothers are co-infected with Human Immunodeficiency Virus (HIV) or possess a high viral load. There is no clear data supporting that mode of delivery increases or reduces risk. Breastfeeding is not associated with increased risk of transmission. Premature rupture of membranes, invasive procedures (such as amniocentesis), intrapartum events, or fetal scalp monitoring may increase risk of transmission. In pregnant patients, hepatitis C is diagnosed with a positive ELISA-3 and detectable Hepatitis C Virus (HCV) RNA viral load. Infants born to HCV-infected mothers should be tested for either HCV RNA on at least two separate occasions. Although prevention is not possible, there may be a role for newer direct acting anti-viral medications in the future.

### **[Integrated Hepatitis C Testing and Linkage to Care at a Local Health Department Sexually Transmitted Disease Clinic: Determining Essential Resources and Evaluating Outcomes.](#)**

Rhea S, Seña AC, Hilton A, Hurt CB, Wohl D, Fleischauer A. Sex Transm Dis. 2018 Apr;45(4):229-232. doi: 10.1097/OLQ.0000000000000748.

Guidance about integration of comprehensive hepatitis C virus (HCV)-related services in sexually transmitted disease (STD) clinics is limited. We evaluated a federally funded HCV testing and linkage-to-care program at an STD clinic in Durham County, North Carolina. During December 10, 2012, to March 31, 2015, the program tested 733 patients for HCV who reported 1 or more HCV risk factor; 81 (11%) were HCV-infected (ie, HCV antibody-positive and HCV ribonucleic acid-positive). Fifty-one infected patients (63%) were linked to care. We concluded that essential program resources include reflex HCV ribonucleic acid testing; a dedicated bridge counselor to provide test results, health education, and linkage-to-care assistance; and referral relationships for local HCV management and treatment.

### **[Treatment of hepatitis C virus infection in patients with mixed cryoglobulinemic syndrome and cryoglobulinemic glomerulonephritis.](#)** Rutledge SM1, Chung RT1, Sise ME1. Hemodial Int. 2018 Apr;22 Suppl 1:S81-S96. doi: 10.1111/hdi.12649.

Cryoglobulinemia is a common extrahepatic manifestation of infection with hepatitis C virus (HCV). When signs and symptoms of systemic vasculitis or glomerulonephritis occur in the presence of circulating cryoglobulins, this syndrome is called "mixed cryoglobulinemia syndrome" (MCS). Historically, interferon-based therapies in HCV have been associated with lower rates of viral cure in patients with MCS than in the general HCV-infected population. The advent of direct-acting antiviral therapies have revolutionized the treatment of HCV, dramatically increasing rates of cure. Early studies of first-generation protease inhibitors (telaprevir and boceprevir) in combination with interferon and ribavirin demonstrated HCV cure rates of 67% and complete clinical response rates of vasculitis symptoms in 60% of patients with MCS; however, regimens were poorly tolerated by patients, 22% discontinued treatment early. More recently, all-oral, interferon-free regimens have become available and combination therapies are now being approved for patients with and without renal impairment. Patients with HCV-MCS achieved sustained virologic response in 297 out of 313 patients (95%) treated with direct-acting antiviral therapy, and 85% had a complete or partial clinical response of MCS symptoms. Current direct-acting antiviral therapies are well tolerated in patients with HCV-MCS and only 1.6% discontinued treatment early. Patients with cryoglobulinemic glomerulonephritis

also had an excellent cure rate (94%). The majority improved; 17/52 (33%) experienced full remission and 15/52 (29%) experienced partial remission. There were no reports of worsening kidney function in patients treated with direct-acting antiviral therapies. Less than 5% of patients with HCV-MCS treated with IFN-free direct-acting antiviral therapy required immunosuppression. However, patients with severe vasculitis appear to still require concomitant immunosuppression.

**Direct-Acting Antivirals to Prevent Vertical Transmission of Viral Hepatitis C: When Is the Optimal Time to Treat?** Cervino L1, Hynicka LM1. Ann Pharmacother. 2018 Apr

1:1060028018772181. doi: 10.1177/1060028018772181. [Epub ahead of print]

**OBJECTIVE:** To describe the most current evidence for the use of direct-acting antivirals (DAAs) to treat hepatitis C along the pregnancy-pediatric continuum in the United States.

**DATA SOURCES:** The MEDLINE/PubMed databases were searched (January 1995 to February 2018) for articles in English using the terms: hepatitis C, vertical transmission, pregnancy, pediatrics, ribavirin, interferon, direct acting antivirals, daclatasvir, dasabuvir, elbasvir, glecaprevir, grazoprevir, ledipasvir, ombitasvir, paritaprevir, pibrentasvir, simeprevir, sofosbuvir, and velpatasvir. **STUDY SELECTION AND DATA EXTRACTION:** All relevant studies, meta-analyses, systematic reviews, guidelines, and review articles were evaluated for inclusion. References from pertinent articles were assessed for additional content that was not found during the initial search. **DATA SYNTHESIS:** The primary route of transmission for hepatitis C virus (HCV) in pediatric patients is vertical transmission (VT), with the rate estimated to be 5.8%. Screening for HCV during pregnancy is not routinely part of clinical care, and the data for the use of DAAs in pregnancy is limited. A significant number of infected infants will clear the HCV infection spontaneously, and ledipasvir/sofosbuvir and sofosbuvir have recently been Food and Drug Administration approved for use in pediatric patients older than 12 years. **CONCLUSIONS:** Data to determine the best treatment point along the pregnancy-pediatric continuum are limited; however, given the lack of human data for use of DAAs during pregnancy, low rate of VT, high rate of spontaneous pediatric clearance, and recent approval of DAAs for pediatric patients, treatment of chronically infected children seems to be the optimal strategy currently.

**The Syndemic of Opioid Misuse, Overdose, HCV, and HIV: Structural-Level Causes and Interventions.** Perlman DC1,2, Jordan AE3,4. Curr HIV/AIDS Rep. 2018 Apr;15(2):96-112.

doi: 10.1007/s11904-018-0390-3.

**PURPOSE OF REVIEW:** This article reviews the case for recognizing (1) the epidemics of opioid misuse, overdose, hepatitis C virus, and HIV as a syndemic and (2) the importance of examining and addressing structural factors in responses to this syndemic. We focus on the current syndemic in the US, but also consider data from other locations to highlight the issues existing and arising in various contexts. **RECENT FINDINGS:** Advances in multi-level theory and statistical methods allow sound ecologic and multi-level analyses of the impact of structural factors on the syndemic. Studies of opioid misuse, overdoses, hepatitis C virus, and HIV demonstrate that area-level access to healthcare, medication-assisted treatment of opioid use disorders, sterile injection equipment, and overdose prevention with naloxone, as well as factors such as opioid marketing, income inequality, intensity of policing activities, and health care policies, are related to the prevalence of substance misuse, overdoses, infection risk, and morbidity. Structural variables can predict area-level vulnerability to the syndemic. The

implementation of combined prevention and treatment interventions can control and reverse components of the syndemic. Recognizing and monitoring potent structural factors can facilitate the identification of areas at risk of vulnerability to the syndemic. Further, many structural factors are modifiable through intervention and policy to reduce structural vulnerability and create health-enabling environments. Evidence supports the immediate implementation of broader HCV and HIV testing and substance use screening, medication-assisted treatment, needle/syringe exchange programs, naloxone programs, increased population-level implementation of HCV treatment, and further attention to structural-level factors predicting, and contributing to, area-level vulnerability, such as degrees of opioid marketing, distribution, and prescribing.

**Network-Based Research on Rural Opioid Use: an Overview of Methods and Lessons Learned.** Young AM<sup>1,2</sup>, Rudolph AE<sup>3</sup>, Havens JR<sup>4</sup>. *Curr HIV/AIDS Rep.* 2018 Apr;15(2):113-119. doi: 10.1007/s11904-018-0391-2.

**PURPOSE OF REVIEW:** The purpose of this paper is to provide a thorough overview of methods used for recruitment, network data collection, and network data management in a network-based study of rural people who use drugs (PWUD) and to offer methodological recommendations for future research on rural drug use. **RECENT FINDINGS:** The Social Networks among Appalachian People (SNAP) study recruited a cohort of 503 rural PWUD via respondent-driven sampling (RDS) and has retained more than 80% of eligible participants over 7-9 years. SNAP has yielded important methodological insights, including that (1) RDS referral was non-random and disproportionately involved kin and (2) interviewer-administered questionnaires were successful in eliciting accurate name and age information about network members. The SNAP experience suggests that RDS was a successful recruitment strategy for rural PWUD and questionnaires administered by community-based interviewers in the context of a Certificate of Confidentiality could elicit detailed data on PWUD risk networks.

**Dialysis Facility Screening and Testing Practices in the Era of Improved Hepatitis C Treatment.** Moore MS<sup>1</sup>, Bocour A<sup>2</sup>, Winters A<sup>3</sup>. *J Viral Hepat.* 2018 Apr 6. doi: 10.1111/jvh.12907. [Epub ahead of print]

Patients receiving hemodialysis are at increased risk of hepatitis C virus (HCV) infection, and routine screening is recommended. Highly effective HCV treatments for dialysis patients are newly available and cure >90% of patients in 12 weeks. Dialysis facilities should screen individuals for HCV, confirm infections, and treat or link patients to care and treatment. The New York City (NYC) Department of Health and Mental Hygiene electronically receives all positive HCV antibody and all positive and negative HCV RNA tests for NYC residents. We examined antibody and RNA tests reported by dialysis centers in NYC during January 2014-December 2017 to examine patterns of antibody testing and rates of RNA confirmation. We assessed treatment initiation rates in dialysis patients by examining negative RNA results. There were 2,277 individuals with 7,918 positive HCV antibody tests reported by 112 dialysis facilities during the study period. Dialysis patients testing antibody-positive in 2014 averaged 6.2 additional antibody tests through December 2017. RNA confirmatory testing occurred for 87.6% of individuals, but only 29.4% had RNA testing performed by a dialysis facility. Evidence of HCV treatment initiation was found in only 14.7% of dialysis patients. In conclusion, dialysis facilities order HCV antibody tests for patients who are already antibody-positive and do not consistently order RNA tests to confirm infection for antibody-positive individuals. HCV

treatment initiation rates among patients on dialysis are low. Hemodialysis patients with chronic HCV should be treated to improve individual health outcomes and to prevent transmission in these high-risk settings. This article is protected by copyright. All rights reserved.

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## HEPATOCELLULAR (LIVER) CANCER

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[Hepatocellular carcinoma in the wait-listed patient with hepatitis C virus.](#) Prenner SB1, Kulik L2. *Curr Opin Organ Transplant.* 2018 Apr;23(2):237-243. doi: 10.1097/MOT.0000000000000505.

**PURPOSE OF REVIEW:** To highlight the current data for treatment of hepatitis C virus (HCV) in patients with hepatocellular carcinoma (HCC) awaiting orthotopic liver transplant and incorporation of various factors to decide the optimal time to initiate HCV therapy. **RECENT FINDINGS:** Viral eradication on the waiting list has been found to lead to significant clinical improvement in approximately 20% of HCV-positive patients. However, there have been concerns raised for direct-acting antiviral (DAA) therapy in patients listed with HCC. DAA therapy leading to rapid HCV clearance has been reported to be associated with an increased risk of HCC recurrence, especially when DAA therapy is initiated in close proximity to HCC therapy. Additionally, the presence of viable HCC may significantly lower the chances of achieving sustained virologic response. Lastly, sustained virologic response can decrease the organ pool in HCV-positive waitlisted patients. **SUMMARY:** The decision to treat HCV in patients listed for HCC pre vs. postliver transplant will require additional research.

[Hepatocellular carcinoma recurrence in hepatitis C virus-related cirrhosis treated with direct-acting antivirals: a case-control study.](#) Adhoute X1, Penaranda G2, Raoul JL3, et al. *Eur J Gastroenterol Hepatol.* 2018 Apr;30(4):368-375. doi: 10.1097/MEG.0000000000001082.

**BACKGROUND:** Direct-acting antivirals (DAAs) therapy against hepatitis C viral (HCV) infection has markedly improved the sustained viral response. However, recent studies have suggested an unsuspected high rate of hepatocellular carcinoma (HCC) recurrence. **PATIENTS AND METHODS:** A retrospective case-control study was carried out to investigate the impact of DAAs on tumor recurrence in patients with complete response to HCC treatment within our HCV-related cirrhosis cohort. Patients who received [group 1 (G1), n=22] or not [group 2 (G2), n=49] a DAAs therapy were matched 1 : 2 for age, sex, liver function, HCC stage, and treatment. **RESULTS:** Initial HCC were mostly Barcelona Clinic Liver Cancer stage A (95% G1, 94% G2). Sustained viral response with DAAs was achieved in 86% of patients. After a similar median overall follow-up time with similar radiologic surveillance after HCC treatment, 41% of patients developed radiologic tumor recurrence in G1 versus 35% of patients in G2 (P=0.7904). There was no significant difference in time to progression between the two groups [12 (9-16) months G1 vs. 14 (8-21) months G2, P=0.7688], or Barcelona Clinic Liver Cancer stage at recurrence. However, the interval between HCC treatment and antiviral therapy was significantly different among DAAs patients with recurrence and those without recurrence [7.0 (2.5-9.0) months vs. 36.0 (9.0-58.0) months, P=0.0235, respectively]. **CONCLUSION:** In our case-control study, HCV therapy with DAAs does not accelerate or prevent early HCC recurrence compared with untreated patients. The rate of recurrence, time to progression, and HCC pattern are similar. Early DAAs treatment (<12 months) after HCC cure should be discouraged considering the HCC recurrence rate during this period.



[Shear wave elastography predicts hepatocellular carcinoma risk in hepatitis C patients after sustained virological response.](#) Hamada K1,2, Saitoh S3, Nishino N1, Fukushima D1, Horikawa Y1, Nishida S2, Honda M1,2. PLoS One. 2018 Apr 19;13(4):e0195173. doi: 10.1371/journal.pone.0195173. eCollection 2018.

**AIM:** To evaluate the relationship between fibrosis and HCC after sustained virological response (SVR) to treatment for chronic hepatitis C (HCV). **METHODS:** This single-center study retrospectively evaluated 196 patients who achieved SVR after HCV infection. The associations of risk factors with HCC development after HCV eradication were evaluated using univariate and multivariate Cox proportional hazards regression models. **RESULTS:** Among the 196 patients, 8 patients (4.1%) developed HCC after SVR during a median follow-up of 26 months. Multivariate analyses revealed that HCC development was independently associated with age of  $\geq 75$  years (risk ratio [RR] = 35.16),  $\alpha$ -fetoprotein levels of  $\geq 6$  ng/mL (RR = 40.30), and SWE results of  $\geq 11$  kPa (RR = 28.71). **CONCLUSIONS:** Our findings indicate that SWE may facilitate HCC surveillance after SVR and the identification of patients who have an increased risk of HCC after HCV clearance.

[Risk factors for hepatocellular carcinoma by age, sex, and liver disorder status: A prospective cohort study in Korea.](#) Yi SW1,2, Choi JS3, Yi JJ4, Lee YH5, Han KJ3. Cancer. 2018 Apr 18. doi: 10.1002/cncr.31406. [Epub ahead of print]

**BACKGROUND:** To the authors' knowledge, relatively little is known regarding the interaction of risk factors for hepatocellular carcinoma (HCC) with age, sex, and liver disorder status. **METHODS:** The authors followed 504,646 Korean patients aged 40 to 80 years who underwent routine health checkups between 2002 and 2003 until 2013 via linkage to national hospital discharge records. **RESULTS:** HCC occurred in 2744 individuals. In the sex-adjusted and age-adjusted analysis, cirrhosis increased the incidence of HCC by 42-fold, followed by hepatitis B virus (21-fold), hepatitis C virus (HCV; 19-fold), male sex (4.3-fold), and each 5-year age increment (1.24-fold). In the multivariable adjusted analysis, diabetes increased the risk of HCC by 80%, alcohol consumption  $\geq 80$  g/day increased the risk by 75%, alcohol consumption of 40 to 79 g/day increased the risk by 37%, and being a current smoker increased the risk by 25%. The multivariable adjusted hazard ratios of male sex and HCV were 6.27 and 5.72, respectively, at age  $< 50$  years, but were 2.09 and 22.51, respectively, at age  $\geq 70$  years. Each 20 g/day of alcohol consumption increased the risk of HCC by 6% ( $P = .11$ ), 8% ( $P = .02$ ), 16% ( $P < .001$ ), and 30% ( $P < .001$ ), respectively, in individuals aged  $< 50$  years, 50 to 59 years, 60 to 69 years, and 70 to 80 years. In individuals without a liver disorder, body mass index was found to be positively associated with HCC, whereas patients with a liver disorder demonstrated an inverse association. Women had higher adjusted hazard ratios associated with age and cirrhosis compared with men. **CONCLUSIONS:** With advancing age, the effects of alcohol use and HCV on the development of HCC become stronger, whereas the effect of male sex weakens. Lifetime moderate alcohol consumption may cause HCC in the elderly. Smoking increases the risk of HCC irrespective of viral hepatitis, and diabetes increases the risk of HCC independent of cirrhosis. Cancer 2018. © 2018 American Cancer Society.

[Early development of de novo hepatocellular carcinoma after direct-acting agent therapy: comparison with pegylated interferon-based therapy in chronic hepatitis C patients.](#) Yoo SH1, Kwon JH1, Nam SW1, et al. J Viral Hepat. 2018 Apr 16. doi: 10.1111/jvh.12918. [Epub ahead of print]

Patients with chronic hepatitis C who achieve a sustained viral response after pegylated interferon therapy have a reduced risk of hepatocellular carcinoma, but the risk after treatment with direct-acting antivirals is unclear. We compared the rates of early development of hepatocellular carcinoma after direct-acting antivirals and after pegylated interferon therapy. We retrospectively analyzed 785 patients with chronic hepatitis C who had no history of hepatocellular carcinoma (211 treated with pegylated interferon, 574 with direct-acting antivirals) and were followed up for at least 24 weeks after antiviral treatment. De novo hepatocellular carcinoma developed in 6/574 patients receiving direct-acting antivirals and in 1/211 patients receiving pegylated interferon. The cumulative incidence of early hepatocellular carcinoma development did not differ between the treatment groups either for the whole cohort (1.05% vs. 0.47%,  $P = 0.298$ ) or for those patients with Child-Pugh Class A cirrhosis (3.73% vs. 2.94%,  $P = 0.827$ ). Multivariate analysis indicated that alpha-fetoprotein level  $>9.5$  ng/ml at the time of end-of-treatment response was the only independent risk factor for early development of hepatocellular carcinoma in all patients ( $P < 0.0001$ , hazard ratio 176.174, 95% confidence interval 10.768-2882.473) and in patients treated with direct-acting agents ( $P < 0.0001$ , hazard ratio 128.402, 95% confidence interval 8.417-1958.680). In conclusion, the rate of early development of hepatocellular carcinoma did not differ between patients treated with pegylated interferon and those treated with direct-acting antivirals and was associated with the serum alpha-fetoprotein level at the time of end-of-treatment response. This article is protected by copyright. All rights reserved.

[Does interferon-free direct-acting antiviral therapy for hepatitis C after curative treatment for hepatocellular carcinoma lead to unexpected recurrences of HCC? A multicenter study by the Japanese Red Cross Hospital Liver Study Group.](#) Mashiba T1, Joko K1, Kurosaki M2, et al. PLoS One. 2018 Apr 16;13(4):e0194704. doi: 10.1371/journal.pone.0194704. eCollection 2018.

**BACKGROUND AND AIM:** This study aimed to elucidate whether interferon (IFN)-free direct-acting antiviral (DAA) therapy for hepatitis C after curative treatment of hepatocellular carcinoma (HCC) promotes HCC recurrence in a real-world large-scale cohort. **METHODS:** This multicenter study was conducted by the Japanese Red Cross Hospital Liver Study Group. This retrospective study analyzed 516 patients who underwent antiviral treatment for hepatitis C with either IFN ( $n = 148$ ) or IFN-free DAA ( $n = 368$ ) after curative HCC treatment; 78 IFN-treated patients and 347 IFN-free DAA-treated patients achieved sustained virological response (SVR). The recurrence rate of HCC was compared between the antiviral therapies. Logistic analysis and Cox proportional hazards analysis identified factors associated with early recurrence of HCC within 24 weeks of antiviral therapy and recurrence throughout the observation period, respectively. **RESULTS:** AFP at the completion of antiviral therapy, clinical stage of HCC, and non-SVR were independent factors associated with early recurrence of HCC. Among patients who had achieved SVR, the clinical stage of HCC and the level of AFP at completion of antiviral therapy were independent factors associated with early recurrence of HCC. For recurrence throughout the observation period in SVR patients, AFP at completion of antiviral therapy, duration between last HCC treatment to antiviral therapy, and the number of treatments were independent factors. There was no significant difference in the rate of early recurrence of HCC or recurrence throughout the observation period between IFN and IFN-free DAA treated patients. **CONCLUSIONS:** There were no differences in the early recurrence rate of HCC

between patients who underwent IFN and those who underwent IFN-free DAA as antiviral therapies.

[The role of external beam radiotherapy in the treatment of hepatocellular cancer.](#) Chino F1, Stephens SJ1, Choi SS2, et al. *Cancer*. 2018 Apr 12. doi: 10.1002/cncr.31334. [Epub ahead of print]

Hepatocellular carcinoma (HCC) is increasing in incidence and mortality. Although the prognosis remains poor, long-term survival has improved from 3% in 1970 to an 18% 5-year survival rate today. This is likely because of the introduction of well tolerated, oral antiviral therapies for hepatitis C. Curative options for patients with HCC are often limited by underlying liver dysfunction/cirrhosis and medical comorbidities. Less than one-third of patients are candidates for surgery, which is the current gold standard for cure. Nonsurgical treatments include embolotherapies, percutaneous ablation, and ablative radiation. Technological advances in radiation delivery in the past several decades now allow for safe and effective ablative doses to the liver. Conformal techniques allow for both dose escalation to target volumes and normal tissue sparing. Multiple retrospective and prospective studies have demonstrated that hypofractionated image-guided radiation therapy, used as monotherapy or in combination with other liver-directed therapies, can provide excellent local control that is cost effective. Therefore, as the HCC treatment paradigm continues to evolve, ablative radiation treatment has moved from a palliative treatment to both a "bridge to transplant" and a definitive treatment. *Cancer* 2018.

[Incidence of Hepatocellular Carcinoma in Patients with HCV-associated Cirrhosis Treated with Direct-Acting Antiviral Agents.](#) Calvaruso V1, Cabibbo G1, Cacciola I2, et al. *Gastroenterology*. 2018 Apr 12. pii: S0016-5085(18)30441-4. doi: 10.1053/j.gastro.2018.04.008. [Epub ahead of print]

**BACKGROUND & AIMS:** Studies have produced conflicting results of the incidence of hepatocellular carcinoma (HCC) in patients with in hepatitis C virus (HCV)-associated cirrhosis treated with direct-acting antivirals (DAAs). Data from clinics are needed to accurately assess the occurrence rate of HCC in patients with cirrhosis in the real world. **METHODS:** We collected data from a large prospective study of 2249 consecutive patients (mean age, 65.4 years and 56.9% male) with HCV-associated cirrhosis (90.5% Child-Pugh class A, 9.5% Child-Pugh class B) treated with DAAs from March 2015 through July 2016 at 22 academic and community liver centers in Sicily, Italy. HCC occurrence was evaluated by Kaplan-Meier curves. Cox regression analysis was used to identify variables associated with HCC development.

**RESULTS:** A sustained virologic response (SVR) was achieved by 2140 patients (95.2% total; 95.9% of Child Pugh class A and 88.3% of Child Pugh class B patients ( $P < .001$ ). Seventy-eight patients (3.5%) developed HCC during a mean follow-up of 14 months (range, 6-24 months). At 1 year after DAA exposure, HCC developed in 2.1% of Child-Pugh class A patients with an SVR and 6.6% of patients with no SVR; HCC developed in 7.8% of Child-Pugh class B patients with an SVR and 12.4% of patients with no SVR ( $P < .001$  by log-rank test). Albumin level below 3.5 g/dL (hazard ratio, 1.77; 95% CI, 1.12-2.82;  $P = .015$ ), platelets count below  $120 \times 10^9/L$  (hazard ratio, 3.89; 95% CI, 2.11-7.15;  $P < .001$ ), and absence of SVR (hazard ratio, 3.40; 95% CI, 1.89-6.12;  $P < .001$ ) were independently associated increased risk for HCC. The mean interval in time from DAA exposure to an HCC diagnosis was 9.8 months (range, 2-22 months) and did not differ significantly between patients with ( $n=64$ , 9.2 months) and without an SVR ( $n=14$ , 12.0 months) ( $P = .11$ ). A higher proportion of patients with an SVR had a single HCC lesion (78% vs

50% without an SVR;  $P=.009$ ) or HCC lesion less than 3 cm (58% vs 28% without an SVR;  $P=.07$ ). **CONCLUSIONS:** In an analysis of data from a large prospective study of patients with HCV-associated compensated or decompensated cirrhosis, we found that SVR to DAA treatment to reduce the incidence of HCC over a mean follow-up of 14 months.

[Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in chemoprevention of hepatocellular carcinoma: a nationwide high-risk cohort study.](#) Ho CM1,2, Lee CH3, Lee MC4, Zhang JF5, Wang JY6,7, Hu RH1, Lee PH1,2. BMC Cancer. 2018 Apr 10;18(1):401. doi: 10.1186/s12885-018-4292-y.

**BACKGROUND:** Research has revealed that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) may prevent cancers such as hepatocellular carcinoma (HCC). The comparative chemopreventive effects of ACEIs and ARBs in high-risk populations with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection have yet to be investigated. **METHODS:** From 2005 to 2014, high-risk HBV and HCV cohorts of hypertensive patients without HCC history were recruited from three linked national databases of Taiwan, and were classified into two groups based on the ACEI or ARB exposure within the initial six months after initiating antiviral agent. Intergroup differences in clinical characteristics and duration of drug exposure within study period were evaluated. HCC-free survival was compared using the log-rank test. Multivariate Cox regression including time-dependent variables for the use of ACEIs or ARBs and other medications was applied to adjust for confounders. **RESULTS:** Among the 7724 patients with HBV and 7873 with HCV, 46.3% and 42.5%, respectively, had an initial exposure to ACEIs or ARBs. The median durations of exposure were 36.4 and 38.9 months for the HBV and HCV cohorts, respectively. The median durations of ACEI or ARB use during study period between initial exposure and nonexposure groups were 41.8 vs. 18.3 months and 46.4 vs. 22.7 months for the HBV and HCV cohorts, respectively. No significant difference was observed in HCC risk within 7 years between the initial exposure and non-exposure groups. After adjustment for comorbidities, namely liver cirrhosis, diabetes mellitus (DM), and hyperlipidemia, and medications, namely aspirin, metformin, and statins, the hazard ratios (HRs) for ACEI or ARB exposure for HCC risk were 0.97 (95% confidence interval [CI]: 0.81-1.16) and 0.96 (0.80-1.16) in the HBV and HCV cohorts, respectively. In the HCV cohort, the increased HCC risk was associated with ACEI or ARB use in patients without cirrhosis, DM, and hyperlipidemia (HR: 4.53, 95% CI: 1.46-14.1). **CONCLUSION:** Compared with other significant risk and protective factors for HCC, ACEI or ARB use in the HBV and HCV cohorts was not associated with adequate protective effectiveness under standard dosages and may not be completely safe.

[Temporal trends in disease presentation and survival of patients with hepatocellular carcinoma: A real-world experience from 1998 to 2015.](#) Kim NG1, Nguyen PP2, Dang H2, Kumari R2, Garcia G2, Esquivel CO3, Nguyen MH2. Cancer. 2018 Apr 6. doi: 10.1002/cncr.31373. [Epub ahead of print]

**BACKGROUND:** Hepatocellular carcinoma (HCC) is one of the few cancers whose incidence continues to increase. The goal of the current study was to investigate the presentation and survival trends of patients with HCC presenting to a university hospital between 1998 and 2015. **METHODS:** Study data were ascertained by individual chart review with survival data also supplemented by National Death Index query up to December 31, 2015. Patients were divided into three 6-year groups by diagnosis date (1998-2003, 2004-2009, and 2010-2015). **RESULTS:**

A total of 2106 consecutive patients with HCC were included. The majority of patients had either hepatitis C (56.7%) or hepatitis B (22.1%), but cases of nonalcoholic steatohepatitis HCC increased by 68% over the most recent time period. Screening/surveillance identified 61% of HCC cases, but only 31% of these patients underwent curative treatment, which did not increase significantly over time. The overall median survival was 29.8 months (2.48 years) and without improvement over time. On multivariable analysis, Asian or Hispanic ethnicity, meeting Milan criteria, and receiving any of the standard HCC treatments were found to be significantly associated with improved survival, but diagnosis time period and liver disease etiology were not. **CONCLUSIONS:** Over the last 18 years, the percentage of cases of nonalcoholic steatohepatitis HCC has increased but not overall survival. It is interesting to note that only 31% of patients with HCC identified via screening/surveillance received any curative treatment. Further research is needed to better understand the barriers to curative care for patients with HCC and the causes of the lack of improvement in survival in the more recent patient cohort.

**Low Rates of Retention Into Hepatocellular Carcinoma (HCC) Surveillance Program After Initial HCC Screening.** Robinson A1, Tavakoli H1, Cheung R2, Liu B1, Bhuket T1, Wong RJ1. J Clin Gastroenterol. 2018 Apr 6. doi: 10.1097/MCG.0000000000001024. [Epub ahead of print]

**GOALS:** To evaluate rates and predictors of retention into hepatocellular carcinoma (HCC) surveillance beyond initial screening among underserved cirrhosis patients. **BACKGROUND:** Although initial HCC screening among cirrhosis patients remains low, few studies have evaluated retention to HCC surveillance beyond initial screening. **METHODS:** We retrospectively evaluated all consecutive adults with cirrhosis from 2014 to 2017 at a single underserved safety net hospital system to determine rates of HCC surveillance at 6 months and at 1 year beyond initial screening. Rates of HCC surveillance was stratified by sex, race/ethnicity, and etiology of liver disease. Multivariate Cox proportional hazards models evaluated predictors of retention into HCC surveillance. **RESULTS:** Among 235 cirrhosis patients [hepatitis C virus: 35.7%, hepatitis B virus (HBV): 15.7%, alcoholic cirrhosis: 36.2%, nonalcoholic steatohepatitis (NASH): 8.1%], mean age of cirrhosis diagnosis was 54.2±8.9 years. Overall, 74.8% received initial screening within 1 year of cirrhosis diagnosis. Among those who completed initial screening, 47.6% [95% confidence interval (CI), 41.4-54.2] received second surveillance within 1 year. On multivariate analyses, patients with NASH and HBV were significantly more likely to receive second HCC surveillance compared with hepatitis C virus, HBV (hazard ratio, 2.32; 95% CI, 1.18-4.56; P=0.014) and NASH (hazard ratio, 2.49; 95% CI, 1.22-5.11; P=0.012). No sex or race-specific/ethnicity-specific differences in HCC surveillance retention were observed. **CONCLUSIONS:** Although overall rates of initial HCC screening among cirrhosis patients is nearly 75%, retention into continued HCC surveillance is poor, with less than half of patients undergoing subsequent HCC surveillance. Cirrhosis patients with HBV and NASH were more likely to be retained into HCC surveillance.

**ADI-PEG 20 Plus Best Supportive Care versus Placebo Plus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma.** Abou-Alfa G1,2, Qin S3, Ryou BY4, et al. Ann Oncol. 2018 Apr 5. doi: 10.1093/annonc/mdy101. [Epub ahead of print]

**BACKGROUND:** Arginine depletion is a putative target in hepatocellular carcinoma (HCC). HCC often lacks argininosuccinate synthetase, a citrulline to arginine-repleting enzyme. ADI-PEG 20 is a cloned arginine degrading enzyme - arginine deiminase - conjugated with polyethylene glycol. The goal of this study was to evaluate this agent as a potential novel



therapeutic for HCC after first line systemic therapy. **METHODS AND PATIENTS:** Patients with histologically proven advanced HCC and Child-Pugh up to B7 with prior systemic therapy, were randomized 2:1 to ADI-PEG 20 18 mg/m<sup>2</sup> vs. placebo intramuscular (IM) injection weekly. The primary endpoint was overall survival (OS), with 93% power to detect a 4 to 5.6 months increase in median OS (1-sided  $\alpha = 0.025$ ). Secondary endpoints included progression-free survival (PFS), safety, and arginine correlatives. **RESULTS:** 635 patients were enrolled: median age 61, 82% male, 60% Asian, 52% hepatitis B, 26% hepatitis C, 76% stage IV, 91% Child-Pugh A, 70% progressed on sorafenib and 16% were intolerant. Median OS was 7.8 months for ADI-PEG 20 vs 7.4 for placebo ( $p = 0.88$ , HR = 1.02) and median PFS 2.6 months vs. 2.6 ( $p = 0.07$ , HR = 1.17). Grade 3 fatigue and decreased appetite occurred in less than 5% of patients. Two patients on ADI-PEG 20 had  $\geq$  grade 3 anaphylactic reaction. Death rate within 30 days of end of treatment was 15.2% on ADI-PEG 20 vs. 10.4% on placebo, none related to therapy. Post-hoc analyses of arginine assessment at 4, 8, 12 and 16 weeks, demonstrated a trend of improved OS for those with more prolonged arginine depletion. **CONCLUSION:** ADI-PEG 20 monotherapy did not demonstrate an OS benefit in second line setting for HCC. It was well tolerated. Strategies to enhance prolonged arginine depletion and synergize the effect of ADI-PEG 20 are underway.