



Caring Ambassadors Program
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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Successful retreatment with sofosbuvir plus ledipasvir for cirrhotic patients with hepatitis C virus genotype 1b, who discontinued the prior treatment with asunaprevir plus daclatasvir: A case series and review of the literature.](#)

Haga Y1, Kanda T1,2, Yasui S1, et al. Oncotarget. 2017 Dec 29;9(4):5509-5513. doi: 10.18632/oncotarget.23768. eCollection 2018 Jan 12.

BACKGROUND: Interferon-free treatment results in higher sustained virologic response (SVR) rates, with no serious adverse events in hepatitis C virus (HCV)-infected patients. However, in some patients with treatment-failure in HCV NS5A inhibitor-including interferon-free regimens, the treatment-emergent HCV NS5A resistance-associated variants (RAVs), which are resistant to interferon-free retreatment including HCV NS5A inhibitors, are observed. In HCV-infected Japanese patients with daclatasvir and asunaprevir treatment failure, retreatment with sofosbuvir and ledipasvir could lead to only ~70% SVR rates. **CASE SUMMARY:** Three HCV genotype (GT)-1b-infected cirrhotic patients who discontinued the combination of daclatasvir and asunaprevir due to adverse drug reactions within 4 weeks; retreatment with sofosbuvir and ledipasvir combination could result in SVR in these patients without RAVs. One HCV GT-1b-infected cirrhotic patient who discontinued the combination of daclatasvir and asunaprevir due to viral breakthrough at week 10; retreatment with sofosbuvir and ledipasvir combination for this patient with the treatment-emergent HCV NS5A RAV-Y93H resulted in viral relapse at week 4 after the end of the treatment. **CONCLUSION:** Retreatment with sofosbuvir and ledipasvir is effective for HCV GT-1b patients who discontinue the combination of daclatasvir and asunaprevir within 4 weeks. The treatment response should be related to the existence of treatment-emergent HCV NS5A RAVs, but may not be related to the short duration of treatment.

Health-related Quality of Life in Adolescent Patients With Hepatitis C Genotype 1 Treated With Sofosbuvir and Ledipasvir.

Younossi ZM1,2, Stepanova M3, Balistreri W4, et al. J Pediatr Gastroenterol Nutr. 2018 Jan;66(1):112-116. doi: 10.1097/MPG.0000000000001754.

OBJECTIVE: The aim of the study was to assess the effect of treatment with ledipasvir/sofosbuvir (LDV/SOF) on the health-related quality of life (HRQL) of pediatric patients with chronic hepatitis C virus (HCV) infection. **METHODS:** Adolescents (12-17 years) with HCV were treated with LDV/SOF (90/400 mg daily) for 12 weeks. HRQL was assessed using the PedsQLv4.0-SF15 completed by the children and caregivers before, during, and after treatment. **RESULTS:** We included 100 adolescents with HCV genotype 1 infection (14.7±2.0 years, 1% known cirrhosis, 80% treatment-naïve, 97% sustained virologic response-12). At baseline, HRQL the caregiver- perceived HRQL scores were lower than adolescents' self-reported scores (by 6.7-7.9 points, all P<0.01). At the end of 12 weeks of treatment, however, the caregiver-reported HRQL scores showed a significant improvement (+all P<0.04), whereas the adolescents' self-reported scores did not change from the baseline. HRQL scores reported by caregivers remained higher than baseline (by +4.7-+7.5, P<0.01) through 12 weeks after treatment, as did the adolescents' self-reported Emotional Functioning scores (+4.3 from baseline, P=0.0009); observed improvements were sustained after 24 weeks of follow-up (all P<0.04). Multivariate analysis showed that, after adjustment for location, age, and sex, having a history of anxiety and panic disorders were consistent predictors of impaired HRQL in adolescents with HCV infection (P<0.05). **CONCLUSIONS:** Treatment of HCV in adolescents with LDV/SOF is associated with some improvement in HRQL. Caregivers' reports of HRQL in adolescents with HCV significantly increased with treatment and were similar to the adolescent self-reported HRQL after sustained virologic response-12.

Sofosbuvir plus daclatasvir with or without ribavirin in 551 patients with hepatitis C-related cirrhosis, genotype 4.

El-Khayat H1, Fouad Y2, Mohamed HI2, El-Amin H3, Kamal EM2, Maher M4, Risk A5. Aliment Pharmacol Ther. 2018 Mar;47(5):674-679. doi: 10.1111/apt.14482. Epub 2018 Jan 3.

BACKGROUND: The Daclatasvir and Sofosbuvir combination therapy (SOF/DCV) has shown efficacy in patients with chronic hepatitis C in clinical trials. **AIM:** To investigate the efficacy and safety of SOF/DCV for treatment of patients with hepatitis C-related liver cirrhosis genotype 4. **METHODS:** Multicentre study involving 551 patients with liver cirrhosis genotype 4; 432 naïve patients and 119 treatment-experienced patients. All patients received SOF (400 mg) and DCV (60 mg) daily in addition to weight-based ribavirin (RBV) for 12 weeks and when RBV is contraindicated the treatment duration was extended to 24 weeks. **RESULTS:** Sustained virological response at 12 weeks after end of treatment (SVR12) rate was 92% in naïve cirrhotic patients and 87% in previous treated patients (by ITT analysis). Virological failure was infrequent, occurring in 42 patients (8%) overall. Thirty-two (6%) were non responders; and 10 (2%) cases were relapsers, 31 patients (7%) were CTP-A and 11 (13.3%) patients were CTP-B (by ITT analysis). The most common adverse events were anaemia, fatigue, headache, pruritus. Serious side effects were recorded mainly in CTP-B cirrhotic patients including HCC and hepatic encephalopathy. **CONCLUSIONS:** The SOF/DCV combination therapy has proven efficacy and safety in treating patients with hepatitis C-related liver cirrhosis genotype 4 in a large cohort of patients in the real world.

[Real-world treatment of hepatitis C with second-generation direct-acting antivirals: initial results from a multicentre Canadian retrospective cohort of diverse patients.](#) Aspinall AI1, Shaheen AA1, Kochaksaraei GS1, et al. CMAJ Open. 2018 Jan 5;6(1):E12-E18. doi: 10.9778/cmajo.20170059.

BACKGROUND: High hepatitis C cure rates have been observed in registration trials with second-generation direct-acting antivirals. Real-world data also indicate high sustained viral response (SVR) rates. Our objective was to determine real-world SVR rates for patients infected with hepatitis C virus (HCV) who were treated with second-generation direct-acting antivirals in the first 18 months of their availability in Canada. **METHODS:** Four centres in Calgary contributed their treatment data for a diverse patient population including those who had or had not undergone liver transplantation, those coinfecting with HIV and vulnerable populations. We included all patients documented to have started hepatitis C treatment with direct-acting antivirals between October 2014 and April 2016, with follow-up through October 2016. We used multivariate analysis to determine independent predictors of treatment failure. **RESULTS:** Outcome data were available for 351 patients, of whom 326 (92.9%) achieved an SVR (193/206 [93.7%], 57/59 [96.6%] and 44/51 [86.3%] for genotypes 1a, 1b and 3, respectively, $p = 0.2$). Independent predictors of not achieving SVR were older age (adjusted odds ratio [OR] 0.95 [95% confidence interval (CI) 0.90-1.00]), male sex (adjusted OR 0.30 [95% CI 0.10-0.89]) and, in patients with genotype 1a infection, history of hepatocellular carcinoma (adjusted OR 0.13 [95% CI 0.03-0.53]). In the entire cohort, the presence of cirrhosis, genotype and hepatocellular carcinoma were not associated with a lower SVR rate. There were no differences in SVR rate according to treatment centre, HIV coinfection or liver transplantation. Among patients with genotype 3 infection, a significantly lower SVR rate was observed for those treated outside of standard of care than for those treated within standard of care (33.3% v. 89.6%, $p = 0.04$). De novo hepatocellular carcinoma developed in 12 patients (3.4%) despite successful direct-acting antiviral therapy. **INTERPRETATION:** We report high SVR rates in a real-world diverse cohort of HCV-infected patients treated with second-generation direct-acting antivirals. The results highlight the importance of conducting real-world analyses to elucidate clinical factors associated with poorer outcomes that may not be identified in registration trials.

[Safety and Effectiveness of Ledipasvir and Sofosbuvir, With or Without Ribavirin, in Treatment-Experienced Patients with Genotype 1 Hepatitis C Virus Infection and Cirrhosis.](#) Lim JK1, Liapakis AM2, Shiffman ML3, et al. Clin Gastroenterol Hepatol. 2018 Jan 3. pii: S1542-3565(17)31535-5. doi: 10.1016/j.cgh.2017.12.037. [Epub ahead of print]

BACKGROUND & AIMS: We aimed to evaluate the safety and effectiveness of 12 or 24 weeks treatment with ledipasvir and sofosbuvir, with or without ribavirin, in treatment-experienced patients with hepatitis C virus (HCV) genotype 1 infection and cirrhosis in routine clinical practice. Patients were followed in a multi-center, prospective, observational cohort study (HCV-TARGET). **METHODS:** We collected data from 667 treatment-experienced adults with chronic genotype 1 HCV infection who began treatment with ledipasvir and sofosbuvir, with or without ribavirin, from 2011 through September 15, 2016, according to the regional standards of care, at academic ($n=39$) and community ($n=18$) centers in the United States, Canada, Germany, and Israel. Information was collected from medical records and abstracted into a unique centralized data core. Independent monitors systematically reviewed data entries for completeness and accuracy. Demographic, clinical, adverse event, and virologic data were collected every 12 weeks during treatment and during the follow-up period. The primary efficacy

endpoint was sustained virologic response, defined as a level of HCV RNA below the lower limit of quantification or undetectable at a minimum 64 days after the end of treatment (SVR12). The per-protocol population (n=610) was restricted to patients who completed 12 or 24 weeks of treatment (± 2 weeks) and had final virologic outcomes available. **RESULTS:** The per-protocol analysis revealed that 579 patients (93.8%) achieved an SVR12, including 50/51 patients who received ledipasvir and sofosbuvir for 12 weeks (98%), 384/408 patients who received ledipasvir and sofosbuvir for 24 weeks (94.1%), 68/70 patients who received ledipasvir and sofosbuvir with ribavirin for 12 weeks (97.1%), and 57/60 patients who received ledipasvir and sofosbuvir with ribavirin for 24 weeks (95%). On multivariate analysis, neither treatment duration nor the addition of ribavirin was associated with SVR12. Compensated cirrhosis (odds ratio [OR] compared to decompensated cirrhosis, 2.41; 95% CI, 1.16-5.02), albumin ≥ 3.5 g/dL (OR, 3.15; 95% CI 1.46-6.80), or total bilirubin ≤ 1.2 mg/dL (OR 3.34; 95% CI, 1.59-7.00) were associated with SVR12. **CONCLUSIONS:** In an analysis of safety and effectiveness data from the HCV-TARGET study, we found treatment with ledipasvir and sofosbuvir, with or without ribavirin, to be effective and well tolerated by treatment-experienced patients with genotype 1 HCV infection and compensated cirrhosis. There were no significant differences in rate of SVR12 among patients treated with ledipasvir and sofosbuvir for 12 or 24 weeks, with or without ribavirin. Patients with decompensated cirrhosis appear to benefit from the addition of ribavirin or extension of ledipasvir and sofosbuvir treatment to 24 weeks. ClinicalTrials.gov no: NCT10474811.

[Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use \(SIMPLIFY\): an open-label, single-arm, phase 4, multicentre trial.](#)

Grebely J1, Dalgard O2, Conway B3, et al. Lancet Gastroenterol Hepatol. 2018 Jan 5. pii: S2468-1253(17)30404-1. doi: 10.1016/S2468-1253(17)30404-1. [Epub ahead of print]

BACKGROUND: Despite revised guidelines that no longer exclude people who inject drugs (PWID) from treatment for hepatitis C virus (HCV) infection, many clinicians are reluctant to treat recent PWID. This study aimed to evaluate the efficacy of sofosbuvir and velpatasvir therapy in people with chronic HCV infection and recent injection drug use. **METHODS:** In this open-label, single-arm phase 4 trial (SIMPLIFY), we recruited participants with recent injection drug use (past 6 months) and chronic HCV genotype 1-6 infection from seven countries (19 sites). Participants received oral sofosbuvir (400 mg) and velpatasvir (100 mg) once daily for 12 weeks. Therapy was given in 1-week electronic blister packs to record the time and date of each dose. The primary endpoint was the proportion of patients with sustained virological response 12 weeks after completion of treatment (SVR12; defined as HCV RNA <12 IU/mL), analysed in all patients who received at least one dose. This study is registered with ClinicalTrials.gov, number NCT02336139, and follow-up is ongoing to evaluate the secondary endpoint of HCV reinfection. **FINDINGS:** Between March 29, and Oct 31, 2016, we enrolled 103 participants; 29 (28%) of whom were female, nine (9%) had cirrhosis, 36 (35%) had HCV genotype 1, five (5%) had genotype 2, 60 (58%) had genotype 3, and two (2%) had genotype 4. 61 (59%) participants were receiving opioid substitution therapy during the study, 76 (74%) injected in the past month, and 27 (26%) injected at least daily in the past month. 100 (97%) of 103 participants completed treatment; two people were lost to follow-up and one person died from an overdose. There were no virological failures. 97 (94%, 95% CI 88-98) of 103 people achieved SVR12. Three participants with an end-of-treatment response did not have a SVR; two were lost to follow-up and one had reinfection. Drug use before and during treatment did not affect SVR12. Treatment-

related adverse events were seen in 48 (47%) patients (one grade 3, no grade 4). Seven (7%) patients had at least one serious adverse event; only one such event (rhabdomyolysis, resolved) was possibly related to the therapy. One case of HCV reinfection was observed.

INTERPRETATION: HCV treatment should be offered to PWID, irrespective of ongoing drug use. Recent injection drug use should not be used as a reason to withhold reimbursement of HCV therapy. **FUNDING:** Gilead Sciences.

[Twelve weeks of ombitasvir/paritaprevir/r and dasabuvir without ribavirin is effective and safe in the treatment of patients with HCV genotype 1b infection and compensated cirrhosis: results from a real-world cohort study.](#)

Chamorro-de-Vega E1, Gimenez-Manzorro A1, et al. *Expert Opin Drug Saf.* 2018 Mar;17(3):235-241. doi:

10.1080/14740338.2018.1424829. Epub 2018 Jan 11.

OBJECTIVE: To explore the effectiveness and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/r+DSV) for 12 weeks without ribavirin in adults with chronic HCV genotype 1b infection and compensated cirrhosis. **METHODS:** Observational study of a prospective cohort of adult patients with HCV genotype 1b infection and compensated cirrhosis who received 12 weeks of OBV/PTV/r and DSV without ribavirin. Effectiveness was assessed by recording the percentage of patients achieving sustained virological response at week 12 post-treatment (SVR12). Safety outcomes were based on the incidence of adverse events. **RESULTS:** Seventy-eight patients were included. The SVR12 rate was 96.1% (95% CI 89.2-99.2). Adverse events were recorded in 78.0% of patients. Of these, 97.7% were grade 1/2. One patient discontinued treatment prematurely owing to adverse events. Eighty-six interactions were detected in 43 patients (55.1%). Overall, 81.4% of interactions required close monitoring, alteration of drug dosage, or timing of administration. In 7.0% of cases, the interactions arose from contraindications that required the suspension of the concomitant drug. In 11.6% of cases, medicinal plants or foods were withdrawn. **CONCLUSIONS:** The simplified regimen of OBV/PTV/r+DSV administered for 12 weeks is effective and safe in patients with chronic HCV genotype 1b infection and compensated cirrhosis. No adverse reactions related to drug-drug interactions were recorded.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Peripheral TNF \$\alpha\$ elevations in abstinent alcoholics are associated with hepatitis C infection.](#)

Zahr NM1,2. *PLoS One.* 2018 Feb 6;13(2):e0191586. doi:

10.1371/journal.pone.0191586. eCollection 2018.

Substantial evidence supports the view that inflammatory processes contribute to brain alterations in HIV infection. Mechanisms recently proposed to underlie neuropathology in Alcohol Use Disorder (AUD) include elevations in peripheral cytokines that sensitize the brain to the damaging effects of alcohol. This study included 4 groups: healthy controls, individuals with AUD (abstinent from alcohol at examination), those infected with HIV, and those comorbid for HIV and AUD. The aim was to determine whether inflammatory cytokines are elevated in AUD as they are in HIV infection. Cytokines showing group differences included interferon gamma-induced protein 10 (IP-10) and tumor necrosis factor α (TNF α). Follow-up t-tests revealed that TNF α and IP-10 were higher in AUD than controls but only in AUD patients who were seropositive for Hepatitis C virus (HCV). Specificity of TNF α and IP-10 elevations to HCV infection status was provided by correlations between cytokine levels and HCV viral load and

indices of liver integrity including albumin/globulin ratio, fibrosis scores, and AST/platelet count ratio. Because TNF α levels were mediated by HCV infection, this study provides no evidence for elevations in peripheral cytokines in "uncomplicated", abstinent alcoholics, independent of liver disease or HCV infection. Nonetheless, these results corroborate evidence for elevations in IP-10 and TNF α in HIV and for IP-10 levels in HIV+HCV co-infection.

[Designing a B Cell-Based Vaccine against a Highly Variable Hepatitis C Virus.](#) Fuerst TR1,2, Pierce BG1,2, Keck ZY3, Fong SKH3. *Front Microbiol.* 2018 Jan 15;8:2692. doi: 10.3389/fmicb.2017.02692. eCollection 2017.

The ability to use structure-based design and engineering to control the molecular shape and reactivity of an immunogen to induce protective responses shows great promise, along with corresponding advancements in vaccine testing and evaluation systems. We describe in this review new paradigms for the development of a B cell-based HCV vaccine. Advances in test systems to measure in vitro and in vivo antibody-mediated virus neutralization include retroviral pseudotype particles expressing HCV E1E2 glycoproteins (HCVpp), infectious cell culture-derived HCV virions (HCVcc), and surrogate animal models mimicking acute HCV infection. Their applications have established the role of broadly neutralizing antibodies to control HCV infection. However, the virus has immunogenic regions in the viral envelope glycoproteins that are associated with viral escape or non-neutralizing antibodies. These regions serve as immunologic decoys that divert the antibody response from less prominent conserved regions mediating virus neutralization. This review outlines the immunogenic regions on E2, which are roughly segregated into the hypervariable region 1 (HVR1), and five clusters of overlapping epitopes designated as antigenic domains A-E. Understanding the molecular architecture of conserved neutralizing epitopes within these antigenic domains, and how other antigenic regions or decoys deflect the immune response from these conserved regions will provide a roadmap for the rational design of an HCV vaccine.

[APOB codon 4311 polymorphism is associated with hepatitis C virus infection through altered lipid metabolism.](#) Harada R1, Kimura M1, Sato Y1, et al. *BMC Gastroenterol.* 2018 Jan 30;18(1):24. doi: 10.1186/s12876-018-0747-5.

BACKGROUND: It has been reported that some single-nucleotide polymorphisms (SNPs) in lipid regulators such as apolipoproteins and cell surface molecules for hepatitis C virus (HCV) entry into hepatocytes are associated with HCV infection. However, it is unknown how HCV infection is affected by altered lipid metabolism resulting from the SNPs. We investigated the relationship between these SNPs and HCV infection status, and also analyzed the mechanism by which these SNPs mediate HCV infection via lipid metabolism alterations. **METHODS:** Serum lipid and apolipoprotein profiles were tested in 158 HCV-positive and 220 HCV-negative subjects. We selected 22 SNPs in five lipid regulator genes which were related to HCV entry into hepatocytes and to lipid metabolism (APOA1, APOB, SR-B1, LDLR, and APOE), and their polymorphisms were analyzed using the PCR-sequence-specific oligonucleotide probe-Luminex method. **RESULTS:** An APOB N4311S (g.41553a > g) SNP, rs1042034, was significantly associated with HCV positivity; the HCV positivity rate for the minor allele AA genotype was significantly higher than for genotype AG + GG (P = 0.016). Other SNPs except for APOB P2712L SNP rs676210, which is in linkage disequilibrium with rs1042034, showed no significant difference in genotype distribution. The serum level of low density lipoprotein-

cholesterol (LDL-C) in the genotype AA group was significantly lower than in the genotype non-AA group ($P = 0.032$), whereas the triglyceride (TG) level was significantly higher ($P = 0.007$).

CONCLUSION: An APOB SNP, rs1042034, is closely associated with HCV infection through lipid metabolism alteration. The minor allele AA genotype might contribute to facilitating serum LDL uptake into hepatocytes via LDLR by modifying their affinity and interaction and may have an influence on HCV infection by their entry to the liver through the LDLR.

PMCID: PMC5791310 Free PMC Article

[Calcitriol Inhibits HCV Infection via Blockade of Activation of PPAR and Interference with Endoplasmic Reticulum-Associated Degradation.](#) Lin YM1, Sun HY2, Chiu WT3, et al. *Viruses*. 2018 Jan 30;10(2). pii: E57. doi: 10.3390/v10020057.

Vitamin D has been identified as an innate anti-hepatitis C virus (HCV) agent but the possible mechanisms for this issue remain unclear. Here, we clarified the mechanisms of calcitriol-mediated inhibition of HCV infection. Calcitriol partially inhibited HCV infection, nitric oxide (NO) release and lipid accumulation in Huh7.5 human hepatoma cells via the activation of vitamin D receptor (VDR). When cells were pretreated with the activators of peroxisome proliferator-activated receptor (PPAR)- α (Wy14643) and - γ (Ly171883), the calcitriol-mediated HCV suppression was reversed. Otherwise, three individual stimulators of PPAR- $\alpha/\beta/\gamma$ blocked the activation of VDR. PPAR- β (linoleic acid) reversed the inhibition of NO release, whereas PPAR- γ (Ly171883) reversed the inhibitions of NO release and lipid accumulation in the presence of calcitriol. The calcitriol-mediated viral suppression, inhibition of NO release and activation of VDR were partially blocked by an inhibitor of endoplasmic reticulum-associated degradation (ERAD), kifunensine. Furthermore, calcitriol blocked the HCV-induced expressions of apolipoprotein J and 78 kDa glucose-regulated protein, which was restored by pretreatment of kifunensine. These results indicated that the calcitriol-mediated HCV suppression was associated with the activation of VDR, interference with ERAD process, as well as blockades of PPAR, lipid accumulation and oxidative stress.

[Endothelial cell functions impaired by interferon in vitro: Insights into the molecular mechanism of thrombotic microangiopathy associated with interferon therapy.](#) Jia H1, Thelwell C2, Dilger P3, Bird C3, Daniels S2, Wadhwa M3. *Thromb Res*. 2018 Jan 30;163:105-116. doi: 10.1016/j.thromres.2018.01.039. [Epub ahead of print]

INTRODUCTION: Interferon (IFN)- α and IFN- β approved for treatment of chronic hepatitis C viral infection and multiple sclerosis respectively have been linked to thrombotic microangiopathy (TMA) affecting renal function. Since the molecular mechanisms underlying this severe complication remain largely unclear, we aimed to investigate whether IFN affects directly in vitro endothelial cell functions associated with angiogenesis and blood haemostasis, as well as endothelial cell-derived vasodilators of nitric oxide (NO) and prostacyclin.

METHODS: Proliferation and survival of human umbilical vein endothelial cells (HUVECs) were measured by BrdU incorporation and alamarBlue assays. Angiogenesis was evaluated in co-cultures of HUVECs and human dermal fibroblasts. Fibrinolysis molecules were measured with ELISA. NO and prostacyclin were measured using a fluorescent NO-specific probe and a competitive enzyme immunoassay, respectively. **RESULTS:** HUVEC proliferation was dose-dependently inhibited by IFN- β 1a and IFN- β 1b, but not by IFN- α 2a and IFN- α 2b. Consistently, IFN- β 1a and IFN- β 1b also reduced survival of HUVECs, but this again was not observed with IFN- α . However, both IFN subtypes inhibited VEGF-induced development of capillary-like

structures, but the effect of IFN- α was less potent than IFN- β . In addition, both IFN subtypes upregulated interferon inducible protein 10 production from treated co-cultures while suppressing angiogenesis. Furthermore, intracellular NO generation was reduced by IFN- α 2a and IFN- β 1a, whereas prostacyclin release from HUVECs was not affected by IFN. Importantly, both IFN- β 1a- and IFN- β 1b-treated HUVECs showed a marked reduction in urokinase-type plasminogen activator release and a much greater secretion of plasminogen activator inhibitor-1 than tissue-type plasminogen activator compared with untreated cells, suggesting decreased fibrinolytic activity. IFN- α , however was less effective in modulating the fibrinolysis system. **CONCLUSIONS:** We demonstrate the detrimental effects of IFN on endothelial cell functions mediated with angiogenesis and fibrinolysis, which could potentially cause the loss of physiological endothelium thromboresistance and facilitate the development of vascular complications in a clinical setting. Mechanistically, our findings have implications for understanding how IFN therapy can foster the development of TMA.

[Newly discovered hepatitis C virus minicores circulate in human blood.](#) Eng FJ1, El-Shamy A1, Doyle EH1, Klepper A1, Muerhoff AS2, Branch AD1. *Hepatol Commun.* 2017 Nov 12;2(1):21-28. doi: 10.1002/hep4.1125. eCollection 2018 Jan.

Hepatitis C virus (HCV) is one of the most prevalent causes of chronic blood-borne infections worldwide. Despite developments of highly effective treatments, most infected individuals are unaware of their infection. Approximately 75% of infections are in low- and middle-income countries; therefore, continuing research in HCV molecular virology and the development of vaccines and affordable diagnostics is required to reduce the global burden. Various intracellular forms of the HCV nucleocapsid (core) protein are produced in cell culture; these comprise the conventional p21 core and the newly discovered shorter isoforms (minicores). Minicores lack the N-terminus of p21 core. This study was conducted to determine if minicores are secreted in cell culture and more importantly if they circulate in the blood of individuals infected with HCV. We also developed a new monoclonal antibody that detects minicores targeting a C-terminal region common to p21 core and minicores. Direct evidence of minicores requires western blot analysis to distinguish the detection of p21 core from minicores. However, the sensitivity for western blot detection of HCV proteins from blood is nil without their prior purification/enrichment from blood. Therefore, we developed a purification method based on a heparin/Mn+2 precipitation of apolipoprotein B-containing lipoproteins because HCV is thought to circulate as a hybrid lipoviral particle. Minicores are secreted in culture when cells are grown in the presence of human serum. The heparin/Mn+2 precipitate from HCV-infected cell culture supernatants and from the blood of 4 patients with high-titer genotype-1 HCV contained minicores. Conclusion: Minicores are major newly discovered HCV proteins that are secreted and circulate in blood during natural infections. Minicore proteins have translational potential as targets in diagnostic assays and in vaccine development. (*Hepatology Communications* 2018;2:21-28).

[In Vitro Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS3/4A Protease Inhibitor Glecaprevir.](#) Ng T11, Tripathi R2, Reisch T2, et al. *Antimicrob Agents Chemother.* 2017 Dec 21;62(1). pii: e01620-17. doi: 10.1128/AAC.01620-17. Print 2018 Jan.

Glecaprevir (formerly ABT-493) is a novel hepatitis C virus (HCV) NS3/4A protease inhibitor (PI) with pangenotypic activity. It inhibited the enzymatic activity of purified NS3/4A proteases from HCV genotypes 1 to 6 in vitro (half-maximal [50%] inhibitory concentration = 3.5 to 11.3

nM) and the replication of stable HCV subgenomic replicons containing proteases from genotypes 1 to 6 (50% effective concentration [EC₅₀] = 0.21 to 4.6 nM). Glecaprevir had a median EC₅₀ of 0.30 nM (range, 0.05 to 3.8 nM) for HCV replicons containing proteases from 40 samples from patients infected with HCV genotypes 1 to 5. Importantly, glecaprevir was active against the protease from genotype 3, the most-difficult-to-treat HCV genotype, in both enzymatic and replicon assays demonstrating comparable activity against the other HCV genotypes. In drug-resistant colony selection studies, glecaprevir generally selected substitutions at NS3 amino acid position A156 in replicons containing proteases from genotypes 1a, 1b, 2a, 2b, 3a, and 4a and substitutions at position D/Q168 in replicons containing proteases from genotypes 3a, 5a, and 6a. Although the substitutions A156T and A156V in NS3 of genotype 1 reduced susceptibility to glecaprevir, replicons with these substitutions demonstrated a low replication efficiency in vitro. Glecaprevir is active against HCV with most of the common NS3 amino acid substitutions that are associated with reduced susceptibility to other currently approved HCV PIs, including those at positions 155 and 168. Combination of glecaprevir with HCV inhibitors with other mechanisms of action resulted in additive or synergistic antiviral activity. In summary, glecaprevir is a next-generation HCV PI with potent pangenotypic activity and a high barrier to the development of resistance.

HIV/HCV COINFECTION

[Association between depressive symptoms, CD4 count and HIV viral suppression among HIV-HCV co-infected people.](#) Aibibula W1, Cox J1,2,3, Hamelin AM1, et al. *AIDS Care*. 2018 Jan 28;1-7. doi: 10.1080/09540121.2018.1431385. [Epub ahead of print]

Depressive symptoms are associated with poor HIV viral control and immune recovery among people living with HIV. However, no prior studies assessed this association exclusively among people co-infected with HIV-hepatitis C virus (HCV). While people with HIV only and those with HIV-HCV co-infection share many characteristics, co-infected people may become more susceptible to the effects of depressive symptoms on health outcomes. We assessed this association exclusively among people co-infected with HIV-HCV in Canada using data from the Food Security & HIV-HCV Sub-Study (FS Sub-Study) of the Canadian Co-Infection Cohort (CCC). Stabilized inverse probability weighted marginal structural model was used to account for potential time-varying confounders. A total of 725 participants were enrolled between 2012 and 2015. At baseline, 52% of participants reported depressive symptoms, 75% had undetectable HIV viral load, and median CD4 count was 466 (IQR 300-665). People experiencing depressive symptoms had 1.32 times (95% CI: 1.07, 1.63) the risk of having detectable HIV viral load, but had comparable CD4 count to people who did not experience depressive symptoms (fold change of CD4 = 0.96, 95% CI: 0.91, 1.03). Presence of depressive symptoms is a risk factor for incomplete short-term HIV viral suppression among people co-infected with HIV-HCV. Therefore, depressive symptoms screening and related counseling may improve HIV related health outcomes and reduce HIV transmission.

[Interferon-free therapy for treating hepatitis C virus in difficult-to-treat HIV-coinfected patients.](#) Mínguez C1, García-Deltoro M2, Flores J3, et al. *AIDS*. 2018 Jan 28;32(3):337-346. doi: 10.1097/QAD.0000000000001699.

BACKGROUND/AIMS: Data regarding the use of all-oral direct-acting antivirals in HIV/hepatitis C virus (HCV)-coinfected patients with advanced liver fibrosis are required,

because they are generally under-represented in clinical trials. This study sought to evaluate the use of these drugs in a cohort of coinfecting patients, mostly with factors that have previously been recognized as predictors of treatment failure. **METHODS:** COINFEKOVA-2 is an observational, multicenter study conducted in Eastern Spain. Data of all HIV/HCV-coinfecting patients treated with direct-acting antiviral under real-life conditions were retrospectively collected, and factors associated with treatment success or safety were analysed. **RESULTS:** Among 515 included patients, 96% were on antiretroviral therapy and 89.5% had an HIV-RNA less than 50 copies/ml. HCV genotype (G) distribution was 47% G-1a, 20% G-4, 14.4% G-1b, and 12.8% G-3. Patients with cirrhosis were 54.2%, and 46% failed to prior HCV-therapies. Overall, 92.8% patients (95% confidence interval: 90.2-94.9) achieved sustained virologic response (SVR12). Cirrhosis was the only factor associated with treatment failure, and SVR12 rate was significantly lower in patients with liver stiffness at least 21 kPa. Adverse events were reported in 36.7%, but only two patients (0.4%) discontinued treatment because of adverse events. The bivariate analysis showed an association between ribavirin use and an increased risk of adverse events (odds ratio 2.84; 95% confidence interval: 1.95-4.1; $P \leq 0.0001$). **CONCLUSION:** This heterogeneous cohort of coinfecting patients showed a high rate of SVR12. Among cirrhotic patients, those with a liver stiffness at least 21 kPa had a higher probability of treatment failure. Ribavirin use seems to increase the appearance of adverse events.

[Direct-Acting Antivirals Improve Access to Care and Cure for Patients With HIV and Chronic HCV Infection.](#) Collins LF1, Chan A2, Zheng J3, Chow SC3,4, Wilder JM4,5, Muir AJ4,5, Naggie S2,4. *Open Forum Infect Dis.* 2017 Dec 9;5(1):ofx264. doi: 10.1093/ofid/ofx264. eCollection 2018 Jan.

BACKGROUND: Direct-acting antivirals (DAA) as curative therapy for hepatitis C virus (HCV) infection offer >95% sustained virologic response (SVR), including in patients with human immunodeficiency virus (HIV) infection. Despite improved safety and efficacy of HCV treatment, challenges remain, including drug-drug interactions between DAA and antiretroviral therapy (ART) and restrictions on access by payers. **METHODS:** We performed a retrospective cohort study of all HIV/HCV co-infected and HCV mono-infected patients captured in care at our institution from 2011-2015, reflecting the DAA era, to determine treatment uptake and SVR, and to elucidate barriers to accessing DAA for co-infected patients. **RESULTS:** We identified 9290 patients with HCV mono-infection and 507 with HIV/HCV co-infection. Compared to mono-infected patients, co-infected patients were younger and more likely to be male and African-American. For both groups, treatment uptake improved from the DAA/pegylated interferon (PEGIFN)-ribavirin to IFN-free DAA era. One-third of co-infected patients in the IFN-free DAA era required ART switch and nearly all remained virologically suppressed after 6 months. We observed SVR >95% for most patient subgroups including those with co-infection, prior treatment-experience, and cirrhosis. Predictors of access to DAA for co-infected patients included Caucasian race, CD4 count ≥ 200 cells/mm³, HIV virologic suppression and cirrhosis. Time to approval of DAA was longest for patients insured by Medicaid, followed by private insurance and Medicare. **CONCLUSIONS:** DAA therapy has significantly improved access to HCV treatment and high SVR is independent of HIV status. However, in order to realize cure for all, barriers and disparities in access need to be urgently addressed.

[Hepatitis C virus cure does not impact kidney function decline in HIV co-infected patients.](#)

Rossi C1, Saeed S1, Cox J2, et al. AIDS. 2018 Jan 23. doi: 10.1097/QAD.0000000000001750. [Epub ahead of print]

OBJECTIVE: To examine the impact of sustained virologic response (SVR) and illicit (injection and non-injection) drug use on kidney function among hepatitis C virus (HCV) and HIV co-infected individuals. **DESIGN:** Longitudinal observational cohort study of HCV-HIV co-infected patients. **METHODS:** Data from 1,631 patients enrolled in the Canadian Co-Infection Cohort between 2003 and 2016 were analyzed. Patients who achieved SVR were matched 1:2 with chronically infected patients using time-dependent propensity scores. Linear regression with generalized estimating equations was used to model differences in estimated glomerular filtration rates (eGFR) between chronic HCV-infected patients and those achieving SVR. The relationship between illicit drug use and eGFR was explored in patients who achieved SVR. **RESULTS:** We identified 384 co-infected patients who achieved SVR (53% treated with interferon-free antiviral regimens) and 768 propensity-score matched patients with chronic HCV infection. Most patients were male (78%) and White (87%), with a median age of 51 years (interquartile range: 45, 56). During 1,767 person-years of follow-up, 4,041 eGFR measurements were available for analysis. Annual rates of decline in eGFR were similar between patients with SVR [-1.32mL/min/1.73m/year, 95% confidence interval (CI): -1.75, -0.90] and chronic infection (-1.19mL/min/1.73m/year, 95% CI: -1.55, -0.84). Among SVR patients, recent injection cocaine use was associated with rapid eGFR decline (-2.16mL/min/1.73m/year, 95% CI: -4.17, -0.16). **CONCLUSION:** SVR did not reduce the rate of kidney function decline among HCV-HIV co-infected patients. Increased risk of chronic kidney disease in co-infection may not be related to persistent HCV replication but to ongoing injection cocaine use.

[Advances in the treatment of HIV/HCV coinfection in adults.](#) Schlabe S1, Rockstroh JK1. Expert Opin Pharmacother. 2018 Jan;19(1):49-64. doi: 10.1080/14656566.2017.1419185. Direct-acting antivirals (DAA) have revolutionized the modern treatment of chronic hepatitis C (HCV). These highly efficacious, well-tolerated, all-oral HCV regimens allow cure of HCV in over 95% of HCV-monoinfected as well as HIV/HCV-coinfected patients with short treatment durations of 8-12 weeks. Areas covered: This review will address recent developments of DAA-therapy in HIV/HCV-coinfected patients in clinical trials and real life cohorts and evaluate remaining challenges, particularly resistance, drug-drug interactions, acute HCV infection and liver transplantation focusing on HIV/HCV-coinfected patients. Expert opinion: Indeed, all available data have shown that HIV/HCV-coinfection has no impact on HCV-treatment outcome. Management, indication of therapy and follow-up of HCV-infection are now the same for both patient populations. HIV/HCV-coinfected patients however, require careful evaluation of potential drug-drug-interactions between HCV drugs and HIV antiretroviral therapy, medication for substance abuse and other comedication. The few remaining gaps in DAA-therapy in particular treatment of cirrhotic treatment-experienced genotype 3 infections, decompensated cirrhosis, chronic kidney disease and patients with prior DAA treatment failure have mostly been overcome by the development of new HCV agents recently licensed. Clearly, the biggest challenge globally remains the access to treatment and the inclusion of all patient populations affected in particular people who inject drugs (PWID).

COMPLEMENTARY AND ALTERNATIVE MEDICINE

[Cigarette Smoking in Persons Living with Hepatitis C: the National Health and Nutrition Examination Survey \(NHANES\), 1999-2014.](#)

Kim RS1, Weinberger AH2, Chander G3, Sulkowski MS3, Norton B4, Shuter J5. Am J Med. 2018 Jan 30. pii: S0002-9343(18)30081-0. doi: 10.1016/j.amjmed.2018.01.011. [Epub ahead of print]

BACKGROUND: Cigarette smoking is common in persons living with hepatitis C (hepatitis C+), but national statistics on this harmful practice are lacking. A better understanding of smoking behaviors in hepatitis C+ individuals may help in the development of targeted treatment strategies. **METHODS:** We extracted data from the National Health and Nutrition Examination Survey (NHANES) between 1999-2014. Hepatitis C+ were compared to hepatitis C- adults in the entire sample and in the subset of current smokers. Measures included demographics, current smoking, cigarettes/day, nicotine dependence, other tobacco use, substance use, and medical and psychiatric comorbidities. **RESULTS:** Complete smoking and HCV data were available for 39,472 (90.1%) of 43,793 adult participants in NHANES during the study years. Hepatitis C+ smoked at almost triple the rate of hepatitis C- adults (62.4% vs. 22.9%), with no significant difference between hepatitis C+ men and women (64.5% vs. 58.2%). Hepatitis C+ smokers were more likely to smoke daily than hepatitis C- smokers (87.5% vs. 80.0%), but had similar levels of nicotine dependence. Hepatitis C+ smokers were more likely to be older (mean age: 47.1 vs. 41.5), male (69.4% vs. 54.4%), Black (21.2% vs. 12.1%), less educated (any college: 31.8% vs. 42.9%), poor (mean family monthly poverty index: 1.80 vs. 2.47), uninsured (43.9% vs. 30.4%), use drugs (cocaine: 11.1% vs. 3.2%; heroin: 4.0% vs. 0.6%), and be depressed (33.2% vs. 13.5%). Multivariate analyses revealed significant associations of both hepatitis C infection and cigarette smoking with current depression and hypertension. **CONCLUSIONS:** There is a cigarette smoking epidemic embedded within the hepatitis C epidemic in the US. The sociodemographic profile of hepatitis C+ smokers suggests that the implementation of effective tobacco treatment will be challenging. Thoughtful treatment strategies that are mindful of the unique characteristics of this group are needed.

[Check Hep C: A Community-Based Approach to Hepatitis C Diagnosis and Linkage to Care in High-Risk Populations.](#)

Ford MM1, Jordan AE, Johnson N, Rude E, Laraque F, Varma JK, Hagan H. J Public Health Manag Pract. 2018 Jan/Feb;24(1):41-48. doi: 10.1097/PHH.0000000000000519.

CONTEXT: In New York City (NYC), an estimated 146 500 people, or 2.4% of the adult population, have chronic hepatitis C virus (HCV) infection and half may be unaware of their infection. Despite a 2014 state law requiring health care providers to screen for HCV infection in primary care settings, many high-risk HCV-positive persons are not, and a large proportion of those screened do not receive RNA testing to confirm infection, or antiviral therapies.

OBJECTIVE: The NYC Department of Health's Check Hep C program was designed to increase hepatitis C diagnosis and improve linkage to care at community-based organizations.

DESIGN: Coordinated, evidence-based practices were implemented at 12 sites, including HCV antibody testing, immediate blood draw for RNA testing, and patient navigation to clinical services. **RESULTS:** From May 2012 through April 2013, a total of 4751 individuals were tested for HCV infection and 880 (19%) were antibody-positive. Of antibody-positive participants, 678 (77%) had an RNA test, and of those, 512 (76%) had current infection. Of all participants, 1901 were born between 1945 and 1965, and of those, 201 (11%) were RNA-

positive. Ever having injected drugs was the strongest risk factor for HCV infection (40% vs 3%; adjusted odds ratio [AOR] = 19.1), followed by a history of incarceration (18% vs 4%; AOR = 2.2). Of the participants with current infection, 85% attended at least 1 follow-up hepatitis C medical appointment. Fourteen patients initiated hepatitis C treatment at a Check Hep C site and 6 initiators achieved cure. **CONCLUSION:** The community-based model successfully identified persons with HCV infection and linked a large proportion to care. The small number of patients initiating hepatitis C treatment in the program identified the need for patient navigation in high-risk populations. Results can be used to inform screening and linkage-to-care strategies and to support the execution of hepatitis C screening recommendations.

Cost-Effectiveness of One-Time Hepatitis C Screening Strategies Among Adolescents and Young Adults in Primary Care Settings. Assoumou SA1,2, Tasillo A1, Leff JA3, et al. Clin Infect Dis. 2018 Jan 18;66(3):376-384. doi: 10.1093/cid/cix798.

BACKGROUND: High hepatitis C virus (HCV) rates have been reported in young people who inject drugs (PWID). We evaluated the clinical benefit and cost-effectiveness of testing among youth seen in communities with a high overall number of reported HCV cases. **METHODS:** We developed a decision analytic model to project quality-adjusted life years (QALYs), costs (2016 US\$), and incremental cost-effectiveness ratios (ICERs) of 9 strategies for 1-time testing among 15- to 30-year-olds seen at urban community health centers. Strategies differed in 3 ways: targeted vs routine testing, rapid finger stick vs standard venipuncture, and ordered by physician vs by counselor/tester using standing orders. We performed deterministic and probabilistic sensitivity analyses (PSA) to evaluate uncertainty. **RESULTS:** Compared to targeted risk-based testing (current standard of care), routine testing increased the lifetime medical cost by \$80 and discounted QALYs by 0.0013 per person. Across all strategies, rapid testing provided higher QALYs at a lower cost per QALY gained and was always preferred. Counselor-initiated routine rapid testing was associated with an ICER of \$71000/QALY gained. Results were sensitive to offer and result receipt rates. Counselor-initiated routine rapid testing was cost-effective (ICER <\$100000/QALY) unless the prevalence of PWID was <0.59%, HCV prevalence among PWID was <16%, reinfection rate was >26 cases per 100 person-years, or reflex confirmatory testing followed all reactive venipuncture diagnostics. In PSA, routine rapid testing was the optimal strategy in 90% of simulations. **CONCLUSIONS:** Routine rapid HCV testing among 15- to 30-year-olds may be cost-effective when the prevalence of PWID is >0.59%.

Recreational Drug and Psychosocial Profile in Chronic Hepatitis C Patients Seeking Antiviral Therapy. George N1, Harrell SM2, Rhodes KD2, Duarte-Rojo A2. Ann Hepatol. 2018 January-February;17(1):76-84. doi: 10.5604/01.3001.0010.7537.

BACKGROUND AND AIMS: Practitioners treating hepatitis C (HCV) provide healthcare to a special population with high rates of substance abuse and psychiatric disorders. We investigated the psychosocial profile in HCV patients and tested what variables affect commencement of antiviral therapy. **MATERIAL AND METHODS:** Recreational drug use (RDU), marijuana (THC), alcohol use, and psychiatric history were initially investigated with a questionnaire prior to history and physical. Following an educational intervention, we reinterrogated patients for RDU and THC use, and revision of initial statement was documented. Variables affecting commencement of antiviral therapy were analysed with logistic regression. **RESULTS:** Out of 153 patients, 140 (92%) answered the questionnaire. Intervention increased total yield by 6%, however, 39% (11/28) of those initially denying use revised their statement. Drug screening

identified 9 more patients with RDU/THC use. Half of patients consuming alcohol were heavy drinkers, and psychiatric disease was identified in 54%. Only 73 (48%) of 139 patients eligible for antivirals received treatment. Multivariable analysis revealed that younger patients (OR = 1.04, 95% CI 1.01-1.08), and those testing positive on drug screen (OR = 0.41, 95% CI 0.19-0.92) were less likely to be treated. Denial by insurance and loss to follow-up were the most common reasons for not starting antiviral treatment. **CONCLUSION:** Substance abuse is highly prevalent among HCV patients, and it is difficult to tell prior from current users. Integral care of HCV patients should include a diligent screen for substance abuse and rehabilitation referral, aiming to increase the pool of patients eligible for antiviral therapy. This can only be achieved through a multidisciplinary approach.

Sofosbuvir induced steven Johnson Syndrome in a patient with hepatitis C virus-related cirrhosis. Verma N1, Singh S2, Sawatkar G3, Singh V1. Hepatol Commun. 2017 Nov 11;2(1):16-20. doi: 10.1002/hep4.1126. eCollection 2018 Jan.

Sofosbuvir is an imperative drug used in treatment regimens for hepatitis C virus (HCV). It is considered relatively safe with fewer adverse effects than other treatments. Here, we report a rare and potentially serious, dermatologic, adverse effect following the use of sofosbuvir. A 35-year-old man with genotype 3-related HCV cirrhosis presented with decompensated ascites and jaundice following 7 weeks of therapy with peginterferon alpha-2a and oral ribavirin. After peginterferon withdrawal and stabilization, oral sofosbuvir and ribavirin were started; 10 days later, he developed itching over the trunk and legs, followed by multiple papules and vesicles over an erythematous base. Over the next 15 days, the rash progressed with the formation of blisters and peeling skin. Simultaneously, the oral mucosa and lips developed crusting and painful erosions. Considering drug-induced Steven John Syndrome (SJS), sofosbuvir and ribavirin were withdrawn and the patient was treated with topical emollients, steroids, and supportive care. The lesions improved over the next 4 weeks, with some residual hyperpigmentation. Rechallenge with sofosbuvir alone at one eighth the dose resulted in similar skin and mucosal lesions after 2 months; these lesions also improved after sofosbuvir withdrawal. The Algorithm of Drug Causality for Epidermal Necrolysis score was 7, which suggested sofosbuvir as the very probable drug resulting in SJS in our patient. Conclusion: The appearance of SJS following sofosbuvir use is an important and potentially fatal complication from a drug that serves as the backbone of several HCV treatment regimens. Treating physicians must use sofosbuvir with caution and consider withholding or discontinuing this drug in patients with such severe dermatologic manifestations. (Hepatology Communications 2018;2:16-20).

Proton nuclear magnetic resonance-based metabonomic models for non-invasive diagnosis of liver fibrosis in chronic hepatitis C: Optimizing the classification of intermediate fibrosis. Batista AD1, Barros CJP2, Costa TBBC2, et al. World J Hepatol. 2018 Jan 27;10(1):105-115. doi: 10.4254/wjh.v10.i1.105.

AIM: To develop metabonomic models (MMs), using ¹H nuclear magnetic resonance (NMR) spectra of serum, to predict significant liver fibrosis (SF: Metavir ≥ F2), advanced liver fibrosis (AF: METAVIR ≥ F3) and cirrhosis (C: METAVIR = F4 or clinical cirrhosis) in chronic hepatitis C (CHC) patients. Additionally, to compare the accuracy of the MMs with the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4). **METHODS:** Sixty-nine patients who had undergone biopsy in the previous 12 mo or had clinical cirrhosis were included. The presence of any other liver disease was a criterion for

exclusion. The MMs, constructed using partial least squares discriminant analysis and linear discriminant analysis formalisms, were tested by cross-validation, considering SF, AF and C. **RESULTS:** Results showed that forty-two patients (61%) presented SF, 28 (40%) AF and 18 (26%) C. The MMs showed sensitivity and specificity of 97.6% and 92.6% to predict SF; 96.4% and 95.1% to predict AF; and 100% and 98.0% to predict C. Besides that, the MMs correctly classified all 27 (39.7%) and 25 (38.8%) patients with intermediate values of APRI and FIB-4, respectively. **CONCLUSION:** The metabonomic strategy performed excellently in predicting significant and advanced liver fibrosis in CHC patients, including those in the gray zone of APRI and FIB-4, which may contribute to reducing the need for these patients to undergo liver biopsy.

[Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide.](#)

Maucort-Boulch D1,2,3,4, de Martel C5, Franceschi S5, Plummer M5. *Int J Cancer*. 2018 Jan 31. doi: 10.1002/ijc.31280. [Epub ahead of print]

High-quality data on liver cancers by probable cause are scarce in many regions of the world. The United Nations recently set a goal of eliminating viral hepatitis as a major public health threat by 2030. We aimed to estimate the number of new cases of cancers attributable to hepatitis B virus (HBV) and hepatitis C virus (HCV) at a global, regional and country level, and by development status. We used data on the prevalence of HBV and HCV in hepatocellular carcinoma from a systematic review including 119,000 cases in 260 studies covering 50 countries. A statistical model was constructed to extrapolate empirical data to countries without prevalence data. Country-specific numbers of liver cancer cases attributable to HBV and HCV were calculated using data from GLOBOCAN 2012. Globally, 770,000 cases of liver cancer occurred worldwide in 2012, of which 56% (95% CI: 52-60) were attributable to HBV and 20% (95% CI: 18-22) to HCV. Currently, HBV causes approximately two out of three cases of liver cancer in less developed countries but one in four cases in more developed countries and shows a much higher degree of geographical aggregation in Eastern Asia and sub-Saharan Africa than HCV. These estimates help set priorities for liver cancer prevention. High-coverage HBV vaccination will be transformational in HBV-endemic countries but the prevention of HCV transmission and the treatment of chronic carriers of both viruses requires new scalable solutions.

[Hepatitis C virus re-treatment in the era of direct-acting antivirals: projections in the USA.](#)

Chhatwal J1,2,3, Chen Q1,2, Ayer T4, Bethea ED1,2,3, Kanwal F5,6, Kowdley KV7, Wang X8, Roberts MS9, Gordon SC10. *Aliment Pharmacol Ther*. 2018 Jan 29. doi: 10.1111/apt.14527. [Epub ahead of print]

BACKGROUND: The introduction of oral direct-acting antivirals (DAAs) has dramatically changed the landscape of HCV treatment. However, a small percentage of patients fail to achieve sustained virologic response (SVR). Understanding the number of people who fail on DAAs and require re-treatment is important for budget impact and disease burden projections. **AIM:** To quantify the number of HCV patients who fail to achieve SVR on oral DAAs (NS5A vs. non-NS5A) and require re-treatment. **METHODS:** We used a mathematical model to simulate clinical management of HCV in the USA, which included the implementation of HCV screening, treatment, and disease progression. We simulated different waves of DAA treatment and used real-world data to extract SVR rates and market shares of available therapies. **RESULTS:** Our model projected that the number of people living without viraemia (i.e. cured) would increase from 0.70 million in 2014 to 1.78 million by 2020. Between 2014 and 2020, 1.50 million people would receive treatment with DAAs, of whom 124 000 (8.3%) are projected to

fail to achieve SVR. Among those treatment failures, 66 600 (53.7%) patients would fail treatment with NS5A inhibitors and 69 600 (56.1%) would have cirrhosis. During the same period, 34 200 people would progress to decompensated cirrhosis and 27 300 would develop hepatocellular carcinoma after failing to achieve SVR. **CONCLUSIONS:** Even in the era of highly effective DAAs, a significant number of patients will fail to achieve SVR and will require re-treatment options. Timely and effective re-treatment is essential to prevent the long-term sequelae of HCV.

[Reducing patient and provider knowledge gaps: An evaluation of a community informed hepatitis C online course.](#) Buller-Taylor T1, McGuinness L2, Yan M3, Janjua NZ4. Patient Educ Couns. 2018 Jan 10. pii: S0738-3991(18)30008-9. doi: 10.1016/j.pec.2018.01.008. [Epub ahead of print]

OBJECTIVES: Hepatitis C (HCV) knowledge gaps are associated with lower levels of engagement in (HCV) care which contributes to HCV-related morbidity and mortality. Knowledge gaps may be exacerbated by rapid changes in HCV care/treatment. Cost-effective, timely and easy-to-implement education is needed to address knowledge gaps and foster HCV engagement. **METHODS:** We developed a free, one-hour, online course for patients and providers. Online and facilitated course events were evaluated. Outcome measures included: pre/post-scores, perceived knowledge gains and increased capacity to educate/encourage engagement in HCV care. **RESULTS:** Total pre-post-test gains were significant ($p < .001$) across groups. Over 50% of participants reported: perceived knowledge gains of "A lot" or higher; the course increased their capacity to educate and encourage client engagement in care by "A lot" or higher. **CONCLUSIONS:** The evaluation confirmed ongoing patient and provider HCV knowledge gaps, significantly reduced those gaps, and increased provider's capacity to educate and encourage client engagement in HCV care. **PRACTICE IMPLICATIONS:** The course is an effective tool to address knowledge gaps that might lower engagement in care. It is available to patients to use in the privacy of their own home or for providers for their personal use, to use with individuals or patient groups.

[Understanding hepatitis C intervention success: Qualitative findings from the HepCATT study.](#) Harris M1, Bonnington O1, Harrison G2, Hickman M3, Irving W2; HepCATT team. J Viral Hepat. 2018 Jan 25. doi: 10.1111/jvh.12869. [Epub ahead of print]

The United Kingdom has committed to eliminating viral hepatitis as a public health threat. Innovative interventions for marginalised populations are required to realise this goal. In 2016, the HepCATT study team implemented a complex hepatitis C (HCV) intervention in three English drug treatment services, with five controls. We report qualitative study findings from two intervention sites to explore intervention success and transferability potential. The intervention comprised multiple components, including a nurse facilitator, peer support and education initiatives. Qualitative data were generated at baseline (2014) and post-intervention (2016) at two sites through in-depth interviews, focus groups and observations. The 96 participants comprised drug service and intervention providers and clients with an injecting history. Data were triangulated and thematically analysed. Client engagement with a HCV treatment service rose from 16 at baseline to 147 in 2016. There was no comparable increase at the five control sites. Baseline testing and treatment barriers included: limited HCV knowledge; fear of diagnosis and treatment; precarious living circumstances and service-specific obstacles. Treatment engagement was aided by: intervention timeliness; improved communication

structures; personalised care; streamlined testing and treatment pathways; peer support. Multiple interrelated components influenced the increased levels of treatment engagement documented in HepCATT. The nurse facilitator, involved in implementation and innovation, was key to intervention success. Baseline barriers correspond with international literature - indicating transferability potential. Control data indicate that biomedical innovation alone is not sufficient to increase engagement amongst the most marginalised. Sustainable resourcing of community services is crucial to effect change. This article is protected by copyright. All rights reserved.

HEPATOCELLULAR (LIVER) CANCER

[The hepatitis C viral nonstructural protein 5A stabilizes growth-regulatory human transcripts.](#) Guo L1,2,3, Sharma SD4, Debes J1, et al. Nucleic Acids Res. 2018 Jan 29. doi: 10.1093/nar/gky061. [Epub ahead of print]

Numerous mammalian proto-oncogene and other growth-regulatory transcripts are upregulated in malignancy due to abnormal mRNA stabilization. In hepatoma cells expressing a hepatitis C virus (HCV) subgenomic replicon, we found that the viral nonstructural protein 5A (NS5A), a protein known to bind to viral RNA, also bound specifically to human cellular transcripts that encode regulators of cell growth and apoptosis, and this binding correlated with transcript stabilization. An important subset of human NS5A-target transcripts contained GU-rich elements, sequences known to destabilize mRNA. We found that NS5A bound to GU-rich elements in vitro and in cells. Mutation of the NS5A zinc finger abrogated its GU-rich element-binding and mRNA stabilizing activities. Overall, we identified a molecular mechanism whereby HCV manipulates host gene expression by stabilizing host transcripts in a manner that would promote growth and prevent death of virus-infected cells, allowing the virus to establish chronic infection and lead to the development of hepatocellular carcinoma.

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

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

compared with untreated patients. The rate of recurrence, time to progression, and HCC pattern are similar. Early DAAs treatment (<12 months) after HCC cure should be discouraged considering the HCC recurrence rate during this period.

[Hepatitis C Virus mediated metastasis in hepatocellular carcinoma as a therapeutic target for cancer management.](#) Khera L1, Paul C1, Kaul R1. *Curr Drug Metab.* 2018 Jan 28. doi: 10.2174/1389200219666180129110942. [Epub ahead of print]

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer associated deaths. The prognosis is relatively poor in cases where Hepatitis C Virus (HCV) is associated as its causative agent mainly due to increased risk of metastasis. Tumor metastasis can be defined as the transfer of cancer from one organ to another which is not directly connected to it. Metastasis is the major cause of all cancer related deaths. HCV infection is associated with expression of multiple pro-metastatic factors in HCC patients. Several HCV encoded proteins have been reported to directly induce pro-metastasis cellular functions. HCV-induced HCC has a greater chance of recurrence than any non-viral and Hepatitis B Virus (HBV) induced HCC. In view of recent advances in understanding of evolutionary dynamics of tumor, it has been argued that trying to control cancer by preventing its spread may ultimately prove to be a better approach than striving to cure it. Inhibiting the metastasis can render the cancer much easier to handle as a disease; thereby substantially increasing the survival period in patients. Host cell protein Nm23-H1 is a known suppressor of tumor metastasis and has been shown to be modulated by proteins encoded by different viruses associated with cancers. Nm23-H1 is, therefore, an important therapeutic target for virus mediated malignancies. This review is an attempt to summarize the current state of understanding of cancer cell metastasis in HCV induced tumors, and argues for approaches based on targeting host and viral factors critical for cancer metastasis as therapeutic targets.

[Persistence of hepatocellular carcinoma risk in hepatitis c patients with a response to ifn and cirrhosis regression.](#) D'Ambrosio R1, Aghemo A2,3, Rumi MG4, et al. *Liver Int.* 2018 Jan 27. doi: 10.1111/liv.13707. [Epub ahead of print]

BACKGROUND AND AIM: In patients with HCV-related cirrhosis, a SVR may lead to cirrhosis regression. Whether histological changes translate into prevention of long-term complications, particularly hepatocellular carcinoma (HCC) is still unknown. This was investigated in a cohort of histological cirrhotics who had been prospectively followed-up for 10 years after the achievement of a SVR to IFN. **METHODS:** 38 SVR cirrhotics who underwent a liver biopsy (LB) 5 years post-SVR were prospectively followed to assess the impact of cirrhosis regression on clinical endpoints. **RESULTS:** During a follow-up of 86 (30-96) months from LB, no patients developed clinical decompensation, whilst 5 (13%) developed HCC after 79 (7-88) months. The 8-year cumulative probability of HCC was 17%, without differences between patients with or without cirrhosis regression [19% (95% CI 6-50%) vs. 14% (95% CI 4-44%), p=0.88]. Patients who developed or did not an HCC had similar rates of residual cirrhosis (p=1.0), collagen content (p=0.48), METAVIR activity (p=0.34), portal inflammation (p=0.06) and steatosis (p=0.17). At baseline, patients who developed an HCC had higher γ GT (HR 1.03, 95% CI 1.00-1.06; p=0.014) and glucose (HR 1.02, 95% CI 1.00-1.02; p=0.012) values; moreover, they had increased Forns Score (HR 12.8, 95% CI 1.14-143.9; p=0.039), Lok Index (HR 6.24, 95% CI 1.03-37.6; p=0.046) and PLF (HR 19.3, 95% CI 1.72-217.6; p=0.016) values.

One regressor died of lung cancer. The 8-year cumulative survival probability was 97%, independently on cirrhosis regression (96% vs. 100%, $p=1.0$) or HCC (100% vs. 97%, $p=1.0$). **CONCLUSIONS:** Post-SVR cirrhosis regression does not prevent HCC occurrence. This article is protected by copyright. All rights reserved.

[Evaluating screening approaches for hepatocellular carcinoma in a cohort of HCV related cirrhosis patients from the Veteran's Affairs Health Care System.](#) Tayob N1, Richardson P2,3, White DL2,3, Yu X4, Davila JA2,3, Kanwal F2,3, Feng Z5, El-Serag HB2,3. BMC Med Res Methodol. 2018 Jan 4;18(1):1. doi: 10.1186/s12874-017-0458-6.

BACKGROUND: Hepatocellular carcinoma (HCC) has limited treatment options in patients with advanced stage disease and early detection of HCC through surveillance programs is a key component towards reducing mortality. The current practice guidelines recommend that high-risk cirrhosis patients are screened every six months with ultrasonography but these are done in local hospitals with variable quality leading to disagreement about the benefit of HCC surveillance. The well-established diagnostic biomarker α -Fetoprotein (AFP) is used widely in screening but the reported performance varies widely across studies. We evaluate two biomarker screening approaches, a six-month risk prediction model and a parametric empirical Bayes (PEB) algorithm, in terms of their ability to improve the likelihood of early detection of HCC compared to current AFP alone when applied prospectively in a future study. **METHODS:** We used electronic medical records from the Department of Veterans Affairs Hepatitis C Clinical Case Registry to construct our analysis cohort, which consists of serial AFP tests in 11,222 cirrhosis control patients and 902 HCC cases prior to their HCC diagnosis. The six-month risk prediction model incorporates routinely measured laboratory tests, age, the rate of change in AFP over the past year with the current AFP. The PEB algorithm incorporates prior AFP screening values to identify patients with a significant elevated level of AFP at their current screen. We split the analysis cohort into independent training and validation datasets. All model fitting and parameter estimation was performed using the training data and the algorithm performance was assessed by applying each approach to patients in the validation dataset. **RESULTS:** When the screening-level false positive rate was set at 10%, the patient-level true positive rate using current AFP alone was 53.88% while the patient-level true positive rate for the six-month risk prediction model was 58.09% (4.21% increase) and PEB approach was 63.64% (9.76% increase). Both screening approaches identify a greater proportion of HCC cases earlier than using AFP alone. **CONCLUSIONS:** The two approaches show greater potential to improve early detection of HCC compared to using the current AFP only and are worthy of further study.

[Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis.](#) Tang A1,2, Hallouch O3, Chernyak V4, Kamaya A5, Sirlin CB6. Abdom Radiol (NY). 2018 Jan;43(1):13-25. doi: 10.1007/s00261-017-1209-1.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer mortality worldwide. Incidence rates of liver cancer vary widely between geographic regions and are highest in Eastern Asia and sub-Saharan Africa. In the United States, the incidence of HCC has increased since the 1980s. HCC detection at an early stage through surveillance and curative therapy has considerably improved the 5-year survival. Therefore, medical societies advocate systematic screening and surveillance of target populations at particularly high risk for developing HCC to facilitate early-stage detection. Risk factors for HCC include cirrhosis, chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV),

excess alcohol consumption, non-alcoholic fatty liver disease, family history of HCC, obesity, type 2 diabetes mellitus, and smoking. Medical societies utilize risk estimates to define target patient populations in which imaging surveillance is recommended (risk above threshold) or in which the benefits of surveillance are uncertain (risk unknown or below threshold). All medical societies currently recommend screening and surveillance in patients with cirrhosis and subsets of patients with chronic HBV; some societies also include patients with stage 3 fibrosis due to HCV as well as additional groups. Thus, target population definitions vary between regions, reflecting cultural, demographic, economic, healthcare priority, and biological differences. The Liver Imaging Reporting and Data System (LI-RADS) defines different patient populations for surveillance and for diagnosis and staging. We also discuss general trends pertaining to geographic region, age, gender, ethnicity, impact of surveillance on survival, mortality, and future trends.