



Caring Ambassadors Program
Hepatitis C Newsletter
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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11.](#) Murray KF1, Balistreri WF2, Bansal S3, et al. Hepatology. 2018 Aug 2. doi: 10.1002/hep.30123. [Epub ahead of print]

Currently, there are no interferon-free treatments available for HCV-infected patients younger than 12 years of age. We evaluated the safety and effectiveness of the all-oral regimen ledipasvir-sofosbuvir ± ribavirin, in HCV-infected children aged 6 to <12 years. In an open-label study, patients aged 6 to <12 years received ledipasvir 45 mg- sofosbuvir 200 mg as two fixed-dose combination tablets 22.5/100 mg once daily, with or without ribavirin, for 12 or 24 weeks, depending on HCV genotype and cirrhosis status. The primary efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). Twelve patients underwent intensive pharmacokinetic sampling to confirm the appropriateness of the ledipasvir and sofosbuvir dosages. 92 patients were enrolled (88 genotype 1, 2 genotype 3, and 2 genotype 4), with a median age of 9 years (range, 6-11). Most were perinatally infected (97%) and treatment-naïve (78%). Two were confirmed to have cirrhosis, while the degree of fibrosis was unknown in 55 patients. The overall SVR12 rate was 99% (91/92, 95% CI 94-100%). The single patient not reaching SVR relapsed 4 weeks after completing 12 weeks of treatment. The most common adverse events were headache and pyrexia. One patient had 3 serious adverse events: tooth abscess, abdominal pain, and gastroenteritis, which were considered to be not related to study treatment. The area under the concentration-time curve and maximum concentration values for sofosbuvir, its primary metabolite GS-331007, and ledipasvir, were within predefined pharmacokinetic equivalence boundaries (50%-200%) compared to values in adults in phase 2/3 of the ledipasvir and sofosbuvir studies. **CONCLUSIONS:** Ledipasvir-sofosbuvir was well tolerated and highly effective in children 6 to <12 years old with chronic HCV. This article is protected by copyright. All rights reserved.

[Sofosbuvir based regimens in the treatment of chronic hepatitis C genotype 1 infection in African-American patients: a community-based retrospective cohort study.](#) Gayam V1, Tiongson B1, Khalid M1, et al. Eur J Gastroenterol Hepatol. 2018 Aug 21. doi: 10.1097/MEG.0000000000001233. [Epub ahead of print]

BACKGROUND: Direct-acting antiviral (DAA) drugs have been highly effective in the treatment of chronic hepatitis C (HCV) infection. Limited data exist comparing the safety,

tolerability, and efficacy of DAAs in African-American (AA) patients with chronic hepatitis C genotype 1 (HCV GT-1) in the community practice setting. We aim to evaluate treatment response of DAAs in these patients. **PATIENTS AND METHODS:** All the HCV GT-1 patients treated with DAAs between January 2014 and January 2018 in a community clinic setting were retrospectively analyzed. Pretreatment baseline patient characteristics, treatment efficacy with a sustained virologic response at 12 weeks post-treatment (SVR12), and adverse reactions were assessed. **RESULTS:** Two-hundred seventy-eight patients of AA descent were included in the study. One-hundred sixty-two patients were treated with ledipasvir/sofosbuvir (SOF)±ribavirin, 38 were treated with simeprevir/SOF±ribavirin, and 38 patients were treated with SOF/velpatasvir. Overall, SVR at 12 weeks was achieved in 94.6% in patients who received one of the three DAA regimens (93.8% in ledipasvir/SOF group, 92.1% in simeprevir/SOF group, and 97.4% in SOF/velpatasvir group). Previous treatment experience, HCV RNA levels and HIV status had no statistical significance on overall SVR achievement (P=0.905, 0.680, and 0.425, respectively). Compensated cirrhosis in each of the treatment groups did not influence overall SVR of 12. The most common adverse effect was fatigue (27%). None of the patients discontinued the treatment because of adverse events. **CONCLUSION:** In the real-world setting, DAAs are safe, effective, and well tolerated in African-American patients with chronic HCV GT-1 infection with a high overall SVR rate of 94.6%. Treatment rates did not differ on the basis of previous treatment and compensated cirrhosis status. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Association Between Vitamin D Levels and Treatment Response to Direct-Acting Antivirals in Chronic Hepatitis C: A Real-World Study.

Gayam V1, Mandal AK1, Khalid M1, Mukhtar O1, Gill A1, Garlapati P1, Tiongson B1, Sherigar J2, Mansour M1, Mohanty S2. Gastroenterology Res. 2018 Aug;11(4):309-316. doi: 10.14740/gr1072w. Epub 2018 Feb 8.

BACKGROUND: Low serum vitamin D levels in chronic hepatitis C (CHC) is associated with advanced liver fibrosis; and there remains an imprecise relationship with the treatment response based on the vitamin D levels. Previous studies have shown conflicting results on the vitamin D levels, and association with treatment response in CHC treated with interferon-based regimens.

METHODS: Patients with CHC treated with direct-acting antivirals (DAAs) between January 2016 and December 2017 in the community clinic setting were retrospectively analyzed.

Pretreatment baseline patient characteristics, treatment efficacy with the sustained virologic response at 12 weeks post-treatment (SVR 12) were assessed in CHC patients with deficient, insufficient, and normal levels of vitamin D measured before the initiation of DAA therapy.

RESULTS: Two hundred and ninety-one patients were included in the study. Direct-acting antivirals included in the study were ledipasvir/sofosbuvir ± ribavirin, ombitasvir + paritaprevir + ritonavir + dasabuvir ± ribavirin, and sofosbuvir/velpatasvir. An overall sustained virologic response was achieved in 95% (n = 276) of patients. SVR 12 rates among patients with vitamin D deficiency, vitamin D insufficiency and normal vitamin D levels were 92%, 96.2%, and 97.2% respectively and was not statically significant (P = 0.214). A total of 71 patients were cirrhotic. The prevalence of vitamin D insufficiency (20 - 29.9 ng/mL) and deficiency (< 20 ng/mL) was significantly higher in cirrhotic patients (P = 0.01). Despite this, pretreatment vitamin D levels

did not show any impact on the virologic response. The most common adverse effect observed was fatigue. None of the patients had to discontinue the treatment due to adverse events.

CONCLUSIONS: DAAs are safe and effective with a high overall SVR 12 in CHC and treatment response does not depend on the pretreatment vitamin D levels. The prevalence of both vitamin D insufficiency and deficiency was observed to be higher in cirrhotic cohorts compared to non-cirrhotic counterparts.

[Hepatitis C infection substantially reduces survival of alcohol-dependent patients.](#)

Muga R1, Sanvisens A1, Jarrin I2, Fuster D1, Bolao F3, Tor J1, Muñoz A4. Clin Epidemiol. 2018 Aug 1;10:897-905. doi: 10.2147/CLEP.S162308. eCollection 2018.

BACKGROUND: Heavy alcohol use is associated with life-threatening complications including progressive liver disease. We aimed to analyze the impact of hepatitis C virus (HCV) infection on survival and liver-related death in alcohol-dependent patients. **PATIENTS AND METHODS:** This is a longitudinal study in patients seeking treatment of alcohol abuse between 2000 and 2010. Information on alcohol use characteristics, alcoholic liver disease, and HCV infection were obtained at entry. Cumulated mortality and causes of death were ascertained through clinical records and death registry. **RESULTS:** A total of 819 patients (81.6% men) underwent ethanol detoxification; age was 44 (inter-quartile range [IQR] 38-51) years; the duration of heavy alcohol use was 14 (IQR 6-24) years; and the alcohol consumption was 190 (IQR 120-250) g/day. The prevalence of HCV infection was 15.8%. There were 129 (16.9%) deaths during 5,117 persons-year (p-y) of follow-up (median follow-up 6.4 [IQR 4.3-9.2] years); 31 (24.6%) deaths were observed among the HCV-positive patients, and 98 (15.4%) deaths were observed among the HCV-negative patients. The mortality rate was significantly ($P=0.03$) higher among the HCV-positive patients (3.84×100 p-y; 95% confidence interval [CI]: 2.70, 5.46) than among the HCV-negative patients (2.27×100 p-y; 95% CI: 1.86, 2.77). Survival times for the HCV infected patients were 34% shorter (time ratio relative to HCV negative: 0.66; 95% CI: 0.51, 0.86). The main causes of death in the HCV-positive and -negative patients were liver-related mortality (48.4%) and neoplasia (22.4%), respectively. The liver-related mortality was significantly higher among the HCV-positive patients (adjusted sub-distribution hazard ratio [asHR] 3.65; 95% CI: 1.72, 7.78; $P=0.001$). **CONCLUSION:** HCV infection compromises the survival of patients with alcohol abuse/dependence. The new direct antiviral agents for the treatment of HCV infection may result in better clinical outcomes.

[Characterization of hepatitis C virus resistance to grazoprevir reveals complex patterns of mutations following on-treatment breakthrough that are not observed at relapse.](#)

Bonsall D1, Black S2, Howe AY2, Chase R2, Ingravallo P2, Pak I2, Brown A1, Smith DA1, Bowden R1, Barnes E1. Infect Drug Resist. 2018 Aug 8;11:1119-1135. doi: 10.2147/IDR.S156581. eCollection 2018.

PURPOSE: A detailed analysis of hepatitis C virus (HCV) resistance-associated substitutions (RASs) is required to understand why people fail direct-acting antiviral therapies. This study was conducted to assess RASs in an analysis of 2 trials evaluating the second-generation NS3/4A protease inhibitor grazoprevir (GZR) in combination with peginterferon/ribavirin. **PATIENTS AND METHODS:** From a total of 113 participants with HCV genotype 1 infection, RASs were evaluated in 25 patients who relapsed and 6 patients with on-treatment virologic breakthrough using consensus Sanger and clonal sequence analysis of NS3/NS4a genes, with in vitro testing of replicon mutants. Next-generation sequencing (NGS) was used in a subset of participants to

assess minority variants and the evolution of the whole viral genome. **RESULTS:** Baseline RASs did not predict treatment failure. Relapse was most commonly associated with RASs at D168, although additional RASs (Y56, R155 and A156) were also detected, particularly in participants with on-treatment breakthrough. Treatment-emergent RASs usually reverted to wild-type (WT), suggesting these mutations were associated with a negative fitness cost (confirmed using in vitro assays). NGS was the most sensitive assay for the detection of minor variants. Significant viral sequence divergence (up to 5.9% codons) was observed across whole genomes in association with the acquisition and reversion of RASs. **CONCLUSION:** Relapse with GZR and peginterferon/ribavirin is commonly associated with single RASs in NS3 that generally revert to WT, while breakthrough follows more complex patterns of viral resistance. NGS suggests that large diverse pools of viral quasispecies that emerge with RASs facilitate rapid viral evolution.

[Hepatic decompensation during paritaprevir/ritonavir/ombitasvir/dasabuvir treatment for genotype 1b chronic hepatitis C patients with advanced fibrosis and compensated cirrhosis.](#)

Hsieh YC1, Jeng WJ1,2,3, Huang CH1,2, et al. PLoS One. 2018 Aug 23;13(8):e0202777. doi: 10.1371/journal.pone.0202777. eCollection 2018.

BACKGROUND AND AIM: Hepatic decompensation is a severe on-treatment adverse event for chronic hepatitis C treated with paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD). Till now, few papers regarding on-treatment hepatic decompensation have been reported. The study aims to analyze the general feature and predictive factors of on-treatment hepatic decompensation in hepatitis C virus (HCV) genotype 1b-infected patients with advanced fibrosis and compensated cirrhosis who receive treatment with PrOD. **METHODS:** A real-world cohort enrolled 189 HCV genotype 1b patients with advanced fibrosis and compensated cirrhosis treated with 12-week PrOD. Clinical and laboratory data were analyzed between patients with and without on-treatment hepatic decompensation. **RESULTS:** The sustained virologic response rate at 12 weeks after treatment was 97.3% in HCV subtype 1b patients with advanced fibrosis and cirrhosis. On-treatment hyperbilirubinemia (total bilirubin >2 mg/dL) occurred in 27 (14.3%) patients, and the incidence of the increase of total and direct form bilirubin was significantly different during treatment between patients with Child-Turcotte-Pugh score 5 and score 6. Five (18.5%) hyperbilirubinemia patients progressed to hepatic decompensation. Older age (adjusted OR: 1.2, 95% CI: 1.0-1.4) and albumin \leq 3.6 g/dL (adjusted OR: 10.4, 95% CI: 1.3-81.2) may be two predictors for on-treatment hepatic decompensation by multivariate analysis. **CONCLUSIONS:** PrOD is an effective direct-acting antiviral agent for antiviral therapy in HCV genotype 1b patients with advanced fibrosis and cirrhosis. Hyperbilirubinemia is possibly the early warning feature of on-treatment hepatic decompensation. This serious adverse event of on-treatment hepatic decompensation is not common. Older age and low baseline albumin level may be predictive factors.

[Sofosbuvir Based Regimens in the Treatment of Chronic Hepatitis C with Compensated Liver Cirrhosis in Community Care Setting.](#)

Gayam V1, Mandal AK1, Khalid M1, Mukhtar O1, Gill A1, Garlapati P1, Khalid M2, Mansour M1. Int J Hepatol. 2018 Aug 1;2018:4136253. doi: 10.1155/2018/4136253. eCollection 2018.

BACKGROUND: Direct-acting antiviral (DAA) drugs have been highly effective in the treatment of chronic hepatitis C (CHC) infection. We aim to evaluate the treatment response of Sofosbuvir based DAA in CHC patients with compensated liver cirrhosis as limited data exists in

the real-world community setting. **METHODS:** All the CHC patients with compensated liver cirrhosis treated with Sofosbuvir based DAAs between January 2014 and December 2017 in a community clinic setting were retrospectively analyzed. Pretreatment baseline patient characteristics, treatment efficacy with the sustained virologic response at 12 weeks posttreatment (SVR12), and adverse reactions were assessed. **RESULTS:** One hundred and twelve patients with CHC infection and concurrent compensated cirrhosis were included in the study. Black patients represented the majority of the study population (64%). Eighty-seven patients were treated with Ledipasvir/Sofosbuvir (LDV/SOF) ±Ribavirin and 25 patients were treated with Sofosbuvir/Velpatasvir (SOF/VEL). Overall, SVR 12 after treatment was achieved in 90% in patients who received one of the two DAA regimens (89.7% in LDV/SOF group and 92% in SOF/VEL group). SVR 12 did not vary based on age, sex, body mass index, baseline HCV viral load, HCV/HIV coinfection, type of genotype, and prior treatment status. Apart from a low platelet count, there were no other factors associated with a statistical difference in SVR 12($p=0.002$) between the two regimens. Fatigue (35%) was the most common adverse effect and no patients discontinued treatment due to adverse effects. **CONCLUSION:** In the community care setting, Sofosbuvir based DAAs are safe, effective with high overall SVR, and well tolerated in patients with CHC patients with compensated liver cirrhosis.

[Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort.](#) Rossi C1, Butt ZA2, Wong S3, et al. J Hepatol. 2018 Aug 22. pii: S0168-8278(18)32288-8. doi: 10.1016/j.jhep.2018.07.025. [Epub ahead of print]

BACKGROUND & AIMS: Direct-acting antiviral therapies (DAA) are an important tool for hepatitis C virus (HCV) elimination. However, reinfection among people who inject drugs (PWID) may hamper elimination targets. Therefore, we estimated HCV reinfection rates among DAA-treated individuals, including PWID. **METHODS:** We analyzed data from the British Columbia Hepatitis Testers Cohort which included ~1.7 million individuals screened for HCV in British Columbia, Canada. We followed HCV-infected individuals treated with DAAs who achieved a sustained virologic response (SVR) and had ≥ 1 subsequent HCV RNA measurement to April 22nd, 2018. Reinfection was defined as a positive RNA measurement after SVR. PWID were identified using a validated algorithm and classified based on recent (<3 years) or former (≥ 3 years before SVR) use. Crude reinfection rates per 100 person-years (PYs) were calculated. Poisson regression was used to model adjusted incidence rate ratios (IRRs) and 95% CIs. **RESULTS:** Of 4,114 individuals who met the inclusion criteria, most were male ($n = 2,692$, 65%), born before 1965 ($n = 3,411$, 83%) and were either recent ($n = 875$, 21%) or former PWID ($n = 1,793$, 44%). Opioid-agonist therapy (OAT) was received by 19% of PWID. We identified 40 reinfections during 2,767 PYs. Reinfection rates were higher among recent (3.1/100 PYs; IRR 6.7; 95% CI 1.9-23.5) and former PWID (1.4/100 PYs; IRR 3.7; 95% CI 1.1-12.9) than non-PWID (0.3/100 PYs). Among recent PWID, reinfection rates were higher among individuals born after 1975 (10.2/100 PYs) and those co-infected with HIV (5.7/100 PYs). Only one PWID receiving daily OAT developed reinfection. **CONCLUSIONS:** Population-level reinfection rates remain elevated after DAA therapy among PWID because of ongoing exposure risk. Engagement of PWID in harm-reduction and support services is needed to prevent reinfections. **LAY SUMMARY:** Direct-acting antivirals are an effective tool for the treatment of hepatitis C virus, enabling the elimination of the virus. However, some patients who have been successfully treated with direct-acting antivirals are at risk of reinfection. Our findings showed that the risk of

reinfection was highest among people with recent injection drug use. Among people who inject drugs, daily use of opioid-agonist therapy was associated with a lower risk of reinfection.

[Evaluation of accuracy of elastography point quantification versus other noninvasive modalities in staging of fibrosis in chronic hepatitis C virus patients.](#) Fouad R1, Elbaz T1, Abdel Alem S1, et al. Eur J Gastroenterol Hepatol. 2018 Aug;30(8):882-887. doi: 10.1097/MEG.0000000000001151.

BACKGROUND: Elastography point quantification (ElastPQ) is a newly noninvasive method incorporated into a conventional ultrasound system for staging of liver fibrosis in patients with chronic liver diseases. **AIM:** The aim was to evaluate ElastPQ reproducibility and its accuracy in staging of liver fibrosis in hepatitis C virus (HCV) patients in comparison with transient elastography (TE) and fibrosis scores [FIB-4 and aspartate aminotransferase-to-platelet ratio index (APRI)] using liver biopsy as a reference standard and also to predict the sensitivity and specificity of ElastPQ as well as proposing a cut-off for advanced fibrosis. **PATIENTS AND METHODS:** A single-center, cross-sectional study enrolled 72 chronic HCV patients. Baseline demographic and laboratory data were recorded. ElastPQ and TE were performed. Fibrosis scores were calculated. The performance of ElastPQ was compared with that of TE and noninvasive methods (FIB-4, APRI) using liver biopsy as a reference standard using receiver operating characteristic curve analysis. **RESULTS:** ElastPQ is a valuable diagnostic tool for the diagnosis of $F \geq 1$, $F \geq 2$, and $F \geq 3$, with area under the receiver operating characteristic curve of 0.79, 0.74, and 0.83, respectively. The best cut-off values for ElastPQ were 4.9, 6.6, and 10.7 kPa for mild fibrosis, significant fibrosis, and advanced fibrosis, respectively. ElastPQ correlated positively with all other fibrosis indices (TE, APRI, and FIB-4) as well as liver biopsy. Area under the curve for the diagnosis of advanced fibrosis (F3/F4) using ElastPQ was 0.83 at a cut-off value of 10.7 kPa ($P < 0.01$). **CONCLUSION:** ElastPQ is a promising noninvasive US-based method for assessing liver fibrosis in HCV-related chronic liver disease patients with good diagnostic performance comparable to that of liver biopsy and TE.

[Short Duration AL-335, Odalasvir, With/Without Simeprevir, in Patients With HCV GT1 or 3 Infection Without Cirrhosis.](#) Gane EJ1, Stedman CA2, Schwabe C1, Vijgen L3, Chanda S4, Kakuda TN4, Fry J4, Blatt LM4, McClure MW4. Hepatology. 2018 Aug 2. doi: 10.1002/hep.30126. [Epub ahead of print]

This open-label, Phase IIa study assessed the safety, pharmacokinetics, and efficacy of direct-acting antiviral agent (DAA) regimens in patients with chronic hepatitis C virus (HCV) infection. Multiple 6-12-week oral regimens of 400-800 mg once daily (QD) AL-335 + 50 mg QD/every other day odalasvir ± 75-150 mg QD simeprevir were evaluated in treatment-naïve, HCV genotype (GT)1/3-infected patients without cirrhosis. Safety/pharmacokinetic parameters, HCV-RNA, and sequencing data were assessed. Treatment regimens for later study cohorts were adjusted based on emerging data. In total, 112 patients were enrolled. Three serious treatment-emergent adverse events occurred, one of which (Wenckebach) was possibly related to high odalasvir exposure and resulted in premature discontinuation of study drugs. No other clinically significant safety findings were identified. GT1-infected patients receiving 3-DAA for 6-8 weeks achieved 100% sustained virologic response 12 and 24 weeks after end of treatment (SVR12/24). GT1-infected patients receiving 2-DAA or GT3-infected patients receiving 3-DAA had SVR12/24 <90%, whether treated for 8 or 12 weeks. Virologic failure was associated with the emergence of generally persistent NS5A and/or transient NS5B resistance-associated

substitutions (RASs) in most patients. Pharmacokinetic characteristics of the three drugs were also elucidated. **CONCLUSIONS:** In treatment-naïve subjects without cirrhosis, AL-335 + odalasvir + simeprevir for 6-8 weeks was generally safe and highly efficacious against HCV GT1. However, inadequate efficacy was observed for the 2-DAA regimen in GT1-infected subjects and the 3-DAA regimen in GT3-infected subjects. This article is protected by copyright. All rights reserved.

[A comprehensive assessment of patient reported symptom burden, medical comorbidities, and functional well being in patients initiating direct acting antiviral therapy for chronic hepatitis C: Results from a large US multi-center observational study.](#) Evon DM1, Stewart

PW2, Amador J2, et al. PLoS One. 2018 Aug 1;13(8):e0196908. doi:

10.1371/journal.pone.0196908. eCollection 2018.

BACKGROUND: Symptom burden, medical comorbidities, and functional well-being of patients with chronic hepatitis C virus (HCV) initiating direct acting antiviral (DAA) therapy in real-world clinical settings are not known. We characterized these patient-reported outcomes (PROs) among HCV-infected patients and explored associations with sociodemographic, liver disease, and psychiatric/substance abuse variables. **METHODS AND FINDINGS:** PROP UP is a large US multicenter observational study that enrolled 1,600 patients with chronic HCV in 2016-2017. Data collected prior to initiating DAA therapy assessed the following PROs: number of medical comorbidities; neuropsychiatric, somatic, gastrointestinal symptoms (PROMIS surveys); overall symptom burden (Memorial Symptom Assessment Scale); and functional well-being (HCV-PRO). Candidate predictors included liver disease markers and patient-reported sociodemographic, psychiatric, and alcohol/drug use features. Predictive models were explored using a random selection of 700 participants; models were then validated with data from the remaining 900 participants. The cohort was 55% male, 39% non-white, 48% had cirrhosis (12% with advanced cirrhosis); 52% were disabled or unemployed; 63% were on public health insurance or uninsured; and over 40% had markers of psychiatric illness. The median number of medical comorbidities was 4 (range: 0-15), with sleep disorders, chronic pain, diabetes, joint pain and muscle aches being present in 20-50%. Fatigue, sleep disturbance, pain and neuropsychiatric symptoms were present in over 60% and gastrointestinal symptoms in 40-50%. In multivariable validation models, the strongest and most frequent predictors of worse PROs were disability, unemployment, and use of psychiatric medications, while liver markers generally were not. **CONCLUSIONS:** This large multi-center cohort study provides a comprehensive and contemporary assessment of the symptom burden and comorbid medical conditions in patients with HCV treated in real world settings. Pain, fatigue, and sleep disturbance were common and often severe. Sociodemographic and psychiatric markers were the most robust predictors of PROs. Future research that includes a rapidly changing population of HCV-infected individuals needs to evaluate how DAA therapy affects PROs and elucidate which symptoms resolve with viral eradication. **TRIAL REGISTRATION:** (Clinicaltrial.gov: NCT02601820).

CONFLICT OF INTEREST STATEMENT: Donna M. Evon has received research funding from Gilead. Michael Fried has received research funding from and served as a consultant for AbbVie, BMS, Gilead, and Merck, and TARGET PharmaSolutions. Stock in TARGET PharmaSolutions is held in an independently managed trust. Anna S. Lok has received research support from AbbVie, BMS, Gilead, and Merck; and served as an advisor for Gilead. Richard K. Sterling has received research support from AbbVie, BMS, Gilead, Merck, and Roche and served as a consultant for Merck, Bayer, Salix, AbbVie, Gilead, Jansen, ViiV, Baxter, and Pfizer.

Joseph K. Lim has received research support (paid to Yale University) and served as a consultant for Bristol-Myers Squibb and Gilead. Nancy Reau has received research funding (paid to Rush) from AbbVie and Intercept and has served as a consultant for AbbVie, Gilead, Merck, and BMS. Souvik Sarkar served on a Gilead and Abbvie Advisory Board. David R. Nelson has received research grant support from AbbVie, BMS, Gilead, Janssen, and Merck. K. Rajender Reddy is an Ad-Hoc Advisor to Gilead, BMS, Janssen, Merck, and Abbvie and has received research support from Gilead, BMS, Janssen, Merck, and AbbVie (paid to the University of Pennsylvania). Adrian M. Di Bisceglie has received research support from AbbVie, BMS and Gilead and has served on advisory boards for AbbVie, BMS and Merck. Paul Stewart has served as a consultant to TARGET PharmaSolutions. Jipcy Amador served as a biostatistics intern at TARGET PharmaSolutions in 2017. Carol E. Golin and Bryce Reeve declare that they have no conflict of interests to disclose. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

[Perinatal Transmission of Hepatitis C Virus: Defining the Cascade of Care.](#) Epstein RL1, Sabharwal V2, Wachman EM3, Saia KA4, Vellozzi C5, Hariri S5, Linas BP6. J Pediatr. 2018 Aug 28. pii: S0022-3476(18)30899-0. doi: 10.1016/j.jpeds.2018.07.006. [Epub ahead of print]

OBJECTIVES: The US National Viral Hepatitis Action Plan calls for major efforts to expand hepatitis C virus (HCV) diagnosis and treatment; prenatal care settings are potential venues for expanding HCV testing. We aimed to characterize the HCV diagnostic cascade for women and infants and investigate factors associated with linkage and follow-up. **STUDY DESIGN:** We used electronic health records for a 10-year cohort of 879 women with opioid use disorder from an obstetric clinic serving women with substance use disorders. **RESULTS:** Altogether, 744 women (85%) were screened for HCV; 510 (68%) were seropositive, of whom 369 (72%) had nucleic acid testing performed and of these 261 (71%) were viremic. Of 404 infants born to HCV-seropositive women, 273 (68%) were tested at least once for HCV, 180 (45%) completed the American Academy of Pediatrics-recommended perinatal HCV screening, and 5 (2.8%) were diagnosed with HCV infection and linked to care. More recent delivery date (2014-2015) was associated with maternal linkage to care (aOR, 2.5; 95% CI, 1.4-4.7). Maternal coinfection with HIV (aOR, 9.0; 95% CI, 1.1-72.8) and methadone maintenance therapy, compared with buprenorphine (aOR, 1.5; 95% CI, 0.9-2.5), were associated with higher rates of infant HCV testing. **CONCLUSIONS:** HCV prevalence among pregnant women with opioid use is high and infant HCV screening is imperfect. Programmatic changes to improve both mother and infant follow-up may help to bridge identified gaps in the cascade to cure.

[Multicenter Experience using Ledipasvir/Sofosbuvir ± RBV to Treat HCV GT 1 Relapsers after Simeprevir and Sofosbuvir Treatment.](#) Aqel B, Leise M1, Vargas HE2, Watt KD1, Keaveny AP3, Zhang N4, Zhang N4, Pungpapong S3. Ann Hepatol. 2018 Aug 24;17(5):815-821. doi: 10.5604/01.3001.0012.3142.

INTRODUCTION AND AIM: Approximately 10%-15% of patients with hepatitis C genotype 1 (HCV GT1) experience virological relapse after all-oral antiviral regimen using simeprevir (SMV) and sofosbuvir (SOF). The efficacy and safety of treating such relapsers using ledipasvir/sofosbuvir (LDV/SOF) with/without ribavirin (RBV) has been limited. **OBJECTIVE:** Report the virological response and safety of LDV/SOF with/without RBV for 12-24 weeks in treating HCV GT1 relapsers after SMV + SOF. **MATERIAL AND METHODS:** Patients treated with standardized clinical protocol utilizing LDV/SOF with/without RBV at three

transplant centers were retrospectively reviewed. **RESULTS:** Forty-five patients (29% post-LT, 82% male, 13% non-white, 73% subtype 1a, 86% IL28B CT/TT, 78% F3-4) started LDV/SOF with/without RBV at a median of 22 weeks (range 7-55 weeks) after the last dose of SMV+SOF treatment. Thirty-seven patients received LDV/SOF for 24 weeks (24/37 patients with RBV) and eight patients received LDV/SOF for 12 weeks (5/8 patients with RBV). RBV dose was adjusted for renal function. Sixteen patients who were RBV-ineligible received LDV/SOF without RBV for 12 or 24 weeks. SVR 12 was achieved in 96% (43/45) of patients. Baseline viral load, RBV use, or GT1 subtype did not impact SVR 12. Minimal adverse events were reported in those without RBV; 45% of patients who received RBV developed significant anemia requiring RBV dose reduction and/or discontinuation. In LT recipients, minimal immunosuppression dose adjustments were required and no biopsy-proven acute rejection occurred. **CONCLUSIONS:** Treatment with LDV/SOF with/without RBV for 12-24 weeks was very well tolerated and resulted in high SVR 12 rates (96%) in HCV GT1 relapsers to SMV + SOF treatment.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Negative regulation of MAVS-mediated antiviral signaling by the mitochondrial protein LRPPRC during HCV infection.](#) Refolo G1, Ciccocanti F1, Di Rienzo M1, et al. *Hepatology*. 2018 Aug 2. doi: 10.1002/hep.30149. [Epub ahead of print]

Hepatitis C virus (HCV) is highly efficient in establishing a chronic infection, having evolved multiple strategies to suppress the host antiviral responses. The HCV non-structural 5A (NS5A) protein, in addition to its role in viral replication and assembly, has long been known to hamper the interferon (IFN) response. However, the mechanism of this inhibitory activity of NS5A remains partly characterized. In a functional proteomic screening carried out in HCV replicon cells, we identified the mitochondrial protein LRPPRC as an NS5A binding factor. Notably, we found that downregulation of LRPPRC expression results in a significant inhibition of HCV infection, which is associated to an increased activation of the IFN response. Moreover, we showed that LRPPRC acts as a negative regulator of the mitochondrial-mediated antiviral immunity, by interacting with MAVS and inhibiting its association with TRAF3 and TRAF6. Finally, we demonstrated that NS5A is able to interfere with MAVS activity in a LRPPRC-dependent manner. Overall, our results indicate that NS5A contributes to the inhibition of innate immune pathways during HCV infection by exploiting the ability of LRPPRC to inhibit MAVS-regulated antiviral signaling. This article is protected by copyright. All rights reserved.

[Resistance Analysis of a 3-Day Monotherapy Study with Glecaprevir or Pibrentasvir in Patients with Chronic Hepatitis C Virus Genotype 1 Infection.](#) Ng T11, Pilot-Matias T2, Tripathi R3, et al. *Viruses*. 2018 Aug 28;10(9). pii: E462. doi: 10.3390/v10090462.

Glecaprevir (an NS3/4A protease inhibitor) and pibrentasvir (an NS5A inhibitor) are potent and pangenotypic hepatitis C virus (HCV) direct-acting antivirals. This report describes the baseline polymorphisms and treatment-emergent substitutions in NS3 or NS5A detected in samples from HCV genotype 1-infected patients receiving 3-day monotherapy of glecaprevir or pibrentasvir, respectively. None of the NS3 polymorphisms detected in the 47 baseline samples collected prior to glecaprevir monotherapy conferred reduced susceptibility to glecaprevir. The NS3 A156T substitution, which conferred resistance to glecaprevir but had low replication efficiency, emerged in one genotype 1a-infected patient among the 35 patients with available post-baseline sequence data. Baseline NS5A polymorphisms were detected in 12 of 40 patients prior to

pibrentasvir monotherapy; most polymorphisms were single-position NS5A amino acid substitutions that did not confer resistance to pibrentasvir. Among the 19 patients with available post-baseline NS5A sequence data, 3 had treatment-emergent NS5A substitutions during pibrentasvir monotherapy. All treatment-emergent NS5A substitutions were linked multiple-position, almost exclusively double-position, substitutions that conferred resistance to pibrentasvir. Replicons engineered with these double-position substitutions had low replication efficiency. In conclusion, resistance-conferring substitutions emerged in a small number of genotype 1-infected patients during glecaprevir or pibrentasvir monotherapy; unlike other NS5A inhibitors, pibrentasvir did not select single-position NS5A substitutions during monotherapy.

[Gut Dysbiosis Associated With Hepatitis C Virus Infection.](#) Inoue T1, Nakayama J2, Moriya K3, et al. Clin Infect Dis. 2018 Aug 31;67(6):869-877. doi: 10.1093/cid/ciy205.

BACKGROUND: Little is known about the effect of hepatitis C virus (HCV) infection on gut microbiota and the relationship between alteration of gut microbiota and chronic hepatitis C (CHC) progression. We performed a comparative study of gut microbiota composition between CHC patients and healthy individuals. **METHODS:** Fecal samples from 166 CHC patients were compared with those from 23 healthy individuals; the gut microbiota community was analyzed using 16S ribosomal RNA gene sequencing. CHC patients were diagnosed with persistently normal serum alanine aminotransferase without evidence of liver cirrhosis (LC) (PNALT, n = 18), chronic hepatitis (CH, n = 84), LC (n = 40), and hepatocellular carcinoma in LC (n = 24). **RESULTS:** Compared with healthy individuals, bacterial diversity was lower in persons with HCV infection, with a decrease in the order Clostridiales and an increase in Streptococcus and Lactobacillus. Microbiota dysbiosis already appeared in the PNALT stage with the transient increase in Bacteroides and Enterobacteriaceae. Predicted metagenomics of microbial communities showed an increase in the urease gene mainly encoded by viridans streptococci during CHC progression, consistent with a significantly higher fecal pH in CH and LC patients than in healthy individuals or those in the PNALT stage. **CONCLUSIONS:** HCV infection is associated with gut dysbiosis, even in patients with mild liver disease. Additionally, overgrowth of viridans streptococci can account for hyperammonemia in CH and LC. Further studies would help to propose a novel treatment strategy because the gut microbiome can be therapeutically altered, potentially reducing the complications of chronic liver disease.

[Cellular Membrane Trafficking Machineries Used by the Hepatitis Viruses.](#) Inoue J1, Ninomiya M1, Shimosegawa T1, McNiven MA2. Hepatology. 2018 Aug;68(2):751-762. doi: 10.1002/hep.29785.

While the life cycles of hepatitis viruses (A, B, C, D, and E) have been modestly characterized, recent intensive studies have provided new insights. Because these viruses "hijack" the membrane trafficking of the host cell machinery during replicative propagation, it is essential to determine and understand these specific cellular pathways. Hepatitis B virus (HBV) and hepatitis C virus are well known as leading causes of liver cirrhosis and hepatocellular carcinoma. While substantial inroads toward treating hepatitis C virus patients have recently been made, patients with HBV continue to require lifelong treatment, which makes a thorough understanding of the HBV life cycle essential. Importantly, these viruses have been observed to "hijack" the secretory and endocytic membrane trafficking machineries of the hepatocyte. These can include the canonical clathrin-mediated endocytic process that internalizes virus through cell surface receptors. While these receptors are encoded by the host genome for normal hepatocellular

functions, they also exhibit virus-specific recognition. Further, functions provided by the multivesicular body, which include endosomal sorting complexes required for transport, are now known to envelope a variety of different hepatitis viruses. In this review, we summarize the recent findings regarding the cellular membrane trafficking machineries used by HBV in the context of other hepatitis viruses. (Hepatology 2018; 00:000-000).

[The correlation of HCV RNA and HCV core antigen in different genotypes of HCV.](#) Xiang Y1, Lai XF1, Chen P1, Yang Y1. J Clin Lab Anal. 2018 Aug 1:e22632. doi: 10.1002/jcla.22632. [Epub ahead of print]

BACKGROUND: To analyze the correlation of HCV RNA and HCV core antigen (HCV cAg) in different genotypes of HCV. **METHODS:** One hundred and six patients who were diagnosed with HCV infection by HCV RNA test were included in the study. HCV genotypes were detected by PCR fluorescent probe. Detected HCV cAg's expression in serum quantitatively and qualitatively with chemiluminescent micro-particle immuno assay (CMIA) and enzyme-linked immunosorbent assay (ELISA), respectively, and compared positive rates. Analyzed the correlation of HCV RNA and HCV cAg in different genotypes. **RESULTS:** Distribution of HCV genotypes in 106 HCV infected patients were as follows: 1b genotype 46 (43.4%); 2a genotype 7 (6.6%); 3a genotype 18 (17.0%); 3b genotype 3 (2.8%); 6a genotype 9 (8.5%); 1b/3b mixed type 13 (12.3%); and unidentified type 10 (9.4%). Positive rates of HCV cAg detected by CMIA and ELISA were 100% and 56%, respectively, with statistical significance ($\chi^2 = 60.38$, $P = 0.000$). HCV cAg in 1b genotype group was higher than that in 3b and 1b/3b genotype groups, with statistical significance ($U = 3.0$, $P = 0.006$, $U = 165$, $P = 0.014$). HCV RNA and HCV cAg in genotype 1b demonstrated a positive correlation ($r = 0.894$, $P = 0.04$). **CONCLUSION:** Major genetic subtype of HCV genotype was 1b. Compared with ELISA, detection of HCV cAg by CMIA increased the positive rate and facilitated early diagnosis and treatment of HCV-infected patients. With the increase in HCV RNA load and the expression of HCV cAg, HCV cAg could be an early indicator for the diagnosis of HCV infection in 1b genotype.

[Functional study of the C-terminal part of hepatitis C virus E1 ectodomain.](#) Moustafa RI1,2, Haddad JG1,3, Linna L1, et al. Virology. 2018 Aug 1. pii: JVI.00939-18. doi: 10.1128/JVI.00939-18. [Epub ahead of print]

In the HCV envelope glycoproteins E1 and E2, which form a heterodimer, E2 is the receptor binding protein and the major target of neutralizing antibodies, whereas the function of E1 remains less characterized. To investigate E1 functions, we generated a series of mutants in the conserved residues of the C-terminal region of the E1 ectodomain in the context of an infectious clone. We focused our analyses on two regions of interest. The first region is located in the middle of the E1 glycoprotein (between amino acids (aa) 270 and 291), which contains a conserved hydrophobic sequence and was proposed to constitute a putative fusion peptide. The second series of mutants was generated in the aa314-342 region, which has been shown to contain two alpha helices ($\alpha 2$ and $\alpha 3$) by NMR studies. Twenty out of the twenty-two generated mutants were either attenuated or noninfectious. Several mutations modulated the virus's dependence on claudin-1 and the scavenger receptor BI co-receptors for entry. Most of the mutations in the putative fusion peptide region affected virus assembly. Conversely, mutations in the α -helix 315-324 residues M318, W320, D321, and M322 resulted in a complete loss of infectivity without any impact on E1E2 folding and on viral assembly. Further characterization of the W320A mutant in the HCVpp model indicated that the loss of infectivity was due to a

defect in viral entry. Together, these results support a role for E1 in modulating HCV interaction with its co-receptors and in HCV assembly. They also highlight the involvement of α -helix 315-324 in a late step of HCV entry. Importance: HCV is a major public health problem worldwide. The virion harbors two envelope proteins, E1 and E2, which are involved at different steps of the viral life cycle. Whereas E2 has been extensively characterized, the function of E1 remains poorly defined. Here we characterized the function of the putative fusion peptide and the region containing alpha helices of the E1 ectodomain, which had been previously suggested to be important for virus entry. We could confirm the importance of these regions for the virus infectivity. Interestingly, we found several residues modulating the virus's dependence on several HCV receptors, thus highlighting the role of E1 in the interaction of the virus with cellular receptors. Whereas mutations in the putative fusion peptide affected HCV infectivity and morphogenesis, several mutations in the α 2 helix region led to a loss of infectivity with no effect on assembly, indicating a role of this region in virus entry.

HIV/HCV COINFECTION

[Effects of sofosbuvir-based hepatitis C treatment on the pharmacokinetics of tenofovir in HIV/HCV-coinfected individuals receiving tenofovir disoproxil fumarate.](#) MacBrayne CE1, Marks KM2, Fierer DS3, et al. J Antimicrob Chemother. 2018 Aug 1;73(8):2112-2119. doi: 10.1093/jac/dky146.

BACKGROUND: The nucleotide analogues tenofovir and sofosbuvir are considered to have low potential for drug interactions. **OBJECTIVES:** To determine the effect of sofosbuvir-based HCV treatment on plasma concentrations of tenofovir and cellular concentrations of tenofovir diphosphate. **METHODS:** HIV-infected participants with acute HCV were treated for 12 weeks with sofosbuvir+ribavirin in Cohort 1 or 8 weeks with ledipasvir/sofosbuvir in Cohort 2 of AIDS Clinical Trials Group study 5327. Only participants taking tenofovir disoproxil fumarate were included in this analysis. Tenofovir in plasma, tenofovir diphosphate in dried blood spots and tenofovir diphosphate in PBMCs were measured pre-HCV therapy and longitudinally during the study using validated LC/MS-MS. **RESULTS:** Fifteen and 22 men completed Cohorts 1 and 2, respectively. In Cohort 1, tenofovir diphosphate was 4.3-fold higher (95% CI geometric mean ratio 2.46-7.67; P= 0.0001) in dried blood spots and 2.3-fold higher (95% CI 1.09-4.92; P = 0.03) in PBMCs following 12 weeks of sofosbuvir+ribavirin versus study entry. Tenofovir in the plasma was unchanged. In Cohort 2, tenofovir diphosphate was 17.8-fold higher (95% CI 12.77-24.86; P < 0.0001) in dried blood spots after 8 weeks of ledipasvir/sofosbuvir versus study entry. Tenofovir plasma concentrations were 2.1-fold higher (95% CI 1.44-2.91; P = 0.0005). Despite the increase in cellular tenofovir diphosphate concentrations, only a small decline in CLCR (6%-7%) was observed in both cohorts between study entry and end of treatment. **CONCLUSIONS:** These data indicate an unexpected drug interaction with tenofovir disoproxil fumarate and sofosbuvir at the cellular level. Additional studies are needed to determine the mechanism and clinical significance.

[Similar Sustained Virologic Response in Real-World and Clinical Trial Studies of Hepatitis C/Human Immunodeficiency Virus Coinfection.](#) Sikavi C1, Najarian L1, Saab S2,3. Dig Dis Sci. 2018 Aug 9. doi: 10.1007/s10620-018-5215-0. [Epub ahead of print]

BACKGROUND: Clinical trials evaluating efficacy of direct-acting antiviral (DAA) therapies demonstrate sustained virologic response (SVR) rates greater than 90% in patients infected with

hepatitis C (HCV) and human immunodeficiency virus (HIV). However, generalizability of this data to real-world coinfecting populations is unknown. **AIM:** We aim to compare efficacy data from clinical trials to effectiveness data of real-world observational studies that evaluate oral interferon-free HCV treatment regimens in patients infected with HIV and HCV.

METHODS: We included English-language studies on PubMed and MEDLINE databases from inception until October 2017. Eight clinical trials and 11 observational studies reporting on efficacy data and effectiveness data, respectively, of interferon-free oral DAA regimens in HCV/HIV coinfecting patients, were included. **RESULTS:** Of patients in the eight clinical trials evaluated, 93.1% (1218/1308) achieved SVR12; of the 11 real-world observational studies, 90.8% (2269/2499) achieved SVR12. Relative risk between those treated in clinical trials versus observational studies was 0.98. Patients with genotype 1 infection, African-American patients, cirrhotic patients, and patients with prior HCV treatment experience had similar rates of SVR in real-world and clinical trial cohorts. **CONCLUSION:** SVR among real-world HCV/HIV coinfecting populations treated with DAA regimens is similar to SVR of patients studied in clinical trials. Historically negative predictors of achieving SVR during the era of interferon-based treatments, such as those with cirrhosis, prior HCV treatment failure, GT1 infection, and African-American race, are not associated with a significantly lower SVR in real-world populations treated with various DAA regimens.

[The Association of PNPLA3, COX-2 and DHCR7 Polymorphisms with Advanced Liver Fibrosis in Patients with HCV Mono- Infection and HCV/HIV Co-Infection](#) Kiatbumrung

R1, Chuaypen N, Payungporn S, Avihingsanon A, Tangkijvanich P. Asian Pac J Cancer Prev. 2018 Aug 24;19(8):2191-2197.

There is increasing evidence that host genetic variations may influence the natural history of chronic hepatitis C virus (HCV) infection. The aim of this study was to determine the association between single nucleotide polymorphisms (SNPs) of PNPLA3 (rs738409), COX-2 (rs689465) and DHCR7 (rs12785878) and advanced liver fibrosis in Thai patients. A total of 220 patients with HCV mono-infection, 200 patients with HCV/HIV co-infection and 200 healthy controls were enrolled. The SNPs were detected by allelic discrimination using real-time PCR with TaqMan probes. Liver stiffness measurement (LSM) was assessed by transient elastography. Our results showed that the distribution of the studied SNPs were not significantly different between the HCV mono- and co-infected groups. The frequencies AG and GG genotypes of rs689465 and GG genotype of rs12785878 were less commonly found in the HCV mono- and co-infected groups compare with healthy controls ($P < 0.01$). Among patients with HCV infection, older age, HIV co-infection, GG genotype of rs738409 and GG genotype of rs689465 were independently associated with advanced liver fibrosis ($LSM \geq 9.5$ kPa) in multivariate analysis. Moreover, the percentage of patients with advanced liver fibrosis increased significantly along with the accumulated numbers of these risk genotypes. In conclusion, PNPLA3 (rs738409) and COX-2 (rs689465) polymorphisms were associated with advanced liver fibrosis in patients with HCV mono- and co-infection, suggesting that these variants might play an important role in progressive liver fibrosis in these patients.

[Care2Cure: A randomized controlled trial protocol for evaluating nurse case management to improve the hepatitis C care continuum within HIV primary care.](#) Starbird LE1, Han

HR1, Sulkowski MS2, Budhathoki C3, Reynolds NR1, Farley JE1. Res Nurs Health. 2018 Aug 28. doi: 10.1002/nur.21903. [Epub ahead of print]

Co-infection with HIV and hepatitis C virus (HCV) results in a threefold increase in relative risk of progression to end stage liver disease and cirrhosis compared to HCV alone. Although curative treatments exist, less than one quarter of people with HCV are linked to care, and even fewer have received treatment. The Care2Cure study is a single-blinded, randomized controlled trial to improve the HCV care continuum among people co-infected with HIV. This ongoing study was designed to test whether a nurse case management intervention can (i) improve linkage to HCV care and (ii) decrease time to HCV treatment initiation among 70 adults co-infected with HIV who are not engaged in HCV care. The intervention is informed by the Andersen Behavioral Model of Health Services Use and consists of nurse-initiated referral, strengths-based education, patient navigation, appointment reminders, and care coordination for drug-drug interactions in the setting of HIV primary care. Validated instruments are used to measure participant characteristics including HCV knowledge, substance use, and depression. The primary outcome is linkage to HCV care (yes/no) within 60 days. In this protocol paper, we describe the first clinical trial to examine the effects of a nurse case management intervention to improve the HCV care continuum among people co-infected with HIV/HCV in the era of all-oral HCV treatment. We describe our work in progress, challenges encountered, and strategies to engage this hard-to-reach population.

[Drug-Drug Interaction Studies Between Hepatitis C Virus Antivirals Sofosbuvir/Velpatasvir and Boosted and Unboosted Human Immunodeficiency Virus Antiretroviral Regimens in Healthy Volunteers.](#) Mogalian E1, Stamm LM1, Osinusi A1, Brainard DM1, Shen G1, Ling KHJ1, Mathias A1. Clin Infect Dis. 2018 Aug 31;67(6):934-940. doi: 10.1093/cid/ciy201.

BACKGROUND: Combining antiviral regimens in the hepatitis C virus (HCV)/human immunodeficiency virus (HIV)-coinfected population can be complex as they share overlapping mechanisms for elimination that may result in drug interactions. The pharmacokinetics, safety, and tolerability of sofosbuvir/velpatasvir (SOF/VEL) with multiple antiretroviral (ARV) regimens were evaluated. **METHODS:** Healthy volunteers were enrolled into 2 phase 1, open-label, randomized, multiple-dose, cross-over studies. SOF/VEL and ARV regimens were administered alone and in combination; ARVs (and pharmacokinetic enhancers) included atazanavir (ATV), cobicistat (COBI), darunavir (DRV), dolutegravir (DTG), efavirenz (EFV), elvitegravir (EVG), emtricitabine (FTC), lopinavir (LPV), raltegravir (RAL), rilpivirine (RPV), ritonavir (RTV), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF). Geometric least squares means ratios (coadministration:alone) and 90% confidence intervals were constructed for area under the plasma concentration-time curve over the dosing interval, maximum concentration, and trough, for all analytes. Safety and tolerability were also evaluated. **RESULTS:** In total, 237 participants were enrolled. No clinically relevant differences in the pharmacokinetics (PK) of SOF, SOF metabolite GS-331007, or VEL were observed other than an approximate 50% decrease in VEL exposure when administered with EFV/FTC/TDF. No clinically relevant differences in the PK of ARVs were observed when administered with SOF/VEL. Study treatments were well tolerated, including no observed creatinine clearance changes during evaluation of TDF-containing regimens. **CONCLUSIONS:** SOF/VEL and ARV regimens including ATV, COBI, DRV, DTG, EVG, FTC, LPV, RAL, RPV, RTV, TAF, or TDF may be coadministered without dose adjustment. Use of SOF/VEL with EFV-containing regimens is not recommended due to an approximate 50% reduction in VEL exposure.

Meeting the Challenge: Hepatitis C Virus and HIV Care Experiences Among HIV Specialty Providers. Adams LM1, Balderson B2, Packett BJ 2nd3. AIDS Patient Care STDS. 2018 Aug;32(8):314-320. doi: 10.1089/apc.2018.0006.

Hepatitis C virus (HCV) is frequently comorbid with HIV infection and is independently associated with a significant increase in all-cause mortality among HIV-positive adults. HIV specialists' role and experiences in treating HCV has been understudied, especially among those providers who actively treat patients with HCV. We conducted a brief online survey of HIV specialists (physicians, nurse practitioners, physician assistants, and prescribing pharmacists) who treat patients with HCV to examine their experiences with treating these patients (HCV monoinfected, HIV/HCV coinfecting). Survey questions assessed providers' annual caseloads, barriers, and facilitators to providing HCV care, likelihood of providing HCV treatment to patients with various risk factors, and the extent to which their HCV screening practices aligned with CDC (Centers for Disease Control) guidelines for patients from various risk groups. A total of 168 HIV care providers were included in analyses. Nearly all specialists surveyed actively treated HIV/HCV coinfecting patients, while fewer treated any HCV monoinfected patients. Providers' screening practices typically aligned with guidelines across patient groups, but their likelihood of prescribing HCV treatment to patients varied across patients' risk profiles. Providers endorsed high levels of knowledge to treat HCV-infected patients, but highlighted key barriers to providing optimal care. Given that HIV specialists are an active group treating patients with HCV, they may benefit from specialized guidance on managing HCV in patients with complex histories, including comorbid HIV infection.

Real-World Impact of Direct Acting Antiviral Therapy on Health-Related Quality of Life in HIV/Hepatitis C Co-Infected Individuals. Saeed S1,2, Moodie EE1, Strumpf E1,3, et al. J Viral Hepat. 2018 Aug 23. doi: 10.1111/jvh.12985. [Epub ahead of print]

Clinical trial results of direct acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) have shown improvements in health-related quality of life (HR-QoL). However, the extent to which these results are broadly generalizable to real-world settings is unknown. We investigated the real-world impact of oral DAA therapy on HR-QoL among individuals co-infected with HIV/HCV. We used data from the Canadian HIV/HCV Co-Infection Cohort Study that prospectively follows 1795 participants from 18 centers. Since 2007, clinical, lifestyle, and HR-QoL data have been collected biannually through self-administered questionnaires and chart review. HR-QoL was measured using the EQ-5D instrument. Participants initiating oral DAAs, having at least one visit before treatment initiation and at least one visit after DAA treatment response was ascertained were included. Successful treatment response was defined as a sustained viral response (SVR). Segmented multivariate linear mixed models were used to evaluate the impact of SVR on HR-QoL, controlling for pre-treatment trends. 227 participants met our eligibility criteria, 93% of whom achieved SVR. Before treatment, the EQ-5D utility index decreased 0.6 percentage-point/year (95% CI, -0.9, -0.3) and health state was constant over time. The immediate effect of SVR resulted in an increase of 2.3-units (-0.1, 4.7) in patients' health state and 2.0 percentage-point increase (-0.2, 4.0) in utility index. Health state continued to increase post-SVR by 1.4 units/year (-0.9, 3.7), while utility trends post-SVR plateaued over the observation period. Overall using real-world data, we found modest improvements in HR-QoL following SVR, compared to previously published clinical trials. This article is protected by copyright. All rights reserved.

[High Cure Rates With Grazoprevir-Elbasvir With or Without Ribavirin Guided by Genotypic Resistance Testing Among Human Immunodeficiency Virus/Hepatitis C Virus-coinfected Men Who Have Sex With Men.](#) Braun DL^{1,2}, Hampel B^{1,2}, Kouyos R^{1,2}, et al.

Clin Infect Dis. 2018 Aug 13. doi: 10.1093/cid/ciy547. [Epub ahead of print]

BACKGROUND: This study was performed to investigate the efficacy and safety of grazoprevir-elbasvir guided by baseline resistance-associated substitutions (RASs) in the Swiss HCVree Trial (clinicaltrials.gov NCT02785666). **METHODS:** We performed hepatitis C virus (HCV) RNA screening among all men who have sex with men (MSM) enrolled in the Swiss HIV Cohort Study. Individuals with replicating HCV genotype 1 or 4 infection were eligible for grazoprevir-elbasvir treatment. Genotype 1a-infected individuals with baseline RASs and genotype 4-infected individuals with prior failure of HCV treatment received 16 weeks of grazoprevir-elbasvir combined with ribavirin. All other individuals received 12 weeks of grazoprevir-elbasvir alone. Patients reporting unprotected sex with occasional partners were offered a HCV risk reduction-oriented behavioral intervention. **RESULTS:** We screened 3722 MSM and identified 177 (4.8%) with replicating infection. A total of 122 individuals (3.3%) were eligible for study treatment. Six of 76 patients infected with genotype 1a (7.3%) harbored baseline RASs. Sustained virological response after 12 weeks of follow-up was achieved in 121 patients (99%), including all with genotype 1a infection. Overall, 8 serious adverse events occurred, none of which was related to the study drug. Seventy-five percent of eligible MSM participated in the risk counseling program. **CONCLUSIONS:** Grazoprevir-elbasvir for 12 or 16 weeks, with or without ribavirin, achieved high cure rates and had an excellent safety profile. Unique to other studies, the treatment duration was guided by the presence of baseline RASs among genotype 1a-infected individuals, and the treatment phase was accompanied by an HCV risk reduction-oriented behavioral intervention. This successful population-wide treatment approach lays the groundwork to achieve HCV elimination in coinfecting MSM.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[The Burden of Untreated HCV Infection in Hospitalized Inmates: a Hospital Utilization and Cost Analysis.](#) Wurcel AG^{1,2}, Burke DJ³, Wang JJ⁴, Engle B⁵, Noonan K⁶, Knox TA⁵, Kim AY⁷, Linas BP⁴. J Urban Health. 2018 Aug;95(4):467-473. doi: 10.1007/s11524-018-0277-z.

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

hospital utilization with HCV cure could help offset treatment costs. Policy discussions on HCV treatment in corrections should be informed by the costs of untreated HCV infection.

[Electronic Reminders Increase Hepatitis C Screening, referral, treatment and cure.](#) Jones H1, Patel P1, Sears D1. J Viral Hepat. 2018 Aug 23. doi: 10.1111/jvh.12988. [Epub ahead of print]

In 2013, the United States Preventative Services Task Force released a recommendation that patients born between 1945 and 1965 (baby boomers) be screened for Hepatitis C virus antibody (anti-HCV). To increase Hepatitis C screening, treatment, and number of cures for the baby boomer population at Scott & White Medical Center-Temple in Central Texas through Electronic Medical Record (EMR) reminders, an Institutional Review Board-approved prospective study comparing hepatitis C screening one year before and one year after EMR reminder activation was performed. Laboratory results, clinic referrals, and outcomes of hepatitis C treatment were determined. After implementing the EMR reminder, the number and percentage of baby boomers screened for hepatitis C increased from 1.87% to 14.14%. In conclusion, EMR reminders are an effective way to increase screening, referral, treatment, and cure for Hepatitis C in the baby boomer population. This is a simple strategy which can be easily implemented in the majority of practices in the United States that utilize the same EMR system. Additional components, such as HIV screening, can be quickly added, and individual providers and divisions can run their own actionable reports. This article is protected by copyright. All rights reserved.

[Hepatitis C treatment for difficult to access populations; can telementoring \(as distinct from telemedicine\) help?](#) Mohsen W1, Chan P1,2, Whelan M1, et al. Intern Med J. 2018 Aug 8. doi: 10.1111/imj.14072. [Epub ahead of print]

INTRODUCTION: Hepatitis C (HCV) is curable, treatment of difficult to access populations (DTAPs) presents unique challenges. Project ECHO® (PE), a tele-mentoring program, adopted to support clinicians treating DTAPs. **AIMS:** Determine if the PE model supports primary care clinicians treating HCV. Compare cohort of PE patients with those in a tertiary liver clinic (TLC). **METHODS:** Weekly PE group video conferences were conducted. Clinical information, laboratory indices, psychosocial elements, and treatment outcomes including Sustained Virological Response (SVR) data were recorded in the first 100 consecutive cases and retrospectively compared to 100 consecutive patients seen at a tertiary liver clinic from July 2016 to April 2017. **RESULTS:** Some patient characteristics were similar between PE and TLC: gender (72% male vs 75% male: $p=0.23$), median age (45 vs 50, $p=0.344$), proportion of treatment naïve patients (95.0% vs 90.9%). Treatment for HCV was commenced in 78% of the PE patients and 81% of the TLC patients. 67 of the TLC patients and 60 PE patients have confirmed SVR. PE patients are more likely to have ongoing substance use (44% vs 17% $p<0.001$), active IVDU (32% vs 17% $p<0.001$) and polysubstance abuse (26% vs 7% $p<0.001$) and were more likely to be taking opioid substitution therapy (OST) (74% vs 20% $p<0.001$). Indigenous patients were three times more greatly represented in PE (15% vs 5% $p = 0.018$). **CONCLUSION:** Project ECHO® is an effective model to support primary healthcare providers treating HCV in DTAPs with similar rates of treatment uptake and SVR compared to patients in TLCs This article is protected by copyright. All rights reserved.

[Effect of Interferon-Free Regimens on Disparities in Hepatitis C Treatment of US](#)

[Veterans](#). Barnett PG1, Joyce VR2, Lo J2, Gidwani-Marszowski R3, Goldhaber-Fiebert JD4, Desai M5, Asch SM6, Holodniy M7, Owens DK8. Value Health. 2018 Aug;21(8):921-930. doi: 10.1016/j.jval.2017.12.025. Epub 2018 Mar 7.

OBJECTIVES: To determine whether implementation of interferon-free treatment for hepatitis C virus (HCV) reached groups less likely to benefit from earlier therapies, including patients with genotype 1 virus or contraindications to interferon treatment, and groups that faced treatment disparities: African Americans, patients with HIV co-infection, and those with drug use disorder. **METHODS:** Electronic medical records of the US Veterans Health Administration (VHA) were used to characterize patients with chronic HCV infection and the treatments they received. Initiation of treatment in 206,544 patients with chronic HCV characterized by viral genotype, demographic characteristics, and comorbid medical and mental illness was studied using a competing events Cox regression over 6 years. **RESULTS:** With the advent of interferon-free regimens, the proportion treated increased from 2.4% in 2010 to 18.1% in 2015, an absolute increase of 15.7%. Patients with genotype 1 virus, poor response to previous treatment, and liver disease had the greatest increase. Large absolute increases in the proportion treated were observed in patients with HIV co-infection (18.6%), alcohol use disorder (11.9%), and drug use disorder (12.6%) and in African American (13.7%) and Hispanic (13.5%) patients, groups that were less likely to receive interferon-containing treatment. The VHA spent \$962 million on interferon-free treatments in 2015, 1.5% of its operating budget. **CONCLUSIONS:** The proportion of patients with HCV treated in VHA increased sevenfold. The VHA was successful in implementing interferon treatment in previously undertreated populations, and this may become the community standard of care.

[HCV elimination among people who inject drugs. Modelling pre- and post-WHO](#)

[elimination era](#). Gountas I1,2, Sypsa V1, Blach S2, Razavi H2, Hatzakis A1. PLoS One. 2018 Aug 16;13(8):e0202109. doi: 10.1371/journal.pone.0202109. eCollection 2018.

BACKGROUND: Elimination of hepatitis C virus (HCV) among people who inject drugs (PWID) is a costly investment, so strategies should not only focus on eliminating the disease, but also on preventing disease resurgence. The aims of this study are to compute the minimum necessary antiviral therapies to achieve elimination with and without the additional expansion of harm reduction (HR) programs and to examine the sustainability of HCV elimination after 2030 if treatment is discontinued. **METHOD:** We considered two types of epidemic (with low (30%) and high (50%) proportion of PWID who engage in sharing equipment (sharers)) within three baseline chronic HCV (CHC) prevalence settings (30%, 45% and 60%), assuming a baseline HR coverage of 40%. We define sustainable elimination strategies, those that could maintain elimination results for a decade (2031-2040), in the absence of additional treatment.

RESULTS: The model shows that the optimum elimination strategy is dependent on risk sharing behavior of the examined population. The necessary annual treatment coverage to achieve HCV elimination under 45% baseline CHC prevalence, without the simultaneous expansion of HR programs, ranges between 4.7-5.1%. Similarly, under 60% baseline CHC prevalence the needed treatment coverage varies from 9.0-10.5%. Increasing HR coverage from 40% to 75%, reduces the required treatment coverage by 6.5-9.8% and 11.0-15.0% under 45% or 60% CHC prevalence, respectively. In settings with $\leq 45\%$ baseline CHC prevalence, expanding HR to 75% could prevent the disease from rebounding after elimination, irrespective of the type of the epidemic. In high chronic HCV prevalence, counseling interventions to reduce sharing are also

needed to maintain the HCV incident cases in low levels. **CONCLUSIONS:** Harm reduction strategies have a vital role in HCV elimination strategy, as they reduce the required number of treatments to eliminate HCV and they provide sustainability after the elimination. The above underlines that HCV elimination strategies should be built upon the existing HR services, and argue for HR expansion in countries without services.

[Economically Efficient Hepatitis C Virus Treatment Prioritization Improves Health](#)

Outcomes: Hepatitis C Virus Treatment Prioritization. Cipriano LE^{1,2,3,4,5,6}, Liu S^{1,2,3,4,5,6}, Shahzada KS^{1,2,3,4,5,6}, Holodniy M^{1,2,3,4,5,6}, Goldhaber-Fiebert JD^{1,2,3,4,5,6}. Med Decis Making. 2018 Aug 22;272989X18792284. doi: 10.1177/0272989X18792284. [Epub ahead of print]

BACKGROUND: The total cost of treating the 3 million Americans chronically infected with hepatitis C virus (HCV) represents a substantial affordability challenge requiring treatment prioritization. This study compares the health and economic outcomes of alternative treatment prioritization schedules. **METHODS:** We developed a multiyear HCV treatment budget allocation model to evaluate the tradeoffs of 7 prioritization strategies. We used optimization to identify the priority schedule that maximizes population net monetary benefit (NMB). We compared prioritization schedules in terms of the number of individuals treated, the number of individuals who progress to end-stage liver disease (ESLD), and population total quality-adjusted life years (QALYs). We applied the model to the population of treatment-naïve patients with a total annual HCV treatment budget of US\$8.6 billion. **RESULTS:** First-come, first-served (FCFS) treats the fewest people with advanced fibrosis, prevents the fewest cases of ESLD, and gains the fewest QALYs. A schedule developed from optimizing population NMB prioritizes treatment in the first year to patients with moderate to severe fibrosis who are younger than 65 years, followed by older individuals with moderate to severe fibrosis. While this strategy yields the greatest population QALYs, prioritization by disease severity alone prevents more cases of ESLD. Sensitivity analysis indicated that the differences between prioritization schedules are greater when the budget is smaller. A 10% annual treatment price reduction enabled treatment 1 year sooner to several patient subgroups, specifically older patients and those with less severe liver fibrosis. **CONCLUSION:** In the absence of a sufficient budget to treat all patients, explicit prioritization targeting younger people with more severe disease first provides the greatest health benefits. We provide our spreadsheet model so that decision makers can compare health tradeoffs of different budget levels and various prioritization strategies with inputs tailored to their population.

[Successful Implementation of a Shared Medical Appointment Model for Hepatitis C Treatment at a Community Health Center.](#)

Hodges J1, Reyes J2, Campbell J3, Klein W3, Wurcel A2,4. J Community Health. 2018 Aug 21. doi: 10.1007/s10900-018-0568-z. [Epub ahead of print]

Highly efficacious direct acting antiviral (DAA) therapy for treatment of Hepatitis C Virus (HCV) infection is largely inaccessible to communities facing a shortage of available specialist providers. Though less demanding than previous interferon regimens, DAA therapy requires patients to adhere to 8-12 weeks of daily treatment, which can be challenging for some patient populations. Duffy Health Center, located on Cape Cod, Massachusetts, provides integrated medical, mental health and case management services to people who are homeless or at risk for homelessness. The goal of this manuscript is to evaluate the outcomes of treatment of HCV

infection with a shared medical appointment (SMA) model. The primary outcome was sustained virologic response (SVR-12), or HCV RNA \leq 15 IU/mL at 12 weeks post-treatment. There were 102 patients recruited, with a total of 104 treatments administered. Over three-fourths of patients who attended one SMA visit (78 of 102) continued in SMA for the duration of treatment. Of these patients opting for SMA, 99% (77 of 78) completed the full treatment course, and 91% (71 of 78) of SMA patients achieved SVR-12. DAA therapy provided by non-specialist providers using the SMA model yielded comparable response rates to those achieved by specialist providers, and has the potential to substantially increase access to HCV treatment for patient populations within high-risk communities.

[Evaluating HCV screening, linkage to care, and treatment across insurers.](#) Mulligan K1, Sullivan J, Yoon L, Chou J, Van Nuys K. Am J Manag Care. 2018 Aug 1;24(8):e257-e264.

OBJECTIVES: We examined how a population susceptible to hepatitis C virus (HCV) moves through the HCV screening and linkage-to-care (SLTC) continuum across insurance providers (Medicare, Medicaid, commercial) and identified opportunities for increasing the number of patients who complete the SLTC process and receive treatment. **STUDY DESIGN:** Discrete-time Markov model. **METHODS:** A cohort of 10,000 HCV-susceptible patients was simulated through the HCV SLTC process using a Markov model with parameters from published literature. Three scenarios were explored: baseline, in which each step required a separate visit and all infected saw a specialist; reflex, which reflexed antibody and RNA testing; and consolidated, which reflexed antibody, RNA, fibrosis staging, and genotype testing into 1 step, with an optional specialist visit. For each scenario, we estimated the number of patients lost at each stage, yield, and cost. **RESULTS:** Streamlining the SLTC process by reducing the number of required visits results in more patients completing the process and receiving treatment. Among antibody-positive patients, 76% of those with Medicaid and 71% of those with Medicare and commercial insurance are lost to follow-up in baseline. In reflex and consolidated, these proportions fall to 26% and 27% and 4% and 5%, respectively. The cost to identify and link 1 additional infected patient to care ranges from \$1586 to \$2546 in baseline and \$212 to \$548 in consolidated. Total cost, inclusive of treatment, ranges from \$1.0 million to \$3.1 million in baseline and increases to \$3.8 million to \$15.1 million in reflex and \$5.3 million to \$21.0 million in consolidated. **CONCLUSIONS:** Reducing steps in the HCV SLTC process increases the number of patients who learn their HCV status, receive appropriate care, and initiate treatment.

[Six-Month Emergency Department Use among Older Adults Following Jail Incarceration.](#)

Humphreys J1, Ahalt C2, Stijacic-Cenzer I2, Widera E3, Williams B4. J Urban Health. 2018 Aug;95(4):523-533. doi: 10.1007/s11524-017-0208-4.

Although the number of older adults who are arrested and subject to incarceration in jail is rising dramatically, little is known about their emergency department (ED) use or the factors associated with that use. This lack of knowledge impairs the ability to design evidence-based approaches to care that would meet the needs of this population. This 6-month longitudinal study aimed to determine the frequency of 6-month ED use among 101 adults aged 55 or older enrolled while in jail and to identify factors associated with that use. The primary outcome was self-reported emergency department use within 6 months from baseline. Additional measures included baseline socio-demographics, physical and mental health conditions, geriatric factors (e.g., recent falls, incontinence, functional impairment, concern about post-release safety), symptoms (pain and other symptoms), and behavioral and social health risk factors (e.g., substance use disorders,

recent homelessness). Chi-square tests were used to identify baseline factors associated with ED use over 6 months. Participants (average age 60) reported high rates of multimorbidity (61%), functional impairment (57%), pain (52%), serious mental illness (44%), recent homelessness (54%), and/or substance use disorders (69%). At 6 months, 46% had visited the ED at least once; 21% visited multiple times. Factors associated with ED use included multimorbidity ($p = 0.01$), functional impairment ($p = 0.02$), hepatitis C infection ($p = 0.01$), a recent fall ($p = 0.03$), pain ($p < 0.001$), loneliness ($p = 0.04$), and safety concerns ($p = 0.01$). In this population of older adults in a county jail, geriatric conditions and distressing symptoms were common and associated with 6-month community ED use. Jail is an important setting to develop geriatric care paradigms aimed at addressing comorbid medical, functional, and behavioral health needs and symptomatology in an effort to improve care and decrease ED use in the growing population of criminal justice-involved older adults.

[Prevalence and sociodemographic disparities of Hepatitis C in Baby Boomers and the US adult population.](#) Moore KJ1, Gauri A1, Koru-Sengul T2. *J Infect Public Health.* 2018 Aug 28. pii: S1876-0341(18)30118-7. doi: 10.1016/j.jiph.2018.08.003. [Epub ahead of print]

BACKGROUND: The US Baby Boomer (BB) generation is associated with high rates of Hepatitis C virus (HCV) infection. There is limited literature detailing age-specific risk factors for HCV infection. Using a nationally representative sample, this study examines US adult HCV prevalence and age-specific risk factors for chronic HCV infection. **METHODS:** We analyzed data from National Health and Nutrition Examination Survey (NHANES) for years 1999-2012. Age was divided into three categories: BB, younger than BB (YG) and older than BB (OG). HCV status was determined by the presence of a positive HCV antibody and a positive HCV RNA. Sociodemographic variables were analyzed by HCV status. Multivariable logistic regression models adjusting for sociodemographic variables were fitted to identify age-specific risk factors for HCV positivity. **RESULTS:** The overall prevalence of chronic HCV was 1.19% with a US population estimate of 2,347,852 US adults. BB had the highest prevalence at 2.23%, accounting for over 74% of all chronic HCV cases. HCV prevalence was highest among all ages (1.83%) and BB (2.71%) in 2001-2002 survey cycle. Among BB, males, non-Hispanic blacks, positive blood transfusion history, current and former smoker, and living below the poverty line were significant predictors of chronic HCV positivity. **CONCLUSION:** This study highlights the elevated prevalence of chronic HCV among BB and identifies age-specific risk factors for chronic HCV infection. As the BB population ages, it is important to use these generation-specific risk factors that can guide health professionals in targeted screening and public health prevention efforts.

[Exploring Lifetime Accumulation of Criminal Justice Involvement and Associated Health and Social Outcomes in a Community-Based Sample of Women who Use Drugs.](#) Lorvick J1, Comfort M2, Kral AH2, Lambdin BH2. *J Urban Health.* 2018 Aug;95(4):584-593. doi: 10.1007/s11524-017-0204-8.

Among people who use illegal drugs, engagement with the criminal justice (CJ) system often involves an ongoing, intermittent series of arrests, incarcerations, and periods of community supervision. The potential associations between the lifetime accumulation of CJ involvement and social and health outcomes is largely unexplored. In a cross-sectional sample of women who use crack, heroin, and/or methamphetamine recruited from communities in Oakland, CA ($N = 624$), we developed an approach to characterize CJ accumulation. We used latent class analysis (LCA),

a multivariate person-centered method that assumes an unobserved categorical variable that divides a population into a small number of mutually exclusive and exhaustive classes. Using observed measures of incarceration and community supervision as indicator variables, we developed a model of CJ accumulation that elucidates patterns of involvement as lived by the women in the sample. Based on model fit statistics, we selected a three-class model and labeled the classes "low," "medium," and "high." We then explored associations between the classes of CJ accumulation and health and health-related outcomes using logistic regression. The odds of homelessness (p for trend = 0.004), transience (p for trend = 0.017), and recent victimization (p for trend = 0.023) were higher among women in higher accumulation classes. Higher class of CJ accumulation was associated with higher odds of reporting unmet need for physical health care (p for trend < 0.001) and mental health care (p for trend = 0.002). The odds of physical health conditions, such as hepatitis C infection (p for trend < 0.001) and mental health conditions, such as depression (p for trend = 0.003), also increased with higher class of accumulation. While the findings described here are limited by the cross-sectional nature of the study, they suggest that CJ accumulation is a potentially meaningful concept for assessing associations between the CJ system and health-related issues.

[Unique Challenges of Hepatitis C in Infants, Children, and Adolescents.](#) Espinosa C1, Jhaveri R2, Barritt AS 4th3. Clin Ther. 2018 Aug;40(8):1299-1307. doi: 10.1016/j.clinthera.2018.07.010. Epub 2018 Aug 11.

PURPOSE: Hepatitis C, a chronic disease with deadly consequences, is no longer predominantly a disease of older people. **METHODS:** A limited search was conducted of the relevant literature on 2 topics: (1) the impact of hepatitis C on infants exposed by vertical transmission; and (2) the impact of hepatitis C infection on infected children and adolescents. The findings were supplemented by the first-hand experience of the authors. **FINDINGS:** Young people, including women of childbearing age, infants, children, and adolescents, are being especially affected by hepatitis C infection secondary to the intravenous drug use and opioid epidemic. Unfortunately, estimates of disease in young populations are all misleading because universal screening has not been implemented. **IMPLICATIONS:** Lack of implementation of policies for screening and therapy on most affected populations will be responsible for perpetuation of this infection. In the era of highly effective therapy and a regimen that is approved by the US Food and Drug Administration for children, this outcome is unacceptable.

[Changing Trends in Etiology-Based Annual Mortality From Chronic Liver Disease, From 2007 Through 2016.](#) Kim D1, Li AA2, Gadiparthi C3, Khan MA3, Cholankeril G4, Glenn JS4, Ahmed A4. Gastroenterology. 2018 Aug 31. pii: S0016-5085(18)34762-0. doi: 10.1053/j.gastro.2018.07.008. [Epub ahead of print]

BACKGROUND & AIMS: Although treatment of hepatitis C virus (HCV) infection has improved, the prevalence of alcoholic liver disease (ALD) has been increasing, so we need an updated estimate of the burden and etiology-specific mortality of chronic liver diseases. We studied trends in age-standardized mortality of chronic liver diseases in adults at least 20 years old in the United States from 2007 through 2016. **METHODS:** We collected data from the US Census and National Center for Health Statistics mortality records and identified individuals with HCV infection, ALD, nonalcoholic fatty liver disease, or hepatitis B virus infection using ICD-10 codes. We obtained temporal mortality rate patterns using joinpoint trend analysis with

estimates of annual percentage change (APC). **RESULTS:** Age-standardized HCV-related mortality increased from 7.17 per 100,000 persons in 2007 to 8.14 per 100,000 persons in 2013, followed by a marked decrease during the period in which patients began receiving treatment with direct-acting antiviral agents (from 8.09 per 100,000 persons in 2014 to 7.15 per 100,000 persons in 2016). The APC in HCV mortality increased 2.0%/year from 2007 through 2014 but decreased 6.4%/year from 2014 through 2016. In contrast, age-standardized mortality increased for ALD (APC 2.3% from 2007 through 2013 and APC 5.5% from 2013 through 2016) and nonalcoholic fatty liver disease (APC 6.1% from 2007 through 2013 and APC 11.3% from 2013 through 2016). Mortality related to hepatitis B virus decreased steadily from 2007 through 2016, with an average APC of -2.1% (95% CI -3.0 to -1.2). Etiology-based mortality in minority populations was higher. HCV-related mortality (per 100,000 persons) was highest in non-Hispanic blacks (10.28) and whites (6.92), followed by Hispanics (5.94), and lowest in non-Hispanic Asians (2.33). Non-Hispanic Asians had higher mortality for hepatitis B virus infection (2.82 per 100,000 vs 1.02 for non-Hispanic blacks and 0.47 for non-Hispanic whites). **CONCLUSION:** In our population-based analysis of chronic liver disease mortality in the United States, the decrease in HCV-related mortality coincided with the introduction of direct-acting antiviral therapies, whereas mortality from ALD and nonalcoholic fatty liver disease increased during the same period. Minorities in the United States have disproportionately higher mortality related to chronic liver disease.

[Implementing Treatment of Opioid-Use Disorder in Rural Settings: a Focus on HIV and Hepatitis C Prevention and Treatment.](#) Havens JR1, Walsh SL2, Korthuis PT3, Fiellin DA4,5. *Curr HIV/AIDS Rep.* 2018 Aug;15(4):315-323. doi: 10.1007/s11904-018-0402-3.

PURPOSE OF REVIEW: To describe the epidemiology of opioid-use disorder in the rural United States (U.S.) as it pertains to HIV and hepatitis C transmission and treatment resources. **RECENT FINDINGS:** Heroin and fentanyl analogs have surpassed prescription opioids in their availability in rural opioid markets adding to HIV and hepatitis C (HCV) and overdose risks. Only 18% of rural individuals live in towns with inpatient services which are of limited quality and utility. Opioid treatment programs that provide methadone are not located in rural areas and only 3% of the primary care providers have the ability to prescribe buprenorphine. National models and resources have been established but lack implementation in rural areas leading to ongoing HIV and HCV transmission and overdose. Addressing the adverse impact of opioids in the rural U.S. will require a concerted effort to implement effective treatments according to national standards.

[A Descriptive Analysis of a Community Clinic Providing Hepatitis C Treatment to Poor and Uninsured Patients.](#) Sims OT1,2,3,4, Melton PA5, Ji S6. *J Community Health.* 2018 Aug;43(4):725-730. doi: 10.1007/s10900-018-0476-2.

This study describes clinical characteristics of poor and uninsured patients living with hepatitis C virus (HCV) who received care from a multidisciplinary HCV clinic, reports treatment completion and cure rates, and estimates the cost of HCV medications provided at no cost to uninsured patients. A retrospective chart review was performed and identified 69 uninsured HCV patients who received medical care at Mercy Health Center, a small non-profit community clinic, between January 2008 and March 2015. Three-fourths of the patients were unemployed, a third had multiple HCV exposures, nearly half acquired HCV due to illicit drug use, and more than half had active psychiatric disorders. Of those who received HCV treatment, 81% completed

treatment and 85% were achieved virological cure. The multidisciplinary community clinic provided > \$1.4 million of HCV antivirals at no cost to uninsured patients. Findings suggest a multidisciplinary community clinic comprised of a social worker, pharmacist, gastroenterologist, nurse, nurse practitioner, psychologist, and dietitian can help patients achieve HCV treatment completion and cure rates comparable to traditional physician-led clinics, and successfully manage uninsured and underserved HCV patients—who are often regarded as "difficult-to-treat" patients. Public health social workers and other health professionals are encouraged to advocate for treatment and care of poor and uninsured patients living with HCV in health agencies and health systems, otherwise population-wide reductions in HCV morbidity and mortality will not be realized.

[Hepatitis C Virus Knowledge Among Pregnant Women with Opioid Use Disorder.](#) Krans EE^{1,2}, Rothenberger SD³, Morrison PK⁴, Park SY³, Klocke LC⁵, Turocy MJ⁵, Zickmund S^{6,7}. *Matern Child Health J.* 2018 Aug;22(8):1208-1216. doi: 10.1007/s10995-018-2506-1.

OBJECTIVES: To evaluate Hepatitis C virus (HCV) knowledge and awareness among pregnant women with opioid use disorder (OUD). **METHODS:** From May through November 2015, a one-time survey was distributed to a convenience sample of pregnant women with OUD to assess their knowledge and awareness of (a) risk factors for HCV infection, (b) HCV transmission prevention strategies, (c) hepatotoxic risk reduction and (d) perinatal transmission and neonatal implications of HCV infection. Chi square and Fisher's exact tests were used to compare demographic characteristics and HCV knowledge between participants who were HCV positive and negative. **RESULTS:** Of 179 pregnant women with OUD approached, 169 (94%) completed the survey. Of these, 153 (90.5%) reported at least one risk factor for HCV infection, 85 (50.3%) were HCV positive and 38 (44.7%) of HCV positive women were diagnosed with HCV for the first time during pregnancy. When HCV knowledge was evaluated, 114 (66.7%) responded that sharing eating utensils could transmit HCV, 69 (55.0%) responded that there is a vaccine to prevent HCV and 56 (32.7%) did not identify intranasal drug use as a risk factor for HCV transmission. Among HCV positive women, 61 (71.8%) associated breastfeeding with an increased risk for HCV transmission, 33 (38.1%) failed to identify the importance of pediatric follow-up for HCV-exposed children and 16 (18.8%) perceived the risk of HCV vertical transmission as

HEPATOCELLULAR (LIVER) CANCER

[Hepatitis C virus treatment by direct-acting antivirals in successfully treated hepatocellular carcinoma and possible mutual impact.](#) Hassany M1, Elsharkawy A2, Maged A1, et al. *Eur J Gastroenterol Hepatol.* 2018 Aug;30(8):876-881. doi: 10.1097/MEG.0000000000001152.

BACKGROUND AND AIMS: Treatment of hepatitis C virus (HCV) after successfully treated hepatocellular carcinoma (HCC) becomes possible with the introduction of direct-acting antivirals because of their favorable efficacy, safety, and short period of treatment. Few data are available on the results of treatment using different direct-acting antiviral regimens in successfully treated HCC and a lot of debate about its role in tumor recurrence.

METHODS: Sixty-two HCV-related HCC patients were enrolled in the study after successfully treated HCC; the studied population included either Child-Pugh 'A' or 'B7'. The patients were subcategorized to receive one of the following regimens: group 1: sofosbuvir (SOF)+ribavirin

(RBV) for 24 weeks, group 2: SOF+simeprevir for 12 weeks, group 3: SOF+daclatasvir for 24 weeks, and group 4: SOF+daclatasvir+RBV for 12 weeks. The overall median follow-up period is 12 months after treatment initiation. **RESULTS:** All treatment regimens were tolerable for all patients, with no reported major adverse events during treatment. The overall sustained virologic response rate was 64.5%, with the highest result in group 4 and the lowest result in group 1; 87.5 and 26.7%, respectively. HCC recurrence was observed in 42% of patients; 80.7% of these patients developed recurrence within 6 months of treatment initiation. **CONCLUSION:** Treatment of HCV in successfully treated HCC is feasible, with the best results achieved using multiple direct-acting antivirals and RBV; a high rate of HCC recurrence was observed, especially within the first 6 months of treatment initiation (ClinicalTrials.gov no: NCT02771405).

Prevention of hepatocellular carcinoma with antiviral therapy. Di Bisceglie AM1. S Afr Med J. 2018 Aug 8;108(8b):47-50. doi: 10.7196/SAMJ.2018.v108i8b.13501.

Chronic viral hepatitis types B and C may eventually lead to the development of hepatocellular carcinoma. Although hepatitis B is readily preventable by vaccination, there is growing evidence that antiviral therapy directed against hepatitis B may reduce the risk of liver cancer among those already infected. There is no vaccine against hepatitis C, but the evidence is now strong that antiviral therapy with sustained virological response (viral cure) reduces, but does not eliminate, the risk of hepatocellular carcinoma.

Recurrence of hepatocellular carcinoma after direct acting antiviral treatment for hepatitis C virus infection: Literature review and risk analysis.

Guarino M1, Viganò L2, Ponziani FR3, Giannini EG4, Lai Q5, Morisco F1; Special Interest Group on Hepatocellular carcinoma and new anti-HCV therapies” of the Italian Association for the Study of the Liver. Dig Liver Dis. 2018 Aug 11. pii: S1590-8658(18)30880-6. doi: 10.1016/j.dld.2018.08.001. [Epub ahead of print]

Although studies suggest decreased incident hepatocellular carcinoma (HCC) after treatment with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection, data are conflicting regarding risk and aggressiveness of recurrence in patients who have a history of treated HCC. This review analyses data available in literature in order to elucidate the impact of DAAs on the risk of HCC recurrence after successful treatment of the tumor. Overall 24 papers were identified. The available data cannot be considered definitive, but the initial alarmist data indicating an increased risk of recurrence have not been confirmed by most subsequent studies. The suggested aggressive pattern (rapid growth and vascular invasion) of tumor recurrence after DAAs still remains to be confirmed. Several limitations of the available studies were highlighted, and should drive future researches. The time-to-recurrence should be computed since the last HCC treatment and results stratified for cirrhosis and sustained viral response. Any comparison with historical series is of limited interest because of a number of biases affecting these studies and differences between enrolled patients. Prospective intention-to-treat analyses will be probably the best contribution to drive clinical practice, provided that a randomized trial can be difficult to design.

No difference between direct-acting antivirals for hepatitis C in hepatocellular carcinoma risk. Mun EJ1, Green P2, Berry K2, Ioannou GN3,2. Eur J Gastroenterol Hepatol. 2018 Aug 23. doi: 10.1097/MEG.0000000000001242. [Epub ahead of print]

BACKGROUND AND AIMS: It is unclear whether there are differences between direct-acting antivirals (DAAs) for hepatitis C virus in risk of hepatocellular carcinoma (HCC) after antiviral therapy. We aimed to compare different DAA regimens with respect to risk of de novo HCC following antiviral therapy. **PATIENTS AND METHODS:** We identified 33 137 patients who initiated hepatitis C virus antiviral treatment in the Veterans Affairs healthcare system between 6 December 2013 and 31 December 2015 with one of four DAA-only regimens (\pm ribavirin): paritaprevir/ritonavir/ombitasvir/dasabuvir (n=6289), sofosbuvir (n=4356), sofosbuvir+simeprevir (n=3210), and ledipasvir/sofosbuvir (n=19 282). We retrospectively followed patients until 15 June 2017 to identify incident (de novo) cases of HCC. We used propensity score-adjusted Cox proportional hazards regression to compare different DAA regimens with respect to HCC risk. **RESULTS:** During a mean follow-up of 1.52 years, 741 new cases of HCC were diagnosed after antiviral treatment (annual incidence=1.47%). Patients treated with sofosbuvir+simeprevir had the highest annual HCC incidence (2.47%), followed by sofosbuvir (1.91%), ledipasvir/sofosbuvir (1.26%), and paritaprevir/ritonavir /ombitasvir/dasabuvir (0.95%). However, there were great differences between DAA-treated patients in the prevalence of cirrhosis, markers of advanced fibrosis, thrombocytopenia, and other HCC risk factors. After adjustment for baseline characteristics associated with HCC, there were no significant differences in HCC risk between the four DAA regimens. **CONCLUSION:** There are no significant differences between DAA regimens in HCC risk after antiviral treatment. This suggests that DAAs do not have direct carcinogenic effects as it would be unlikely that different DAAs would have identical carcinogenic effects.

[Development of Models Estimating the Risk of Hepatocellular Carcinoma After Antiviral Treatment for Hepatitis C.](#) Ioannou GN¹, Green PK², Beste LA³, Mun EJ⁴, Kerr KF⁵, Berry K². *J Hepatol.* 2018 Aug 20. pii: S0168-8278(18)32287-6. doi: 10.1016/j.jhep.2018.07.024. [Epub ahead of print]

BACKGROUND AND AIMS: Most patients with hepatitis C virus (HCV) infection will undergo antiviral treatment with direct-acting antivirals (DAA) and achieve sustained virologic response (SVR). We aimed to develop models estimating HCC risk after antiviral treatment. **METHODS:** We identified 45,810 patients who initiated antiviral treatment in the Veterans Affairs (VA) national healthcare system from 1/1/2009 to 12/31/2015, including 29,309 (64%) DAA-only regimens and 16,501(36%) interferon \pm DAA regimens. We retrospectively followed patients until 6/15/2017 to identify incident cases of HCC. We used Cox proportional hazards regression to develop and internally validate models predicting HCC risk using baseline characteristics at the time of antiviral treatment. **RESULTS:** We identified 1412 incident cases of HCC diagnosed at least 180 days after initiation of antiviral treatment during a mean follow-up of 2.5 years (range 1-7.5 years). Models predicting HCC risk after antiviral treatment were developed and validated separately for four sub-groups of patients: cirrhosis/SVR, cirrhosis/no SVR, no cirrhosis/SVR, no cirrhosis/no SVR. Four predictors (age, platelet count, serum AST/ \sqrt ALT ratio and albumin) accounted for most of the prediction with smaller contributions from sex, race-ethnicity, HCV genotype, body mass index, hemoglobin and serum alpha fetoprotein. Fitted models were well-calibrated with very good measures of discrimination. Decision curves demonstrated higher net benefit of using model-based HCC risk estimates to determine whether to recommend screening or not compared to the screen-all or screen-none strategies. **CONCLUSIONS:** We developed and internally validated models that estimate HCC

risk following antiviral treatment. These models are available as web-based tools that can be used to inform risk-based HCC surveillance strategies in individual patients.

Hepatitis C virus-associated hepatocellular carcinoma as a second primary malignancy: exposing an overlooked presentation of liver cancer.

Dandachi D1,2, Hassan M3, Kaseb A4, Angelidakis G2, Torres HA2,4. J Hepatocell Carcinoma. 2018 Aug 2;5:81-86. doi: 10.2147/JHC.S164568. eCollection 2018.

INTRODUCTION: Chronic hepatitis C virus (HCV) infection is one of the leading causes of hepatocellular carcinoma (HCC) worldwide. Antiviral therapy in patients with HCV infection reduces the risk of primary HCC development by 71%-75%. HCV-infected patients with different primary cancers are also at risk for HCC development as a second primary malignancy (HCC-SPM). Limited information is available on the occurrence and characteristics of HCC-SPM. Herein, we determine the prevalence and clinical features of HCV-associated HCC-SPM when compared to primary HCC. **MATERIALS AND METHODS:** Patients with HCV-associated HCC seen at MD Anderson Cancer Center (2011-2017) were enrolled in a prospective observational study. Patients with multiple cancers diagnosed simultaneously or with hepatitis B virus or HIV coinfections were excluded. At enrollment, patients completed a questionnaire on medical history and HCC risk factors. Information on demographics, comorbidities, HCV treatment, tumor characteristics, treatment modalities, and virologic and oncologic outcomes were extracted from the medical records. **RESULTS:** Among 171 consecutive patients with HCV-associated HCC enrolled, 26 (15%) had HCC-SPM. Most of the underlying primary cancers were solid tumors (85%). In 12 (46%) of these patients, the diagnosis was made incidentally while undergoing surveillance for primary malignancies, and the majority (81%) had their primary cancer in remission. Most patients (72%) with documented HCV viral load had chronic viremia due to lack of diagnosis, lack of treatment, or prior unsuccessful treatment of HCV infection and only 28% had undetectable viral load following successful antiviral therapy. The overall median survival for both groups was 29 months (95% CI: 23-35) without difference between groups (p=0.2). **CONCLUSION:** Cancer patients with any malignancies must be screened for HCV as HCC-SPM can develop in 15% of infected patients. Early HCV diagnosis and treatment should be attempted to prevent the development of HCC-SPM, a condition associated with high mortality in cancer survivors.