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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Elevated serum uric acid level was a notable adverse event during combination therapy with sofosbuvir and ribavirin.](#) Sato K1,2, Naganuma A3, Nagashima T4, et al. Hepatol Res. 2017 Aug 19. doi: 10.1111/hepr.12971. [Epub ahead of print]

AIM: Combination therapy with sofosbuvir and ribavirin (SOF/RBV) has been recently available for chronic hepatitis C patients with genotype 2 (CHG2) in Japan. The domestic phase-III clinical trial showed a high antiviral effect with a relatively safe adverse event (AE) profile. Our aim was to report an important AE detected during treatment. **METHODS:** A prospective multi-institutional study of 12-week combination therapy with SOF/RBV for CHG2 was performed to evaluate efficacy and safety. **RESULTS:** The eligible subjects include 142 patients. Out of 50 assessable patients, 16% of the patients were diagnosed with hyperuricemia. The proportions of subjects with grade 1, grade 3 and grade 4 hyperuricemia were 12, 2, and 2%, respectively. Serum uric acid (UA) levels at week 1 of the therapy (W1) were the numerically highest during the therapy in patients with hyperuricemia and a ratio of W1/baseline serum UA levels was significantly higher than that of post-treatment week 4 or 8/baseline serum UA levels in assessable patients. Serum UA levels at W1 were significantly correlated with body mass index. The difference between serum UA levels at W1 and baseline serum UA levels was significantly correlated with that between serum creatinine levels at W1 and baseline serum creatinine levels. **CONCLUSIONS:** Elevated serum UA level was a notable AE associated with the therapy. However, because of the small number of subjects, the exact frequency of AEs should be re-evaluated with larger cohorts. We need to remember that elevated serum UA level might develop during the therapy, especially at W1.

[Safety and efficacy of a fixed-dose combination regimen of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin in participants with and without cirrhosis with chronic hepatitis C virus genotype 1, 2, or 3 infection \(C-CREST-1 and C-CREST-2, part B\): two randomised, phase 2, open-label trials.](#) Lawitz E1, Buti M2, Vierling JM3, et al. Lancet Gastroenterol Hepatol. 2017 Aug 9. pii: S2468-1253(17)30163-2. doi: 10.1016/S2468-1253(17)30163-2. [Epub ahead of print]

BACKGROUND: There is a need for hepatitis C virus (HCV) therapies with excellent efficacy across genotypes and in diverse populations. Part A of the C-CREST-1 and C-CREST-2 trials led to the selection of a three-drug regimen of grazoprevir (MK-5172; an HCV NS3/4A protease inhibitor; 100 mg/day) plus ruzasvir (MK-8408; an NS5A inhibitor; 60 mg/day) plus uprifosbuvir (MK-3682; an HCV NS5B polymerase inhibitor; 450 mg/day). Part B of the studies tested this combination as a single formulation in different treatment durations in a broader population. **METHODS:** Part B of these randomised, phase 2, open-label clinical trials enrolled individuals from 15 countries who were chronically infected with HCV genotypes 1-6 (HCV RNA $\geq 10\,000$ IU/mL) with or without compensated cirrhosis. Those with genotype 1, genotype 2, genotype 4, or genotype 6 were treatment-naïve; those with genotype 3 could be treatment-naïve or treatment-experienced with pegylated interferon and ribavirin. Randomisation occurred centrally using an interactive voice response system and integrated web response system. Participants were randomly assigned to receive treatment for 8, 12, or 16 weeks with a fixed-dose combination of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin. The primary endpoint was the proportion of participants achieving sustained virological response 12 weeks after the end of all study therapy (SVR12), defined as HCV RNA less than the lower limit of quantification (either target detected unquantifiable or target not detected [<15 IU/mL]). The trials are registered at ClinicalTrials.gov, numbers NCT02332707 and NCT02332720. **FINDINGS:** 676 participants were randomly assigned between Feb 18, 2015, and Aug 16, 2016. In all 675 participants who received at least one dose of study drug (full analysis set), SVR12 for the 8-week regimen of grazoprevir, ruzasvir, and uprifosbuvir with and without ribavirin was achieved in 39 (93% [95% CI 81-99]) of 42 participants with genotype 1a, 45 (98% [88-100]) of 46 with genotype 1b, 54 (86% [75-93]) of 63 with genotype 2, 98 (95% [89-98]) of 103 with genotype 3, and seven (100% [59-100]) of seven participants with genotype 4. SVR12 for the 12-week regimen with and without ribavirin was achieved in 87 (99% [95% CI 94-100]) of 88 participants with genotype 1, 61 (98% [91-100]) of 62 with genotype 2, and four (100% [40-100]) of four with genotype 6. Among participants with cirrhosis who were infected with genotype 3, SVR12 for the 12-week regimen with and without ribavirin was achieved in 28 (97% [95% CI 82-100]) of 29 of those who were treatment-naïve and 29 (100% [88-100]) of 29 who were treatment-experienced. SVR12 for the 16-week regimen with and without ribavirin was achieved in 26 (100% [95% CI 87-100]) of 26 participants with genotype 2 infection and 72 (96% [89-99]) of 75 participants with genotype 3 infection. The most common adverse events were headache (143 [22%] of 664), fatigue (129 [19%] of 664), and nausea (83 [13%] of 664). 16 (2%) of 664 participants had serious adverse events. **INTERPRETATION:** The combined regimen of grazoprevir (100 mg/day), ruzasvir (60 mg/day), and uprifosbuvir (450 mg/day) has the potential to provide a simplified treatment for HCV that is effective and well tolerated in most individuals infected with HCV, as well as a shorter duration of treatment in many individuals.

[Ethnic disparities in progression to advanced liver disease and overall survival in patients with chronic hepatitis C: impact of a sustained virological response.](#) Le AK1, Zhao C1,2, Hoang JK1, et al. *Aliment Pharmacol Ther.* 2017 Sep;46(6):605-616. doi: 10.1111/apt.14241. Epub 2017 Aug 2.

BACKGROUND: Chronic hepatitis C (CHC) can lead to cirrhosis and hepatocellular carcinoma (HCC). A sustained virological response (SVR) is associated with improved outcomes, however, its impact on different ethnic groups is unknown. **AIM:** To evaluate ethnic differences in the

natural history of CHC and the impact of SVR. **METHODS:** We conducted a cohort study of 8039 consecutive adult CHC patients seen at two medical centres in California between January 1997 and June 2016. Individual chart review confirmed CHC diagnosis. **RESULTS:** Asian and Hispanic but not African American patients had significantly higher cirrhosis and HCC incidence than Caucasians. On multivariate analysis, Hispanic ethnicity was independently associated with increased cirrhosis (adjusted HR 1.37, CI, confidence interval 1.10-1.71, P=.006) and HCC risk (adjusted HR 1.47, CI 1.13-1.92, P=.004) compared to Caucasian. Asian ethnicity had a significant association with cirrhosis (adjusted HR 1.28, CI 1.02-1.61, P=.034) and HCC risk (adjusted HR 1.29, CI 0.94-1.77, P=.025). In patients who achieved SVR, Hispanic ethnicity was no longer independently associated with cirrhosis (adjusted HR 1.76, CI 0.66-4.71, P=.26) or HCC (adjusted HR 1.05, CI 0.27-4.08, P=.94); nor was Asian ethnicity (adjusted HR 0.62, CI 0.21-1.82, P=.38 for cirrhosis; 2.01, CI 0.63-6.36, P=.24 for HCC). Similar findings were observed with overall survival among the ethnicities by SVR status. **CONCLUSION:** Hispanic and Asian ethnicity was independently associated with increased cirrhosis and HCC risk. Achieving an SVR eliminates the ethnic disparity in liver disease progression and overall survival between Hispanic and Asian vs Caucasian CHC patients.

[Alcohol and substance use, race, and insurance status predict nontreatment for hepatitis C virus in the era of direct acting antivirals: a retrospective study in a large urban tertiary center.](#) Sims OT1, Guo Y, Shoreibah MG, Venkata K, Fitzmorris P, Kommineni V, Romano J, Massoud OI. Eur J Gastroenterol Hepatol. 2017 Aug 29. doi: 10.1097/MEG.0000000000000961. [Epub ahead of print]

OBJECTIVE: Direct acting antivirals (DAAs) have overcome many long-standing medical barriers to hepatitis C virus (HCV) treatment (i.e. host characteristics and medical contraindications) and treatment outcome disparities that were associated with interferon regimens. The public health and clinical benefit of current and forthcoming DAA discoveries will be limited if efforts are not made to examine racial, psychological, and socioeconomic factors associated with being treated with DAAs. This study examined racial, psychological, and socioeconomic factors that facilitate and inhibit patients receiving DAAs for HCV.

PATIENTS AND METHODS: This was a single-center retrospective cohort study at a large urban tertiary center of patients (n=747) who were referred for evaluation and treatment of HCV.

RESULTS: Sixty-eight percent of patients were non-Hispanic White, 31% were African American, and 1% were of other ethnicities. The majority of patients received treatment, but 29% (218/747) did not. Patients who were older [odds ratio (OR)=1.02, 95% confidence interval (CI): 1.01-1.04] and insured (OR=2.73, 95% CI: 1.12-6.97) were more likely to receive HCV treatment. Patients who were African American (OR=0.46, 95% CI: 0.46-1.06), used drugs (OR=0.09, 95% CI: 0.04-0.17), smoked (OR=0.55, 95% CI: 0.37-0.81), and used alcohol (OR=0.11, 95% CI: 0.06-0.20) were less likely to receive HCV treatment. **CONCLUSION:**

Though DAAs have eliminated many historically, long-standing medical barriers to HCV treatment, several racial, psychological and socioeconomic barriers, and disparities remain. Consequently, patients who are African American, uninsured, and actively use drugs and alcohol will suffer from increased HCV-related morbidity and mortality in the coming years if deliberate public health and clinical efforts are not made to facilitate access to DAAs.

[Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial.](#) Kattakuzhy S1, Gross C1,

Emmanuel B1, et al. Ann Intern Med. 2017 Sep 5;167(5):311-318. doi: 10.7326/M17-0118. Epub 2017 Aug 8.

BACKGROUND: Direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection has resulted in high rates of disease cure; however, not enough specialists currently are available to provide care. **OBJECTIVE:** To determine the efficacy of HCV treatment independently provided by nurse practitioners (NPs), primary care physicians (PCPs), or specialist physicians using DAA therapy. **DESIGN:** Nonrandomized, open-label clinical trial initiated in 2015. (ClinicalTrials.gov: NCT02339038). **SETTING:** 13 urban, federally qualified health centers (FQHCs) in the District of Columbia. **PATIENTS:** A referred sample of 600 patients, of whom 96% were black, 69% were male, 82% were treatment naive, and 20% had cirrhosis. Seventy-two percent of the patients had HCV genotype 1a infection. The baseline characteristics of patients seen by each provider type were similar. **INTERVENTION:** Patients were assigned in a nonrandomized but specified manner to receive treatment from 1 of 5 NPs, 5 PCPs, or 6 specialists. All providers underwent an identical 3-hour training session based on guidelines. Patients received treatment with ledipasvir-sofosbuvir, which was provided on site, according to U.S. Food and Drug Administration labeling requirements. **MEASUREMENTS:** Sustained virologic response (SVR). **RESULTS:** 516 patients achieved SVR, a response rate of 86% (95% CI, 83.0% to 88.7%), with no major safety signals. Response rates were consistent across the 3 provider types: NPs, 89.3% (CI, 83.3% to 93.8%); PCPs, 86.9% (CI, 80.6% to 91.7%); and specialists, 83.8% (CI, 79.0% to 87.8%). Patient loss to follow-up was the major cause of non-SVR. **LIMITATION:** Nonrandomized patient distribution; possible referral bias. **CONCLUSION:** In a real-world cohort of patients at urban FQHCs, HCV treatment administered by nonspecialist providers was as safe and effective as that provided by specialists. Nurse practitioners and PCPs with compact didactic training could substantially expand the availability of community-based providers to escalate HCV therapy, bridging existing gaps in the continuum of care for patients with HCV infection. **PRIMARY FUNDING SOURCE:** National Institutes of Health and Gilead Sciences.

[The Real-World Safety and Efficacy of Daclatasvir and Asunaprevir for Elderly Patients.](#)

Taki S1, Tamai H1, Ida Y1, et al. Gut Liver. 2017 Aug 14. doi: 10.5009/gnl17048. [Epub ahead of print]

BACKGROUND/AIMS: Although daclatasvir with asunaprevir was approved in Japan for interferon ineligible or intolerant patients, patients aged ≥ 75 years were excluded in the phase III trial. The present study aimed to evaluate the safety and efficacy of this therapy for elderly patients aged ≥ 75 years and to clarify whether an extremely high sustained virological response (SVR) rate can be achieved, even in a real-world setting when patients with resistance-associated substitutions (RASs) to nonstructural protein 5A (NS5A) inhibitors or prior simeprevir failure are excluded. **METHODS:** Daclatasvir (60 mg) and asunaprevir (100 mg) were orally administered daily for 24 weeks. Patients without pre-existing NS5A RASs and simeprevir failure were enrolled in this study. **RESULTS:** Overall, 110 patients were treated. The median age was 73 years old. The SVR rates of total patients, those aged ≥ 75 years, and those aged < 75 years were 97% (107/110), 98% (46/47), and 97% (61/63), respectively. The treatment of two patients (2%) was discontinued because of adverse events. **CONCLUSIONS:** Daclatasvir with asunaprevir was a safe treatment, even in patients aged ≥ 75 years. When patients without pre-existing NS5A RASs and prior simeprevir failure were selected, an extremely high SVR rate could be achieved irrespective of age.

Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial.

Forns X1, Lee SS2, Valdes J3, et al. Lancet Infect Dis. 2017 Aug 14. pii: S1473-3099(17)30496-6. doi: 10.1016/S1473-3099(17)30496-6. [Epub ahead of print]

BACKGROUND: The once-daily, ribavirin-free, pangenotypic, direct-acting antiviral regimen, glecaprevir coformulated with pibrentasvir, has shown high rates of sustained virological response in phase 2 and 3 studies. We aimed to assess the efficacy and safety of 12 weeks of coformulated glecaprevir and pibrentasvir in patients with hepatitis C virus (HCV) infection and compensated cirrhosis. **METHODS:** We did this single-arm, open-label, multicentre phase 3 study at 40 sites in Belgium, Canada, Germany, South Africa, Spain, and the USA. We enrolled patients aged 18 years or older with HCV genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Patients were either HCV treatment-naïve or had not responded to treatment with interferon or pegylated interferon with or without ribavirin, or sofosbuvir plus ribavirin with or without pegylated interferon. Oral glecaprevir (300 mg) coformulated with pibrentasvir (120 mg) was administered once daily for 12 weeks. The primary efficacy endpoint was sustained virological response at post-treatment week 12 (HCV RNA <15 IU/mL). We assessed efficacy and safety in all patients who received at least one dose of study drug (intention-to-treat population). This study is registered with ClinicalTrials.gov, number NCT02642432.

FINDINGS: Between Dec 7, 2015, and May 4, 2016, we enrolled 146 patients with compensated cirrhosis, of whom 48 (33%) had genotype 1a HCV infection, 39 (27%) had genotype 1b infection, 34 (23%) had genotype 2 infection, 16 (11%) had genotype 4 infection, two (1%) had genotype 5 infection, and seven (5%) had genotype 6 infection. 12 weeks after treatment, 145 patients (99%, 95% CI 98-100) achieved sustained virological response, with one (1%) relapse at post-treatment week 8. We recorded 101 (69%) adverse events, of which 65 (64%) were mild. The most common adverse events were fatigue (n=28 [19%]) and headache (n=20 [14%]). 11 (8%) patients had serious adverse events, none of which were deemed related to study drugs. No patients had elevations in alanine aminotransferase and no patients prematurely discontinued treatment because of adverse events. **INTERPRETATION:** Our results show that 99% of patients treated with once-daily glecaprevir plus pibrentasvir achieved a sustained virological response at 12 weeks. Furthermore, this drug regimen had a favourable safety profile in previously treated or untreated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. These findings could help simplify treatment algorithms and reduce treatment burden.

Vitamin D supplementation improves serum markers associated with hepatic fibrogenesis in chronic hepatitis C patients: A randomized, double-blind, placebo-controlled study.

Komolmit P1,2, Kimtrakool S3, Suksawatamnuay S4,5, Thanapirom K4,5, Chattrasophon K6, Thaimai P4, Chirathaworn C7, Poovorawan Y8. Sci Rep. 2017 Aug 21;7(1):8905. doi: 10.1038/s41598-017-09512-7.

Hepatic fibrosis is the net accumulation of matrix tissue components which controlled by pro-fibrotic enzymes, matrix metalloproteinases (MMPs), and pro-fibrotic cytokine, TGF- β 1, and enzymes, tissue inhibitors of MMPs (TIMPs). Vitamin D (VD) supplementation has been shown to reverse these processes in vitro and in vivo. This study sought to determine the effect of VD supplementation on serum fibrotic markers in chronic hepatitis C (CHC) patients. Fifty-four CHC patients with VD deficiency were randomized into two groups, a VD group (n = 29) and a

placebo group (n = 29). The serum levels of 25-hydroxy VD, TGF- β 1, TIMP-1, MMP2 and MMP9 were measured at baseline and at the end of the 6-week study period. Upon correction of VD levels, TGF- β 1 and TIMP-1 levels were decreased, and the MMP2 and MMP9 levels were significantly increased in the VD group. A comparison of the mean changes (delta) in the markers between groups showed that TGF- β 1 and TIMP-1 levels were significantly decreased and the MMP2 and MMP9 were significantly higher in the VD group than in the placebo group. By using CHC patients as a model, this study provides additional evidence that VD plays an important role in the reversal of hepatic fibrogenesis.

Predictors of early discontinuation of interferon-free direct antiviral agents in patients with hepatitis C virus and advanced liver fibrosis: results of a real-life cohort.

Miotto N1, Mendes LC, Zanaga LP, et al. Eur J Gastroenterol Hepatol. 2017 Aug 10. doi: 10.1097/MEG.0000000000000944. [Epub ahead of print]

AIM: The aim of this study was to determine risk factors for premature treatment discontinuation among patients with hepatitis C and advanced fibrosis with advanced fibrosis treated with interferon (IFN)-free direct antiviral agents (DAA)-based therapy. **PATIENTS AND METHODS:** We included all patients with chronic hepatitis C virus infection and advanced liver fibrosis in whom treatment was initiated with IFN-free DAA therapy at a university hospital from December 2015 through June 2016. We prospectively collected data from medical records using standardized questionnaires and evaluated them using Epi Info 7.1.2.0. The primary outcome was treatment interruption and associated factors. **RESULTS:** In total, 214 patients were included in this study; 180 patients were treated with sofosbuvir (SOF)+ daclatasvir \pm ribavirin (RBV), 31 received SOF+simeprevir \pm RBV, and three were treated with SOF+RBV. Treatment discontinuation rate was 8.9% (19 patients) and cirrhotic decompensation was the main reason [8 (42.1%)]. Among patients with Child B or C cirrhosis (31), 10 (32.2%) prematurely interrupted treatment. The risk factors for treatment discontinuation in univariate analysis were older age (P=0.0252), higher comorbidity index (P=0.0078), higher model for end-stage liver disease (P<0.0001), higher fibrosis index based on the 4 factors (P=0.0122), and lower hemoglobin (P=0.0185) at baseline. Multivariate analysis showed that older age (odds ratio: 1.1, 95% confidence interval: 1.02-1.19) and higher model for end-stage liver disease (odds ratio: 1.27, 95% confidence interval: 1.03-1.56) were associated with premature treatment interruption. **CONCLUSION:** Older age and advanced liver disease were related to treatment interruption. Identification of risk factors associated with treatment discontinuation is important to recognize patients who should be followed up closely during treatment, and those whom possibly may not benefit from immediate DAA treatment or should be followed up closely during treatment.

High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic.

Norton BL1, Fleming J2, Bachhuber MA2, et al. Int J Drug Policy. 2017 Aug 12. pii: S0955-3959(17)30235-9. doi: 10.1016/j.drugpo.2017.07.021. [Epub ahead of print]

BACKGROUND: Though direct acting antivirals (DAAs) promise high cure rates, many providers and payers remain concerned about successful treatment for people who use drugs (PWUD), even among those engaged in opioid agonist treatment (OAT). The efficacy of DAAs among PWUD in real-world settings is unclear. **METHODS:** We conducted a cohort study of patients initiating HCV treatment between January 2014 and August 2015 (n=89) at a primary

care clinic in the Bronx, NY. Onsite HCV treatment with DAAs was performed by an HCV specialist, with support from a care coordinator funded by the NYC Department of Health. We identified four categories of drug use and drug treatment: (1) no active drug use/not receiving OAT (defined as non-PWUD); (2) no active drug use/receiving OAT; (3) active drug use/not receiving OAT; and (4) active drug use/receiving OAT. The primary outcome was SVR at 12 week's post-treatment. **RESULTS:** Overall SVR rates were 95% (n=41/43) for non-PWUD and 96% (n=44/46) for patients actively using drugs and/or receiving OAT [p=0.95]. There were no differences in SVR rates by drug use or drug treatment category. Compared to non-PWUD, those with no active drug use/receiving OAT had 100% SVR (n=15/15; p=1.0), those actively using drugs/not receiving OAT had 90% SVR (n=9/10; p=0.47), and those actively using drugs/receiving OAT had 95% SVR (20/21; p=1.0). **CONCLUSION:** Regardless of active drug use or OAT, patients who received DAA therapy at an urban primary care clinic achieved high HCV cure rates. We found no clinical evidence to justify restricting access to HCV treatment for patients actively using drugs and/or receiving OAT.

[**A different perspective on sofosbuvir-ledipasvir treatment of patients with HCV genotype 1b cirrhosis: The ital-c network study.**](#) Barone M1, Iannone A1, Shahini E1, et al. J Viral Hepat. 2017 Aug 8. doi: 10.1111/jvh.12765. [Epub ahead of print]

The effectiveness of a 12-week course of sofosbuvir-ledipasvir in treatment-experienced HCV genotype 1b-infected patients with cirrhosis is still under debate. Our primary endpoint was to compare the sustained virological response at post-treatment week 12 (SVR12) of sofosbuvir-ledipasvir in combination with ribavirin for 12 weeks, and sofosbuvir-ledipasvir alone for 24 weeks. This was a prospective observational study that enrolled 424 (195 naive, 229 experienced; 164 treated for 12 weeks with Ribavirin and 260 with sofosbuvir-ledipasvir alone for 24 weeks) consecutive HCV genotype 1b-infected patients with cirrhosis. The SVR12 rates were 93.9% and 99.2% in patients treated for 12 and 24 weeks, respectively (P = .002). The baseline characteristics of patients treated for 12 weeks were significantly different from those treated for 24 weeks as regards their younger age (P = .002), prevalence of Child-Pugh class A (P = .002), lower MELD scores (P = .001) and smaller number of nonresponders (P = .04). The shorter treatment was significantly associated with a lower SVR12 in univariate and multivariate analyses (P = .007 and P = .008, respectively). The SVR rate was unaffected by age, gender, BMI, Child-Pugh class, MELD score or previous antiviral treatment. Patients receiving ribavirin experienced more episodes of ascites and headache but less recurrence of hepatocellular carcinoma (HCC), and were prescribed more diuretics and cardiopulmonary drugs. No patient discontinued treatment. The therapeutic regimen of sofosbuvir-ledipasvir plus ribavirin administered for 12 weeks was less effective than sofosbuvir-ledipasvir alone given for 24 weeks. At odds with European guidelines, the recommended 12-week treatment with sofosbuvir-ledipasvir alone might be suboptimal for this setting of patients.

[**Immune responses in DAA treated chronic hepatitis C patients with and without prior RG-101 dosing.**](#) van der Ree MH1, Stelma F1, Willemse SB2, et al. Antiviral Res. 2017 Aug 24. pii: S0166-3542(17)30390-X. doi: 10.1016/j.antiviral.2017.08.016. [Epub ahead of print]

BACKGROUND&AIMS: With the introduction of DAA's, the majority of treated chronic hepatitis C patients (CHC) achieve a viral cure. The exact mechanisms by which the virus is cleared after successful therapy, is still unknown. The aim was to assess the role of the immune system and miRNA levels in acquiring a sustained virological response after DAA treatment in

CHC patients with and without prior RG-101 (anti-miR-122) dosing. **METHODS:** In this multicenter, investigator-initiated study, 29 patients with hepatitis C virus (HCV) genotype 1 (n = 11), 3 (n = 17), or 4 (n = 1) infection were treated with sofosbuvir and daclatasvir ± ribavirin. 18 patients were previously treated with RG-101. IP-10 levels were measured by ELISA. Ex vivo HCV-specific T cell responses were quantified in IFN- γ -ELISpot assays. Plasma levels of miR-122 were measured by qPCR. **RESULTS:** All patients had an SVR12. IP-10 levels rapidly declined during treatment, but were still elevated 24 weeks after treatment as compared to healthy controls (median 53.82 and 39.4 pg/mL, p = 0.02). Functional IFN- γ HCV-specific T cell responses did not change by week 12 of follow-up (77.5 versus 125 SFU/106 PBMC, p = 0.46). At follow-up week 12, there was no difference in plasma miR-122 levels between healthy controls and patients with and without prior RG-101 dosing. **CONCLUSIONS:** Our data shows that successful treatment of CHC patients with and without prior RG-101 dosing results in reduction of broad immune activation, and normalization of miR-122 levels (EudraCT: 2014-002808-25).

[The higher prevalence of truncal obesity and diabetes in American than Chinese patients with chronic hepatitis C might contribute to more rapid progression to advanced liver disease.](#)

Rao H1, Wu E2, Fu S2, Yang M1, Feng B1, Lin A3, Fei R1, Fontana RJ2, Lok AS2, Wei L1. Aliment Pharmacol Ther. 2017 Aug 22. doi: 10.1111/apt.14273. [Epub ahead of print]

BACKGROUND: Chronic hepatitis C virus (HCV) infection is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in the United States (US) and an emerging cause in China. **AIM:** To compare the clinical characteristics of hepatitis C patients in the US and China, and factors influencing disease stage. **METHODS:** Prospective study of 2 cohorts of HCV patients recruited at 1 site in the US and 3 sites in China. Standardised questionnaire on risk factors and medical history were used and diagnosis of cirrhosis and HCC was based on pre-defined criteria. **RESULTS:** One thousand nine hundred and fifty seven patients (1000 US and 957 China) were enrolled. US patients were more likely to be men (61.4% vs 48.5%), older (median age 57 vs 53 years), obese (38.4% vs 16.8%) and diabetic (21.8% vs 10.8%). A significantly higher per cent of US patients had cirrhosis (38.2% vs 16.0%) and HCC (14.1% vs 2.7%). Investigator estimated time at infection in US was 10 years earlier than in Chinese patients but US patients were more likely to have advanced disease even after stratifying for duration of infection. Study site in the US, older age, truncal obesity, diabetes and prior HCV treatment were significant predictors of advanced disease on multivariate analysis. **CONCLUSIONS:** HCV patients in the US had more advanced liver disease than those in China. We speculate that underlying fatty liver disease may be a major contributor to this difference, and management of glycometabolic abnormalities should occur in parallel with anti-viral therapy to achieve optimal outcomes.

[Point-of-care testing for hepatitis C virus infection at alternative and high-risk sites: an Italian pilot study in a dental clinic.](#)

Parisi MR1, Tecco S2, Gastaldi G2, et al. New Microbiol. 2017 Aug 21;40(3). [Epub ahead of print]

The Infectious Diseases Department and the Department of Dentistry of San Raffaele Scientific Institute in Milan conducted a screening and prevention program, the "EASY HCV-test Program," at a dental clinic to increase the identification of unrecognized infections. Using a cross-sectional community-based study design, hygienists in the dental clinic offered patients a hepatitis C virus (HCV) rapid salivary test (OraQuick ADVANCE® Rapid HCV Antibody Test) with pre- and post-test counseling prior to initiation of their oral hygiene routine. From April

2015 to November 2015, the EASY HCV test was offered to 2650 patients visiting the Center of Oral Health and Prevention at the Department of Dentistry at San Raffaele Hospital in Milan. Among them, 2077 eligible volunteers were tested. The test showed positive reactivity in 22 cases; of these, 21 subjects were known to suffer from HCV, and the test confirmed their status. One subject was newly diagnosed with HCV infection. The results of this study suggest EASY HCV test screening conducted in dental clinics may constitute an effective strategy for increasing HCV testing among people at risk for infection.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Monocytes inhibit hepatitis C virus-induced TRAIL expression on CD56bright NK cells.

Mele D1, Mantovani S1, Oliviero B1, Grossi G1, Lombardi A2, Mondelli MU3, Varchetta S4. *J Hepatol.* 2017 Aug 10. pii: S0168-8278(17)32203-1. doi: 10.1016/j.jhep.2017.07.028. [Epub ahead of print]

BACKGROUND AND AIMS: Natural killer (NK) cells play an important role in the pathogenesis of HCV infection. We have previously shown that culture-derived HCV (HCVcc) enhance tumor necrosis-factor-related apoptosis-inducing ligand (TRAIL) expression on healthy but not on HCV-infected patient-derived NK cells, which was likely dependent on accessory cells. Here we sought mechanistic insights involved in altered TRAIL upregulation in this setting. **METHODS:** Peripheral blood mononuclear cells (PBMC) from controls and HCV-infected patients were exposed to HCVcc. Cell depletions were performed to identify cells responsible for NK cell activation. Flow cytometry and ELISA were used to identify the cytokines involved in the NK activation process. **RESULTS:** In HCV-infected patients, soluble factors secreted by control PBMC restored the ability of NK cells to express TRAIL. Of note, CD14+ cell depletion had identical effects upon virus exposure and promoted increased degranulation. Moreover, increased concentrations of IL18 binding protein a (IL18BP_a) and IL36 receptor antagonist (IL36RA) were observed after PBMC exposure to HCVcc in HCV+ patients. HCVcc-induced NK cell TRAIL expression was inhibited by IL18BP_a and IL36RA in control subjects. There were statistically significant correlations between IL18BP_a and indices of liver inflammation and fibrosis, supporting a role for this protein in the pathogenesis of chronic HCV infection. **CONCLUSIONS:** During chronic HCV infection, monocytes play a key role in negative regulation of NK cell activation, predominantly via secretion of inhibitors of IL18 and IL36. **LAY SUMMARY:** Coordination and collaboration between immune cells are essential to fight pathogens. We show here that during HCV infection monocytes secrete IL18 and IL36 inhibitory proteins, reducing NK cell activation, and consequently inhibiting their ability to express TRAIL and kill target cells.

Immunogenicity of an influenza virus-vectored vaccine carrying the hepatitis C virus protein epitopes in mice.

Zhang S1, Sun F1, Ren T1, Duan Y2, Gu H2, Lai C2, Wang Z1, Zhang P1, Wang X3, Yang P4. *Antiviral Res.* 2017 Sep;145:168-174. doi: 10.1016/j.antiviral.2017.07.015. Epub 2017 Aug 1.

Hepatitis C virus (HCV) has a devastating impact on human health, and infections can progress into liver fibrosis, cirrhosis, and hepatocellular carcinoma. There is no effective HCV vaccine. In this study, we rescued a recombinant PR8 influenza viral vector, called rgFLU-HCVCE1E2, carrying the core and envelope glycoprotein (C/E1/E2) epitopes of HCV inserted into the influenza nonstructural protein 1 gene. The morphological characteristics of rgFLU-HCVCE1E2

and the expression of the C/E1/E2 epitopes of HCV were examined. rgFLU-HCVCE1E2 replicated in various cell lines, including MDCK, A549, and Huh7.5 cells. More importantly, in BALB/c mice immunized intranasally twice at a 21-day interval with 104, 105, or 106 TCID₅₀ rgFLU-HCVCE1E2, the viral vector induced a robust antibody response to influenza and HCV and potent IFN- γ and IL-4 secretion in response to HCV antigens in a dose-dependent manner. The rgFLU-HCVCE1E2 virus also stimulated IFN- γ production by virus-specific peripheral blood mononuclear cells in patients with chronic HCV infection. The study demonstrated that rgFLU-HCVCE1E2 carrying HCV antigens is immunogenic in vivo and has potential for the development of a HCV vaccine.

Treatment-Induced Viral Cure of Hepatitis C Virus-Infected Patients Involves a Dynamic Interplay among three Important Molecular Players in Lipid Homeostasis: Circulating microRNA (miR)-24, miR-223, and Proprotein Convertase Subtilisin/Kexin Type 9.

Hyrina A1, Olmstead AD2, Steven P3, Kraiden M4, Tam E5, Jean F6. EBioMedicine. 2017 Aug 24. pii: S2352-3964(17)30337-7. doi: 10.1016/j.ebiom.2017.08.020. [Epub ahead of print]

In patients with chronic hepatitis C virus (HCV) infection, viral hijacking of the host-cell biosynthetic pathways is associated with altered lipid metabolism, which contributes to disease progression and may influence antiviral response. We investigated the molecular interplay among four key regulators of lipid homeostasis [microRNA (miR)-122, miR-24, miR-223, and proprotein convertase subtilisin/kexin type 9 (PCSK9)] in HCV-infected patients (n=72) who achieved a treatment-based viral cure after interferon-based therapy with first-generation direct-acting antivirals. Real-time PCR was used to quantify microRNA plasma levels, and ELISA assays were used to determine plasma concentrations of PCSK9. We report that levels of miR-24 and miR-223 significantly increased in patients achieving sustained virologic response (SVR), whereas the levels of miR-122, a liver-specific cofactor for HCV infection, decreased in these patients. PCSK9 concentrations were significantly increased in SVRs, suggesting that PCSK9 may help impede viral infection. The modulatory effect of PCSK9 on HCV infection was also demonstrated in the context of HCV-infected Huh-7.5.1 cells employing recombinant human PCSK9 mutants. Together, these results provide insights into a novel coordinated interplay among three important molecular players in lipid homeostasis - circulating miR-24, miR-223 and PCSK9 - whose regulation is affected by HCV infection and treatment-based viral cure.

Structure-Based Design of Hepatitis C Virus Vaccines that Elicit Neutralizing Antibody Responses to a Conserved Epitope.

Pierce BG1,2, Boucher EN3, Piepenbrink KH4, et al. J Virol. 2017 Aug 9. pii: JVI.01032-17. doi: 10.1128/JVI.01032-17. [Epub ahead of print]

Despite recent advances in therapeutic options, hepatitis C virus (HCV) remains a severe global disease burden, and a vaccine can substantially reduce its incidence. Due to its extremely high sequence variability, HCV can readily escape the immune response, thus an effective vaccine must target conserved, functionally important epitopes. Using the structure of a broadly neutralizing antibody in complex with a conserved linear epitope from the HCV E2 envelope glycoprotein (residues 412-423; epitope I), we performed structure-based design of immunogens to induce antibody responses to this epitope. This resulted in epitope-based immunogens based on a cyclic defensin protein, as well as a bivalent immunogen with two copies of the epitope on the E2 surface. We solved the x-ray structure of a cyclic immunogen in complex with the HCV1 antibody and confirmed preservation of the epitope conformation and the HCV1 interface. Mice vaccinated with our designed immunogens produced robust antibody responses to epitope I, and

their serum could neutralize HCV. Notably, the cyclic designs induced greater epitope-specific responses and neutralization than the native peptide epitope. Beyond successfully designing several novel HCV immunogens, this study demonstrates the principle that neutralizing anti-HCV antibodies can be induced by epitope-based, engineered vaccines and provides the basis for further efforts in structure-based design of HCV vaccines. **IMPORTANCE:** Hepatitis C virus is a leading cause of liver disease and liver cancer, with approximately 3% of the world's population infected. To combat this virus, an effective vaccine would have distinct advantages over current therapeutic options, yet experimental vaccines have not been successful to date, due in part to the virus's high sequence variability leading to immune escape. In this study we rationally designed several vaccine immunogens based on the structure of a conserved epitope that is the target of broadly neutralizing antibodies. In vivo results in mice indicated that these antigens elicited epitope-specific neutralizing antibodies, with varying degrees of potency and breadth. These promising results suggest that a rational design approach can be used to generate an effective vaccine for this virus.

[**Analysis of Structure-Activity Relationships Based on the Hepatitis C Virus SLIIB Internal Ribosomal Entry Sequence RNA-Targeting GGHYRFK-Cu Complex.**](#) Ross MJ^{1,2}, Fidai I^{1,3}, Cowan JA^{1,3,4,5}. *Chembiochem*. 2017 Sep 5;18(17):1743-1754. doi: 10.1002/cbic.201700228. Epub 2017 Aug 7.

New therapeutics for targeting the hepatitis C virus (HCV) have been released in recent years. Although they are less prone to resistance, they are still administered in cocktails as a combination of drugs targeting various aspects of the viral life cycle. Herein, we aim to contribute to an arsenal of new HCV therapeutics by targeting the HCV internal ribosomal entry sequence (IRES) RNA through the development of catalytic metallodrugs that function to degrade rather than inhibit the target molecule. Based on a previously characterized HCV IRES stem-loop IIB RNA-targeting metallopeptide Cu-GGHYrFK (1·Cu), an all-I analogue (3·Cu) and a series of additional complexes with single alanine substitutions in the targeting domain were prepared and screened to determine the influence each amino acid side chain on RNA localization and recognition, and catalytic reactivity toward the RNA. Additional substitutions of the tyrosine position in complex 3·Cu were also investigated. Good agreement between calculated and measured binding affinities provided support for in silico modeling of the SLIIB RNA binding site and correlations with RNA cleavage sites. Examination of the cleavage products from reaction of the Cu complexes with SLIIB provided mechanistic insights, with the first observation of the 5'-geminal diol and 5'-phosphopropenal as products through the use of a Cu·ATCUN catalytic motif. Together, the data yielded insights into structure-function relationships that will guide future optimization efforts.

[**Cinnamic acid derivatives inhibit hepatitis C virus replication via the induction of oxidative stress.**](#) Amano R¹, Yamashita A¹, Kasai H¹, et al. *Antiviral Res*. 2017 Sep;145:123-130. doi: 10.1016/j.antiviral.2017.07.018. Epub 2017 Aug 2.

Several cinnamic acid derivatives have been reported to exhibit antiviral activity. In this study, we prepared 17 synthetic cinnamic acid derivatives and screened them to identify an effective antiviral compound against hepatitis C virus (HCV). Compound 6, one of two hit compounds, suppressed the viral replications of genotypes 1b, 2a, 3a, and 4a with EC₅₀ values of 1.5-8.1 μM and SI values of 16.2-94.2. The effect of compound 6 on the phosphorylation of Tyr705 in signal transducer and activator of transcription 3 (STAT3) was investigated because a cinnamic acid

derivative AG490 was reported to suppress HCV replication and the activity of Janus kinase (JAK) 2. Compound 6 potently suppressed HCV replication, but it did not inhibit the JAK1/2-dependent phosphorylation of STAT3 Tyr705 at the same concentration. Furthermore, a pan-JAK inhibitor tofacitinib potently impaired phosphorylation of STAT3 Tyr 705, but it did not inhibit HCV replication in the replicon cells and HCV-infected cells at the same concentration, supporting the notion that the phosphorylated state of STAT3 Tyr705 is not necessarily correlated with HCV replication. The production of reactive oxygen species (ROS) was induced by treatment with compound 6, whereas N-acetyl-cysteine restored HCV replication and impaired ROS production in the replicon cells treated with compound 6. These data suggest that compound 6 inhibits HCV replication via the induction of oxidative stress.

[The potential of signal peptide peptidase as a therapeutic target for hepatitis C.](#) Moriishi K1. *Expert Opin Ther Targets*. 2017 Sep;21(9):827-836. doi: 10.1080/14728222.2017.1369959. Epub 2017 Aug 22.

INTRODUCTION: Chronic infection with hepatitis C virus (HCV) causes liver steatosis, cirrhosis, metabolic syndrome with inflammation, and eventually leads to hepatocellular carcinoma. HCV core protein is a well-known capsid protein and pathogenic factor related to lipid accumulation, type 2 diabetes mellitus, and carcinogenesis. Cleavage of the C-terminal transmembrane region by signal peptide peptidase (SPP) is required for maturation of the core protein. Areas covered: Herein, this review details the general aspects of the structure, lifecycle, pathogenesis, and maturation of the HCV core protein, the function of SPP, and clinically available direct-acting antivirals (DAAs). SPP is classified into a group of GXGD-type intramembrane proteases including presenilin-1, which is a component of γ -secretase complex. Several SPP inhibitors were previously identified from γ -secretase inhibitors, but have not yet been improved based on specificity to SPP. Finally, the author discusses the potential of SPP inhibitors for hepatitis C therapy. **EXPERT OPINION:** Currently available DAAs therapies are limited because of different viral genotypes and underlying conditions in each patient. DAA-resistant viruses have also been reported. Development of SPP-selective inhibitors may improve current HCV therapies by decreasing in the emergence of DAA-resistant viruses irrespective of viral genotype.

[Viral persistence, liver disease and host response in Hepatitis C-like virus rat model.](#)

Trivedi S1, Murthy S1, Sharma H1, Hartlage AS1,2, et al. *Hepatology*. 2017 Aug 31. doi: 10.1002/hep.29494. [Epub ahead of print]

The lack of a relevant, tractable, and immunocompetent animal model for hepatitis C virus (HCV) has severely impeded investigations of viral persistence, immunity and pathogenesis. In the absence of immunocompetent models with robust HCV infection, homolog hepaciviruses in their natural host could potentially provide useful surrogate models. We isolated a rodent hepacivirus (RHV) from wild rats (*Rattus norvegicus*), RHV-rn1, acquired the complete viral genome sequence and developed an infectious reverse genetics system. RHV-rn1 resembles HCV in genomic features including the pattern of polyprotein cleavage sites and secondary structures in the viral 5' and 3' UTRs. We used site-directed and random mutagenesis to determine that only the first of the two miR-122 seed sites in viral 5'UTR is required for viral replication and persistence in rats. Next, we used the clone derived virus progeny to infect several inbred and outbred rat strains. Our results determined that RHV-rn1 possesses several HCV-defining hallmarks: hepatotropism, propensity to persist, and the ability of induce gradual

liver damage. Histological examination of liver samples revealed the presence of lymphoid aggregates, parenchymal inflammation and macro/micro vesicular steatosis in chronically infected rats. Gene expression analysis demonstrated that the intrahepatic response during RHV-rn1 infection in rats mirrors that of HCV infection, including persistent activation of interferon signaling pathways. Finally, we determined that the backbone drug of HCV direct acting antiviral (DAA) therapy, Sofosbuvir, effectively suppresses chronic RHV-rn1 infection in rats. Taken together, we developed RHV-rn1 infected rats as a fully immunocompetent and informative surrogate model to delineate the mechanisms of HCV-related viral persistence, immunity and pathogenesis. This article is protected by copyright. All rights reserved.
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Hepatitis C Virus Subverts Human Choline Kinase- α To Bridge Phosphatidylinositol-4-Kinase III α (PI4KIII α) and NS5A and Upregulates PI4KIII α Activation, Thereby Promoting the Translocation of the Ternary Complex to the Endoplasmic Reticulum for Viral Replication. Wong MT1, Chen SS2. *J Virol.* 2017 Jul 27;91(16). pii: e00355-17. doi: 10.1128/JVI.00355-17. Print 2017 Aug 15.

In this study, we elucidated the mechanism by which human choline kinase- α (hCK α) interacts with nonstructural protein 5A (NS5A) and phosphatidylinositol-4-kinase III α (PI4KIII α), the lipid kinase crucial for maintaining the integrity of virus-induced membranous webs, and modulates hepatitis C virus (HCV) replication. hCK α activity positively modulated phosphatidylinositol-4-phosphate (PI4P) levels in HCV-expressing cells, and hCK α -mediated PI4P accumulation was abolished by AL-9, a PI4KIII α -specific inhibitor. hCK α colocalized with NS5A and PI4KIII α or PI4P; NS5A expression increased hCK α and PI4KIII α colocalization; and hCK α formed a ternary complex with PI4KIII α and NS5A, supporting the functional interplay of hCK α with PI4KIII α and NS5A. PI4KIII α inactivation by AL-9 or hCK α inactivation by CK37, a specific hCK α inhibitor, impaired the endoplasmic reticulum (ER) localization and colocalization of these three molecules. Interestingly, hCK α knockdown or inactivation inhibited PI4KIII α -NS5A binding. In an in vitro PI4KIII α activity assay, hCK α activity slightly increased PI4KIII α basal activity but greatly augmented NS5A-induced PI4KIII α activity, supporting the essential role of ternary complex formation in robust PI4KIII α activation. Concurring with the upregulation of PI4P production and viral replication, overexpression of active hCK α -R (but not the D288A mutant) restored PI4KIII α and NS5A translocation to the ER in hCK α stable knockdown cells. Furthermore, active PI4KIII α overexpression restored PI4P production, PI4KIII α and NS5A translocation to the ER, and viral replication in CK37-treated cells. Based on our results, hCK α functions as an indispensable regulator that bridges PI4KIII α and NS5A and potentiates NS5A-stimulated PI4KIII α activity, which then facilitates the targeting of the ternary complex to the ER for viral replication.

IMPORTANCE: The mechanisms by which hCK α activity modulates the transport of the hCK α -NS5A complex to the ER are not understood. In the present study, we investigated how hCK α interacts with PI4KIII α (a key element that maintains the integrity of the "membranous web" structure) and NS5A to regulate viral replication. We demonstrated that HCV hijacks hCK α to bridge PI4KIII α and NS5A, forming a ternary complex, which then stimulates PI4KIII α activity to produce PI4P. Pronounced PI4P synthesis then redirects the translocation of the ternary complex to the ER-derived, PI4P-enriched membrane for assembly of the viral replication complex and viral replication. Our study provides novel insights into the indispensable modulatory role of hCK α in the recruitment of PI4KIII α to NS5A and in NS5A-

stimulated PI4P production and reveals a new perspective for understanding the impact of profound PI4KIII α activation on the targeting of PI4KIII α and NS5A to the PI4P-enriched membrane for viral replication complex formation.

Hepatitis C Virus Lipovirions Assemble in the Endoplasmic Reticulum (ER) and Budd off from the ER to the Golgi Compartment in COPII Vesicles. Syed GH1, Khan M2, Yang S2, Siddiqui A1. J Virol. 2017 Jul 12;91(15). pii: e00499-17. doi: 10.1128/JVI.00499-17. Print 2017 Aug 1.

Hepatitis C virus (HCV) exists as a lipoprotein-virus hybrid lipovirion (LVP). In vitro studies have demonstrated the importance of apolipoproteins in HCV secretion and infectivity, leading to the notion that HCV coopts the secretion of very-low-density lipoprotein (VLDL) for its egress. However, the mechanisms involved in virus particle assembly and egress are still elusive. The biogenesis of VLDL particles occurs in the endoplasmic reticulum (ER), followed by subsequent lipidation in the ER and Golgi compartment. The secretion of mature VLDL particles occurs through the Golgi secretory pathway. HCV virions are believed to latch onto or fuse with the nascent VLDL particle in either the ER or the Golgi compartment, resulting in the generation of LVPs. In our attempt to unravel the collaboration between HCV and VLDL secretion, we studied HCV particles budding from the ER en route to the Golgi compartment in COPII vesicles. Biophysical characterization of COPII vesicles fractionated on an iodixanol gradient revealed that HCV RNA is enriched in the highly buoyant COPII vesicle fractions and cofractionates with apolipoprotein B (ApoB), ApoE, and the HCV core and envelope proteins. Electron microscopy of immunogold-labeled microsections revealed that the HCV envelope and core proteins colocalize with apolipoproteins and HCV RNA in Sec31-coated COPII vesicles. Ultrastructural analysis also revealed the presence of HCV structural proteins, RNA, and apolipoproteins in the Golgi stacks. These findings support the hypothesis that HCV LVPs assemble in the ER and are transported to the Golgi compartment in COPII vesicles to embark on the Golgi secretory route. **IMPORTANCE:** HCV assembly and release accompany the formation of LVPs that circulate in the sera of HCV patients and are also produced in an in vitro culture system. The pathway of HCV morphogenesis and secretion has not been fully understood. This study investigates the exact site where the association of HCV virions with host lipoproteins occurs. Using immunoprecipitation of COPII vesicles and immunogold electron microscopy (EM), we characterize the existence of LVPs that cofractionate with lipoproteins, viral proteins, RNA, and vesicular components. Our results show that this assembly occurs in the ER, and LVPs thus formed are carried through the Golgi network by vesicular transport. This work provides a unique insight into the HCV LVP assembly process within infected cells and offers opportunities for designing antiviral therapeutic cellular targets.

Phosphorylation of Serine 225 in Hepatitis C Virus NS5A Regulates Protein-Protein Interactions. Goonawardane N1, Gebhardt A2, Bartlett C1, Pichlmair A2, Harris M3. J Virol. 2017 Aug 10;91(17). pii: e00805-17. doi: 10.1128/JVI.00805-17. Print 2017 Sep 1.

Hepatitis C virus (HCV) nonstructural protein 5A (NS5A) is a phosphoprotein that plays key, yet poorly defined, roles in both virus genome replication and virion assembly/release. It has been proposed that differential phosphorylation could act as a switch to regulate the various functions of NS5A; however, the mechanistic details of the role of this posttranslational modification in the virus life cycle remain obscure. We previously reported (D. Ross-Thriepland, J. Mankouri, and M. Harris, J Virol 89:3123-3135, 2015, doi:10.1128/JVI.02995-14) a role for

phosphorylation at serine 225 (S225) of NS5A in the regulation of JFH-1 (genotype 2a) genome replication. A phosphoablatant (S225A) mutation resulted in a 10-fold reduction in replication and a perinuclear restricted distribution of NS5A, whereas the corresponding phosphomimetic mutation (S225D) had no phenotype. To determine the molecular mechanisms underpinning this phenotype we conducted a label-free proteomics approach to identify cellular NS5A interaction partners. This analysis revealed that the S225A mutation disrupted the interactions of NS5A with a number of cellular proteins, in particular the nucleosome assembly protein 1-like protein 1 (NAP1L1), bridging integrator 1 (Bin1, also known as amphiphysin II), and vesicle-associated membrane protein-associated protein A (VAP-A). These interactions were validated by immunoprecipitation/Western blotting, immunofluorescence, and proximity ligation assay. Importantly, small interfering RNA (siRNA)-mediated knockdown of NAP1L1, Bin1 or VAP-A impaired viral genome replication and recapitulated the perinuclear redistribution of NS5A seen in the S225A mutant. These results demonstrate that S225 phosphorylation regulates the interactions of NS5A with a defined subset of cellular proteins. Furthermore, these interactions regulate both HCV genome replication and the subcellular localization of replication complexes.

IMPORTANCE Hepatitis C virus is an important human pathogen. The viral nonstructural 5A protein (NS5A) is the target for new antiviral drugs. NS5A has multiple functions during the virus life cycle, but the biochemical details of these roles remain obscure. NS5A is known to be phosphorylated by cellular protein kinases, and in this study, we set out to determine whether this modification is required for the binding of NS5A to other cellular proteins. We identified 3 such proteins and show that they interacted only with NS5A that was phosphorylated on a specific residue. Furthermore, these proteins were required for efficient virus replication and the ability of NS5A to spread throughout the cytoplasm of the cell. Our results help to define the function of NS5A and may contribute to an understanding of the mode of action of the highly potent antiviral drugs that are targeted to NS5A.

[Diabetes mellitus is a significant risk factor for the development of liver cirrhosis in chronic hepatitis C patients.](#) Li X1, Gao Y2, Xu H1,3, Hou J4, Gao P5. *Sci Rep.* 2017 Aug 22;7(1):9087. doi: 10.1038/s41598-017-09825-7.

We explored the association between diabetes mellitus (DM) and the risk of hepatitis C virus (HCV)-related liver cirrhosis in Chinese patients with chronic hepatitis C (CHC). To examine the link between DM and liver cirrhosis, we conducted a case-control study of 210 Chinese CHC patients diagnosed with liver cirrhosis, comparing them to an age- and sex-matched control group of 431 CHC patients without liver cirrhosis. We conducted logistic regression analyses adjusting for demographic features and liver cirrhosis risk factors, and found that DM increased the risk of developing liver cirrhosis 2-fold [adjusted odds ratio (AOR), 2.132; 95% confidence interval (CI), 1.344-3.382]. Furthermore, the proportion of liver cirrhosis patients and CHC-only patients with elevated serum triglycerides (>1.8 mmol/L) were 5.2% and 17.4%, respectively, yielding an AOR of 0.264 (95% CI, 0.135-0.517). Multivariate analyses that stratified the risk of developing HCV-related liver cirrhosis in DM patients by gender revealed that the estimated AOR (95% CI) for males was 0.415 (0.178-0.969). In conclusion, DM was associated with an increased risk of developing liver cirrhosis in CHC patients in China. Furthermore, among patients diagnosed with both CHC and DM, females had an increased risk of liver cirrhosis development.

[New insights into HCV replication in original cells from Aedes mosquitoes.](#) Fallecker C1, Caporossi A2,3, Rechoum Y1,4, et al. *Virology*. 2017 Aug 22;14(1):161. doi: 10.1186/s12985-017-0828-z.

BACKGROUND: The existing literature about HCV association with, and replication in mosquitoes is extremely poor. To fill this gap, we performed cellular investigations aimed at exploring (i) the capacity of HCV E1E2 glycoproteins to bind on Aedes mosquito cells and (ii) the ability of HCV serum particles (HCVsp) to replicate in these cell lines. **METHODS:** First, we used purified E1E2 expressing baculovirus-derived HCV pseudo particles (bacHCVpp) so we could investigate their association with mosquito cell lines from Aedes aegypti (Aag-2) and Aedes albopictus (C6/36). We initiated a series of infections of both mosquito cells (Ae aegypti and Ae albopictus) with the HCVsp (Lat strain - genotype 3) and we observed the evolution dynamics of viral populations within cells over the course of infection via next-generation sequencing (NGS) experiments. **RESULTS:** Our binding assays revealed bacHCVpp an association with the mosquito cells, at comparable levels obtained with human hepatocytes (HepaRG cells) used as a control. In our infection experiments, the HCV RNA (+) were detectable by RT-PCR in the cells between 21 and 28 days post-infection (p.i.). In human hepatocytes HepaRG and Ae aegypti insect cells, NGS experiments revealed an increase of global viral diversity with a selection for a quasi-species, suggesting a structuration of the population with elimination of deleterious mutations. The evolutionary pattern in Ae albopictus insect cells is different (stability of viral diversity and polymorphism). **CONCLUSIONS:** These results demonstrate for the first time that natural HCV could really replicate within Aedes mosquitoes, a discovery which may have major consequences for public health as well as in vaccine development.

HIV/HCV COINFECTION

[Sofosbuvir-based Regimens in HIV/HCV Coinfected Patients after Liver Transplantation: Results from the ANRS CO23 CUPILT Study.](#) Antonini TM1, Coilly A, Rossignol E, et al.

Transplantation. 2017 Aug 24. doi: 10.1097/TP.0000000000001928. [Epub ahead of print]

BACKGROUND: A recurrence of hepatitis C virus after liver transplantation affects survival in HIV/HCV coinfecting patients. This study assessed the efficacy and safety of sofosbuvir-based regimens in HIV/HCV coinfecting patients following liver transplantation. **METHODS:** 29 HIV/HCV coinfecting transplanted patients receiving tacrolimus, cyclosporine or everolimus-based immunosuppressive therapy were enrolled in the CUPILT cohort. Their antiviral treatment combined sofosbuvir, daclatasvir with or without ribavirin (n=10/n=6), or sofosbuvir, ledipasvir with or without ribavirin (n=2/n=11). **RESULTS:** The median delay between liver transplantation and treatment initiation was 37.5 months (IQR 14.4-99.2). The breakdown of HCV genotypes was: G1: 22 patients (75.9%), G3: 3 patients (10.3%) and G4: 4 patients (13.8%). The treatment indications were HCV recurrence (\geq F1 n=23) or fibrosing cholestatic hepatitis (n=6). Before starting sofosbuvir, the HCV viral load and CD4 count were 6.7 log₁₀ IU/mL (IQR 5.9-7.2), and 342 cells/mm³ (IQR 172-483), respectively. At W4, the HCV viral load was <15 IU/mL in 12 patients (42.9%). The overall SVR 12 was 96.6%. No significant drug-drug interactions were observed. **CONCLUSIONS:** Sofosbuvir-based treatment regimens produced excellent results in HIV/HCV coinfecting patients after liver transplantation, suggesting an important change in their prognosis.

[Drug interactions in HIV-infected patients treated for hepatitis C.](#) Soriano V1, Labarga P2, Fernandez-Montero JV3, Mendoza C4, Benítez-Gutiérrez L4, Peña JM1, Barreiro P1. Expert Opin Drug Metab Toxicol. 2017 Aug;13(8):807-816. doi: 10.1080/17425255.2017.1351942. Epub 2017 Jul 13.

INTRODUCTION: The introduction of direct-acting antivirals (DAA) has revolutionized the hepatitis C field. Most hepatitis C patients can now be cured, including those coinfecting with HIV. However, drug-drug interactions (DDI) between DAA and antiretrovirals (ARV) should be known to prevent either toxicity due to drug overexposure or treatment failures due to low drug concentrations. Areas covered: Clinically significant DDI may be classified as major (when co-administration should be contraindicated) or minor (when they require close monitoring, changes in drug dosage or in timing). Strategies for preventing and managing DDI influence response rates in HIV/HCV-coinfecting patients. Pharmacokinetic evidence of interactions from clinical trials and reports from real-world experience are discussed. Expert opinion: The most frequent DDI between DAA and ARV affect drug metabolism by CYP450 induction/inhibition, leading to abnormal drug exposures. Throughout this mechanism interact HCV and HIV boosted protease inhibitors, and most non-nucleoside HCV and HIV polymerase inhibitors. In contrast, HIV and HCV nucleos(t)ide analogue polymerase inhibitors, most HCV NS5A inhibitors and HIV integrase inhibitors (e.g., dolutegravir), do not or only marginally affect CYP450, and therefore are relatively free of DDI. Exposure to some HIV and HCV nucleos(t)ide analogues (e.g., tenofovir and sofosbuvir, respectively) is subject to induction/inhibition of drug transporters (e.g., P-glycoprotein) and requires special attention in patients with renal insufficiency.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[Hepatitis C testing in general practice settings: A cross-sectional study of people who inject drugs in Australia.](#) Butler K1, Day C2, Sutherland R3, van Buskirk J3, Breen C3, Burns L3, Larney S3. Int J Drug Policy. 2017 Aug 5. pii: S0955-3959(17)30210-4. doi: 10.1016/j.drugpo.2017.07.008. [Epub ahead of print]

BACKGROUND: People who inject drugs (PWID) often do not receive confirmatory RNA testing following positive HCV antibody testing. Expanding access to adequate testing and assessment will improve the progression of patients through the HCV care cascade with the potential to improve diagnosis as well as linkage to treatment. We aimed to determine current utilisation of general practitioners (GPs) by PWID in Australia compared to other settings for HCV testing and post-test discussions. **METHODS:** A national sample (n=888) of people who had injected drugs regularly in the past 6 months was interviewed about HCV antibody, RNA testing, and post-test discussions, and the settings where these took place. **RESULTS:** The majority of participants (n=735; 93%) reported antibody testing. Among participants who reported a positive result (n=435), 54% identified their regular GP as the setting where their most recent antibody test was conducted. Confirmatory RNA testing was reported by 60% (n=274) of those who reported being antibody positive. Among those who reported RNA testing (n=257), the most common setting reported was their regular GP (48%). There were no differences in the proportions who recalled post-test discussions at GPs compared to other settings.

CONCLUSION: HCV testing was most frequently undertaken by participants' regular GP. GPs

are currently providing testing and post-test discussions at similar proportions to other more specialised settings. However, RNA testing is incomplete for more than one-third of the antibody positive PWID interviewed. Our findings suggest that the general practice setting is a common and accessible setting for PWID to access HCV testing. Targeting GPs to improve follow-up of positive antibody tests may help to improve patient progression through the HCV care cascade.

[Economic Burden of Hepatitis C Infection.](#) Stepanova M1, Younossi ZM2. Clin Liver Dis. 2017 Aug;21(3):579-594. doi: 10.1016/j.cld.2017.03.012. Epub 2017 Apr 22.

The economic burden of chronic hepatitis C might exceed \$10 billion annually in the United States alone. This disease has a worldwide prevalence of up to 3%, making the global burden of the disease comparably tremendous. The cost of the disease includes direct medical expenses for its hepatic and extrahepatic manifestations, and also indirect costs incurred from impaired quality of life and the loss of work productivity. Recent emergence of treatment options that are not only highly effective and safe but also costly has emphasized the need to study the disease from the economic point of view.

[Seroprevalence of HCV and HIV infection among clients of the nation's longest-standing statewide syringe exchange program: A cross-sectional study of Community Health Outreach Work to Prevent AIDS \(CHOW\) Project participants, Hawai'i, 2012.](#)

Salek TP1, Katz AR2, Lenze SM3, Lusk HM4, Li D5, Des Jarlais DC6. Int J Drug Policy. 2017 Aug 2;48:34-43. doi: 10.1016/j.drugpo.2017.06.009. [Epub ahead of print]

BACKGROUND: The Community Health Outreach Work to Prevent AIDS (CHOW) Project is the first and longest-standing statewide integrated and funded needle and syringe exchange program (SEP) in the US. Initiated on O'ahu in 1990, CHOW expanded statewide in 1993. The purpose of this study is to estimate the prevalences of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection, and to characterize risk behaviors associated with infection among clients of a long-standing SEP through the analysis of the 2012 CHOW evaluation data. **METHODS:** A cross-sectional sample of 130 CHOW Project clients was selected from January 1, 2012 through December 31, 2012. Questionnaires captured self-reported exposure information. HIV and HCV antibodies were detected via rapid, point-of-care FDA-approved tests. Log-binomial regressions were used to estimate prevalence proportion ratios (PPRs). A piecewise linear log-binomial regression model containing 1 spline knot was used to fit the age-HCV relationship. **RESULTS:** The estimated seroprevalence of HCV was 67.7% (95% confidence interval [CI]=59.5-75.8%). HIV seroprevalence was 2.3% (95% CI=0-4.9%). Anti-HCV prevalence demonstrated age-specific patterns, ranging from 31.6% through 90.9% in people who inject drugs (PWID) <30 to ≥60 years respectively. Age (continuous/year) prior to spline knot at 51.5 years (adjusted PPR [APPR]=1.03; 95% CI=1.02-1.05) and months exchanging syringes (quartiles) (APPR=1.92; 95% CI=1.3-3.29) were independently associated with anti-HCV prevalence. **CONCLUSION:** In Hawai'i, HCV prevalence among PWID is hyperendemic demonstrating age- and SEP duration-specific trends. Relatively low HIV prevalence compared with HCV prevalence reflects differences in transmissibility of these 2 blood-borne pathogens and suggests much greater efficacy of SEP for HIV prevention.

[Disease Outcomes in a Cohort of Women Infected by Hepatitis C-Contaminated anti-D Immunoglobulin During 1970s.](#) Garvey P1, Murphy N2, Flanagan P2, et al. J Hepatol. 2017 Aug 23. pii: S0168-8278(17)32249-3. doi: 10.1016/j.jhep.2017.07.034. [Epub ahead of print]

INTRODUCTION: In the mid 1990s, a group of Rh negative women was diagnosed with hepatitis C virus (HCV) genotype 1b infection following administration of contaminated anti-D immunoglobulin in 1977-79. We describe their disease history and estimate the effect of selected host and treatment factors on disease progression. **METHODS:** We conducted a cohort study on the women infected with HCV. Information was collected from records at seven HCV treatment centres on demographics, treatment and health outcomes up to 31st December 2013. We calculated cumulative incidence, case fatality, and sub hazard ratios (SHR) for disease progression using competing risks regression. **RESULTS:** 682 participants were included in the study. Among chronically infected participants (n=374), 35% completed interferon-based antiviral treatment; 42% of whom had a sustained virological response. At the end of 2013, 19%, 1.9%, and 4.9% of chronically infected participants had developed cirrhosis, hepatocellular carcinoma, and liver-related death, respectively, compared with 10%, 0.8%, and 2.4% at the end of 2008. At the end of 2013, 321 (86%) of chronically infected participants remained alive, 247 (77%) of whom were still chronically infected. Factors associated with increased cirrhosis rates included high alcohol intake (aSHR=4.9 (2.5-9.5)) and diabetes mellitus (aSHR=5.0 (2.9-8.8)). **CONCLUSIONS:** Development of liver-related outcomes accelerated with time, with the risk of cirrhosis, hepatocellular carcinoma, and liver-related death doubling in the latest five years of follow-up, particularly in women with high alcohol consumption and diabetes mellitus. We recommend that patients with chronic HCV infection be advised of the additive harmful effect of alcohol, and that data be collected on this cohort after a further five years to capture the effect of subsequent antiviral treatment during this rapidly evolving period in HCV treatment history. **LAY SUMMARY:** In the mid 1990s, a group of women were diagnosed with chronic hepatitis C virus (HCV) infection following receipt of contaminated anti-D immunoglobulin between 1977 and 1979 in Ireland. Seventy-two (19%) developed cirrhosis and 18 had died from liver-related causes (5%) after 36 years of infection. Disease progression accelerated in the latest five years of follow-up, particularly in women with diabetes mellitus and high alcohol consumption. We recommend that patients with chronic HCV infection be advised of the additive harmful effect of high alcohol consumption.

[Hepatitis C in pregnancy: screening, treatment, and management.](#) Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Hughes BL, Page CM, Kuller JA. Am J Obstet Gynecol. 2017 Aug 4. pii: S0002-9378(17)30930-4. doi: 10.1016/j.ajog.2017.07.039. [Epub ahead of print]

In the United States, 1-2.5% of pregnant women are infected with hepatitis C virus, which carries an approximately 5% risk of transmission from mother to infant. Hepatitis C virus can be transmitted to the infant in utero or during the peripartum period, and infection during pregnancy is associated with increased risk of adverse fetal outcomes, including fetal growth restriction and low birthweight. The purpose of this document is to discuss the current evidence regarding hepatitis C virus in pregnancy and to provide recommendations on screening, treatment, and management of this disease during pregnancy. The following are Society for Maternal-Fetal Medicine recommendations. (1) We recommend that obstetric care providers screen women who are at increased risk for hepatitis C virus by testing for antihepatitis C virus antibodies at their first prenatal visit. If initial results are negative, hepatitis C virus screening should be repeated later in pregnancy in women with persistent or new risk factors for hepatitis C virus infection after their initial screening (eg, new or ongoing use of injected or intranasal illicit drugs) (GRADE 1B). (2) We recommend that obstetric care providers screen hepatitis C virus-positive

pregnant women for other sexually transmitted diseases, including HIV, syphilis, gonorrhea, chlamydia, and hepatitis B virus (GRADE 1B). (3) We suggest that patients with hepatitis C virus, including pregnant women, be counseled to abstain from alcohol (Best Practice). (4) We recommend that direct-acting antiviral regimens only be used in the setting of a clinical trial or antiviral treatment should be deferred to the postpartum period as direct-acting antiviral regimens are not currently approved for use in pregnancy (GRADE 1C). (5) We suggest that if invasive prenatal diagnostic testing is requested, women be counseled that data on the risk of vertical transmission are reassuring but limited; amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter (GRADE 2C). (6) We recommend against cesarean delivery solely for the indication of hepatitis C virus (GRADE 1B). (7) We recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy in managing labor in hepatitis C virus-positive women (GRADE 1B). (8) We recommend against discouraging breast-feeding based on a positive hepatitis C virus infection status (GRADE 1A).

[Hepatitis C virus-related complications are increasing in women veterans: A national cohort study.](#) Kramer JR^{1,2}, El-Serag HB^{1,3}, Taylor TJ⁴, White DL^{1,3,2}, Asch SM⁴, Frayne SM⁴, Cao Y¹, Smith DL¹, Kanwal F^{1,3}. *J Viral Hepat.* 2017 Aug 16. doi: 10.1111/jvh.12728. [Epub ahead of print]

There are gender-specific variations in the epidemiology and clinical course of hepatitis C virus (HCV) infection. However, few long-term longitudinal studies have examined trends in the incidence and prevalence of serious liver complications among women compared with men with HCV infection. We used the Veterans Administration Corporate Data Warehouse to identify all veterans with positive HCV viraemia from January 2000 to December 2013. We calculated gender-specific annual incidence and prevalence rates of cirrhosis, decompensated cirrhosis and hepatocellular cancer (HCC) adjusting for age, diabetes, HIV and alcohol use. We also calculated the average annual per cent change (AAPC) for each outcome by gender using piecewise linear regression in the Joinpoint software. We identified 264 409 HCV-infected veterans during 2000-2013, of whom 7162 (2.7%) were women. There were statistically significant increases over time in the incidence rates of cirrhosis, decompensated cirrhosis and HCC for both men and women. The annual-adjusted incidence rates of cirrhosis, decompensated cirrhosis and HCC were higher in men than women for all study years. However, these complications increased at a similar rate in both groups. Specifically, the AAPC for cirrhosis was 13.1 and 15.2, while it was 15.6 and 16.9 for decompensated cirrhosis and 21.0 and 25.3 for HCC in men and women, respectively (all test of parallelism not significant). The results were similar in the prevalence analyses, although AAPCs were slightly smaller for each outcome. In conclusion, we found an ongoing upward trend in the incidence and prevalence of HCV complications in this cohort of HCV-infected women. This increase in cirrhosis complications in women with active HCV infection is similar to those in men. With cure from HCV now becoming a reality, most of the projected burden of HCV is potentially preventable. However, benefits of HCV treatment will need to extend to all patients in order to stem the rising tide of HCV complications.

[The willingness of people who inject drugs in Boston to use a supervised injection facility.](#) León C¹, Cardoso L¹, Mackin S², Bock B¹, Gaeta JM^{1,3}. *Subst Abus.* 2017 Aug 11:0. doi: 10.1080/08897077.2017.1365804. [Epub ahead of print]

BACKGROUND: In Massachusetts, the number of opioid-related deaths has increased 350% since 2000. In the setting of increasing overdose deaths, one potential intervention is Supervised Injection Facilities (SIFs). This study explores willingness of people who inject drugs in Boston to use a SIF and examines factors associated with willingness. **METHODS:** A cross-sectional survey of a convenience sample of 237 people who inject drugs and utilize Boston's needle exchange program (NEP). The drop-in NEP provides myriad harm reduction services and referrals to addiction treatment. The survey was mostly self-administered (92%). **RESULTS:** Results showed positive willingness to use a SIF was independently associated with: use of heroin as main substance (Odds Ratio[OR]:5.47; 95% Confidence Interval[CI]:1.9-15.4; p = 0.0004), public injection (OR:5.09; 95% CI:1.8-14.3; p = 0.002), history of seeking SUD treatment (OR:4.99; 95% CI:1.2-21.1; p = 0.05), having heard of SIF (OR:4.80; 95% CI:1.6-14.8; p = 0.004), Hispanic ethnicity (OR:4.22; 95% CI:0.9-18.8; p = 0.04), frequent NEP use (OR:4.18; 95% CI:1.2-14.7; p = 0.02), current desire for SUD treatment (OR:4.15; 95% CI:1.2-14.7; p = 0.03), hepatitis C diagnosis (OR:3.68; 95% CI:1.2-10.1; p = 0.02), PTSD diagnosis (OR:3.27; 95% CI 1.3-8.4; p = 0.01), report of at least one chronic medical diagnosis (hepatitis C, HIV, hypertension, or diabetes) (OR:3.27; 95% CI:1.2-8.9; p = 0.02), and comorbid medical and mental health diagnoses (OR:2.93; 95% CI:1.2-7.4; p = 0.02). **CONCLUSIONS:** Most respondents (91.4%) reported willingness to use a SIF. Respondents with substance use behavior reflecting high risk for overdose were significantly more likely to be willing to use a SIF. Respondents with behaviors that contribute to public health burden of injection drug use were also significantly more likely to be willing to use a SIF. Results indicate that this intervention would be well utilized by individuals who could most benefit from the model. As part of a broader public health approach, SIFs should be considered to reduce opioid overdose mortality, decrease public health burden of the opioid crisis, and promote access to addiction treatment and medical care.

[Liver toxicity of chemotherapy and targeted therapy for breast cancer patients with hepatitis virus infection.](#) Liu Y1, Li ZY2, Li X1, Wang JN1, Huang QA1, Huang Y3. *Breast.* 2017 Oct;35:191-195. doi: 10.1016/j.breast.2017.08.001. Epub 2017 Aug 8.

BACKGROUND: Chemotherapy has greatly improved the prognosis of breast cancer patients. However, it may also result in undesirable side effects such as hepatitis virus reactivation. Little information is available on the liver toxicity of chemotherapy and targeted therapy for breast cancer patients with hepatitis virus (HBV/HCV) infection. **METHODS:** We performed a retrospective survey of 835 patients diagnosed with breast cancer between January 2010 and December 2015 at our institution. All patients had been screened for HBV/HCV infection at the time of breast cancer diagnosis. We retrospectively investigated the toxicity of chemotherapy and the changes in HBV/HCV load based on a medical record review. **RESULTS:** 52 patients with positive anti-HBV antibody test and 21 patients with positive anti-HCV antibody tests received chemotherapy. 762 patients without HBV and HCV infection served as the control group. The morbidity of liver toxicity and disruptions in chemotherapy attributable to liver toxicity were not significantly different among control group, HBV group and HCV groups (27.7% vs 34.6% vs 42.9%, P = 0.189 and 5.0% vs 9.6% vs 9.5%, P = 0.173, respectively). No patients presented with HBV/HCV reactivation. **CONCLUSION:** Breast cancer patients with HCV can be treated with chemotherapy and targeted therapy with trastuzumab. Breast cancer patients with HBV who accept antiviral therapy can be treated with chemotherapy and targeted therapy with trastuzumab and patients can benefit from prophylactic antiviral therapy before

chemotherapy. However, a multidisciplinary cooperation and closely monitoring liver function during the course of chemotherapy may benefit patients.

Injecting drug use in low and middle-income countries: Opportunities to improve care and prevent harm.

O'Keefe D1,2, Stoové M1,2, Doyle J1,3,4, Dietze P1,2, Hellard M1,2,4. *J Viral Hepat.* 2017 Sep;24(9):714-724. doi: 10.1111/jvh.12741. Epub 2017 Aug 1.

Inadequate response to injecting drug use (IDU) is a significant problem the world over. Low levels of funding, political inaction, poor levels of health service coverage, high prevalence and incidence of IDU-related blood-borne viruses (BBVs) and ongoing stigmatization/marginalization affect people who inject drugs (PWID) regardless of the income status of the country they reside in. These barriers and system failings are, however, exacerbated in low and middle-income countries (LMICs), meaning that the potential consequences of inaction are more pressing. In this narrative review, we describe the levels of IDU and IDU-specific BBV prevalence in LMICs; levels of harm reduction implementation; the consequences of late or insufficient response, the shortcomings of data collection and dissemination; and the barriers to effective LMIC harm reduction implementation. We also exemplify cases where IDU-related harms and BBV epidemics have been successfully curtailed in LMICs, showing that effective response, despite the barriers, is possible. In conclusion, we suggest four key priorities on the basis of the review: confirming the presence or absence of IDU in LMICs, improving the collection and dissemination of national IDU-specific data, increasing the level of harm reduction programme implementation in LMICs, and increasing both national and international advocacy for PWID and attendant public health interventions.

Viral hepatitis screening in transgender patients undergoing gender identity hormonal therapy.

Mangla N1, Mamun R, Weisberg IS. *Eur J Gastroenterol Hepatol.* 2017 Aug 29. doi: 10.1097/MEG.0000000000000950. [Epub ahead of print]

BACKGROUND AND AIM: Viral hepatitis is a global health issue and can lead to cirrhosis, liver failure, and hepatocellular carcinoma. Guidelines for viral hepatitis screening in the transgender population do not exist. Transgender patients may be at higher risk for contracting viral hepatitis due to socioeconomic and behavioral factors. The aim of this study was to measure the quality of screening, prevalence, and susceptibility of viral hepatitis, and to identify barriers to screening in transgender patients undergoing gender identity hormonal therapy. **METHODS:** LGBTQ-friendly clinic visits from transgender patients older than 18 years in New York City from 2012 to 2015 were reviewed. **RESULTS:** Approximately 13% of patients were screened for any viral hepatitis on initial consultation. Screening rates for hepatitis C virus (HCV), hepatitis B virus (HBV), and hepatitis A virus (HAV) at any point were 27, 22, and 20%. HAV screening was performed in 28% of the female to male (FtM) patients and 16% of male to female (MtF) ($P < 0.05$) patients. HBV screening was performed in 30% of FtM patients and 18% of MtF patients ($P < 0.05$). Thirty-one percent of FtM, 24% of MtF, and 17% of genderqueer patients were tested for HCV ($P > 0.05$). Prevalence of HCV, HBV, and HIV in FtM was 0, 0, and 0.44% and that in MtF was 1.78, 0.89, and 1.78%, respectively. Percentage of patients immune to hepatitis A in FtM and MtF subgroups were 55 and 47% ($P > 0.05$). Percentage of patients immune to HBV in FtM and MtF subgroups were 54 and 48% ($P > 0.05$). **CONCLUSION:** This study indicates a significant lack of hepatitis screening in the transgender population and a concerning proportion of patients susceptible to disease.

"I love having benzos after my coke shot": The use of psychotropic medication among cocaine users in downtown Montreal.

Motta-Ochoa R1, Bertrand K2, Arruda N2, Jutras-Aswad D3, Roy É4. Int J Drug Policy. 2017 Aug 18;49:15-23. doi:

10.1016/j.drugpo.2017.07.012. [Epub ahead of print]

BACKGROUND: Cocaine abuse is a major public health issue due to its role in the HIV and hepatitis C virus (HCV) epidemics in North America. A significant area of concern among people who use cocaine (PWUC), injected or smoked, is their frequent misuse of prescription drugs, particularly psychotropic medication (PM), such as tranquilizers, sedatives, stimulants, and antipsychotics. This paper aims to describe and understand practices of PM use among PWUC in downtown Montreal. **METHOD:** Ethnographic methods including participant observation and semi-structured interviews were used in an iterative manner. **RESULTS:** Two thirds of the 50 participants were male. They ranged in age from 20 to 60 and most were homeless. A significant proportion of them reported polydrug use patterns that included frequent concomitant opioid use (heroin and/or prescription opioids (PO)). Benzodiazepine-based tranquilizers and the atypical antipsychotic quetiapine were the most frequently used PM. Routes of PM administration were oral, nasal and, to a lesser degree, intravenous. Five main PM use practices were identified: 1) "downers" from cocaine high (benzodiazepines and quetiapine); 2) enhancers of heroin/PO effects (benzodiazepines); 3) reducers or suppressors of heroin/PO withdrawal symptoms (benzodiazepines); 4) enablers of a different type of "trip" (benzodiazepines); and 5) treatment for mental and physical problems (benzodiazepines and quetiapine). **CONCLUSION:** PM use practices showed several complementary functions that PM fulfill in a context of polydrug use. The soothing and stimulating effects of PM reinforce the patterns of drug use among participants, posing various risks including overdose, HIV/HCV transmission, PM dependence and accidents. The results highlight the need for clinicians to assess clients' substance use patterns when prescribing PM and to question PWUC about PM use. The findings also underline certain unmet service needs in relation to overdose, HIV/HCV and mental health prevention/treatment among cocaine users.

Geographic Disparities in Access to Syringe Services Programs Among Young Persons With Hepatitis C Virus Infection in the United States.

Canary L1, Hariri S1, Campbell C1, Young R2, Whitcomb J3, Kaufman H4, Vellozzi C1. Clin Infect Dis. 2017 Aug 1;65(3):514-517. doi: 10.1093/cid/cix333.

Using commercial laboratory data, we found 80% of 29382 young persons currently infected with hepatitis C virus lived >10 miles from a syringe services program. The median distance was 37 miles, with greater distances in rural areas and Southern and Midwestern states. Strategies to improve access to preventive services are warranted.

HEPATOCELLULAR (LIVER) CANCER

The risks of hepatocellular carcinoma development after HCV eradication are similar between patients treated with peg-interferon plus ribavirin and direct-acting antiviral therapy.

Nagaoki Y1, Imamura M1,2, Aikata H1,2, et al. PLoS One. 2017 Aug 10;12(8):e0182710. doi: 10.1371/journal.pone.0182710. eCollection 2017.

The risk of hepatocellular carcinoma (HCC) development is reduced following viral elimination by interferon therapy in chronic hepatitis C patients. However, the risk in patients treated with interferon-free direct-acting antivirals (DAAs) is unknown. We evaluated chronic hepatitis C patients who achieved viral eradication by pegylated-interferon plus ribavirin (PEG-IFN/RBV, n = 244) or daclatasvir plus asunaprevir (DCV/ASV, n = 154) therapy. None of the patients had prior history of HCC or antiviral therapy. The median observation period after the end of treatment for the PEG-IFN/RBV and DCV/ASV groups were 96 (range 10-196) and 23 (range 4-78) months, respectively. During the observation period, HCC developed in 13 (5.3%) and 7 (4.5%) patients in the PEG-IFN/RBV and DCV/ASV groups, respectively. The cumulative HCC development rate after 1-, 3- and 5-years (0.4%, 3% and 5% for the PEG-IFN/RBV group and 0.6%, 9% and 9% for the DAA group, respectively) were similar between the two groups. Propensity score matching analysis also showed no significant difference in HCC development rates between the two groups. Serum AFP levels decreased to similar levels between PEG-IFN/RBV and DCV/ASV groups following the achievement of viral eradication. The risk for HCC development following viral eradication by IFN-free DAA therapy may be similar to that in IFN-based therapy.

[Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.](#) Waziry R1, Hajarizadeh B2, Grebely J2, Amin J3, Law M2, Danta M4, George J5, Dore GJ2. *J Hepatol.* 2017 Aug 9. pii: S0168-8278(17)32199-2. doi: 10.1016/j.jhep.2017.07.025. [Epub ahead of print]

BACKGROUND: Risk of hepatocellular carcinoma (HCC) occurrence or recurrence following direct-acting antiviral (DAA) HCV therapy remains unclear. The aims of this study were: 1) In patients with HCV-related cirrhosis, to compare the rate of HCC occurrence following DAA versus interferon (IFN)-based cure, and; 2) In patients who received curative HCC treatment, to compare rate of HCC recurrence following DAA versus IFN-based cure. **METHODS:** A search was conducted for reports published between January 2000 and February 2017. Studies were included if they assessed HCC outcomes by type and response to HCV therapy. Random effects meta-analyses were undertaken to determine a combined estimate of HCC incidence rate per 100/person years (py) among patients with a sustained virological response (SVR). **RESULTS:** A total of 41 studies (n=13,875 patients), including 26 on HCC occurrence (IFN=17, DAA=9; prospective=19, retrospective=5, retrospective-prospective=2), and 17 on HCC recurrence (IFN=7, DAA=10; prospective=11, retrospective=5 and retrospective-prospective=1) were included. In studies assessing HCC occurrence, average follow-up was shorter (1.0 versus 5.5 years), and average age older (60 versus 52 years) in DAA studies. In studies assessing HCC recurrence, average follow-up was shorter (1.3 versus 5.0 years), but average age similar (64 versus 66 years) in DAA studies. HCC occurrence was 1.14/100 py (95% CI 0.86, 1.52) and 2.96/100 py (95% CI 1.76, 4.96) in IFN and DAA studies. HCC recurrence was 9.21/100 py (95% CI 7.18, 11.81) and 12.16/100 py (95% CI 5.00, 29.58) in IFN and DAA studies. In meta-regression adjusting for study follow-up and age, DAA therapy was not associated with higher HCC occurrence (RR 0.68, 95% CI 0.18, 2.55, P=0.55) or recurrence (RR 0.62, 95% CI 0.11, 3.45, P=0.56). **CONCLUSION:** There is no evidence for differential HCC occurrence or recurrence risk following SVR from DAA and IFN-based therapy.

[Hepatocellular Carcinoma Surveillance Among Patients With Cirrhosis in a Population-based Integrated Health Care Delivery System.](#)

Singal AG1, Tiro J, Li X, Adams-Huet B, Chubak J. J Clin Gastroenterol. 2017 Aug;51(7):650-655. doi: 10.1097/MCG.0000000000000708.

PURPOSE: Fewer than 1 in 5 patients with cirrhosis receive hepatocellular carcinoma (HCC) surveillance; however, most studies were performed in select patient populations, which may not be informative of practice patterns in population-based community practices. Further, few reported guideline-concordant consistent surveillance rates. **GOALS:** Characterize guideline-concordant HCC surveillance rates and patient-level factors associated with surveillance among a population-based cohort of patients with cirrhosis. **STUDY:** We retrospectively characterized HCC surveillance among cirrhosis patients followed between January 2010 and December 2012 at an integrated health care delivery system in Washington state. Consistent surveillance was defined as an ultrasound every 6 months, and inconsistent surveillance was defined as ≥ 1 ultrasound during the 2-year follow-up period. Univariate and multivariate analyses were conducted to identify correlates of HCC surveillance receipt. **RESULTS:** Of 1137 patients with cirrhosis, 22 (2%) underwent consistent surveillance, 371 (33%) had inconsistent surveillance, and 744 (65%) received no surveillance during follow-up. Correlates of HCC surveillance receipt in multivariate analysis included Gastroenterology/Hepatology subspecialty care [odds ratio (OR), 1.88; 95% confidence interval (CI), 1.44-2.46], Child Pugh B/C cirrhosis (OR, 1.61; 95% CI, 1.07-2.43), elevated aspartate aminotransferase (OR, 1.63; 95% CI, 1.13-2.35), and etiology of liver disease. Compared with hepatitis C-infected patients, patients with hepatitis B infection were more likely to undergo surveillance (OR, 2.72; 95% CI, 1.28-5.81), whereas patients with alcohol-related cirrhosis (OR, 0.63; 95% CI, 0.42-0.93) and nonalcoholic steatohepatitis (OR, 0.39; 95% CI, 0.28-0.56) were less likely to undergo surveillance. **CONCLUSIONS:** Although one third of patients undergo inconsistent HCC surveillance, <2% of patients receive guideline-concordant biannual HCC surveillance.

[Antiviral Therapy in Patients With Chronic Hepatitis C-related Hepatocellular Carcinoma Responding to Palliative Treatment.](#) Yu JH1, Kim JK, Lee KS, Lee JI. J Clin Gastroenterol.

2017 Aug 31. doi: 10.1097/MCG.0000000000000923. [Epub ahead of print]

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

debatable, this study results carefully suggest that HCV-related HCC patients that responded to the initial HCC palliative treatment might benefit from HCV treatment.

Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period.

Pais R1,2, Fartoux L1, Goumard C3, Scatton O3, Wendum D4, Rosmorduc O1, Ratziu V1,2. Aliment Pharmacol Ther. 2017 Aug 31. doi: 10.1111/apt.14261. [Epub ahead of print]

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of hepatocellular carcinoma (HCC) worldwide. NAFLD-HCC often occurs in noncirrhotic liver raising important surveillance issues. **AIM:** To determine the temporal trends for prevalence, clinical characteristics and outcomes of NAFLD-HCC in patients undergoing liver resection. **METHODS:** Consecutive patients with histologically confirmed HCC who underwent liver resection over a 20-year period (1995-2014). NAFLD was diagnosed based on past or present exposure to obesity or diabetes without other causes of chronic liver disease. **RESULTS:** A total of 323 HCC patients were included, 12% with NAFLD. From 1995-1999 to 2010-2014, the prevalence of NAFLD-HCC increased from 2.6% to 19.5%, respectively, $P = .003$, and followed the temporal trends in the prevalence of metabolic risk factors (28% vs 52%, $P = .017$), while hepatitis C-HCC decreased (from 43.6% to 19.5%, $P = .003$). NAFLD-HCC occurred more frequently in the absence of bridging fibrosis/cirrhosis (63% of cases, $P < .001$ compared to other aetiologies). Within the NAFLD group, tumour characteristics were similar between F0-F2 and F3-F4 patients, except for a higher proportion of single nodules (95% vs 54%, $P < .01$). A total of 53% patients had tumour recurrence and 40% died. NAFLD-HCC had similar time to recurrence and survival as HCCs of other aetiologies. Satellite nodules, tumour size, microvascular invasion and male sex but not the aetiology were independently associated with recurrence. **CONCLUSION:** Non-alcoholic fatty liver disease increased substantially over the past 20 years among resectable HCCs. It is now the leading cause of HCC occurring without/or with only minimal fibrosis. NAFLD patients are older, with larger tumours while survival and recurrence rates are as severe as in other aetiologies.