



JUNE 2018

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Incidence and prevalence of antibody to hepatitis C virus in FDNY first responders before and after work at the World Trade Center disaster site.](#) Webber MP^{1,2}, Liu Y², Cohen HW¹, et al. Am J Ind Med. 2018 Jun 20. doi: 10.1002/ajim.22871. [Epub ahead of print]

BACKGROUND: The goals of this study were to assess the impact of work at the World Trade Center (WTC) site in relation to new, post-9/11/2001 (9/11) antibody to hepatitis C Virus (anti-HCV); and, evaluate secular trends in WTC-exposed male Fire Department of New York City (FDNY) Firefighters and Emergency Medical Services (EMS) responders. **METHODS:** FDNY monitors responder health through physical exams and routine blood work. We used descriptive statistics to compare trans-9/11 and post-9/11 incidence and to assess trends in prevalence from 2000 to 2012. **RESULTS:** Trans-9/11 incidence of new anti-HCV was 0.42 per 100 persons compared with post-9/11 incidence of 0.34 ($P = 0.68$). Overall seroprevalence was 1.3%; rates declined from 1.79 per 100 to 0.49 per 100 over time ($P < 0.0001$). **CONCLUSIONS:** Work at the WTC was not associated with new infection. Biennial seroprevalence in responders declined over time, supporting the FDNY decision to discontinue routine annual testing in this cohort.

[Sofosbuvir in combination with daclatasvir or simeprevir for 12 weeks in non-cirrhotic subjects chronically infected with hepatitis C virus genotype 1: a randomized clinical trial.](#)

Junior HP¹, Bricks G², Grandi G², Senise JF², Filho AC². Clin Microbiol Infect. 2018 Jun 12. pii: S1198-743X(18)30466-X. doi: 10.1016/j.cmi.2018.06.007. [Epub ahead of print]

OBJECTIVES: This study aimed to investigate the efficacy and safety of sofosbuvir plus daclatasvir (SOF+DCV) or simeprevir (SOF+SMV) in a randomized, open-label, non-inferiority trial of patients infected with hepatitis c virus (HCV) genotype 1, who were previously unresponsive to pegylated interferon and ribavirin or were treatment-naïve. **METHODS:** Patients were randomly assigned to receive SOF (400 mg once daily) plus DCV (60 mg once daily) or SMV (150 mg once daily) for 12 weeks. The analysis included all participants who received at least one dose of the study drugs. The primary endpoint was sustained virological response 12 weeks after ending treatment (SVR₁₂; HCV RNA measured using COBAS TaqMan RT-PCR [lower limit of detection and quantification of 12 UI/mL]). This study is registered at ClinicalTrials.gov (NCT02624063). **RESULTS:** A total of 125 of 127 enrolled and randomized patients started treatment (SOF+DCV in 65, SOF+SMV in 60). SVR₁₂ was achieved in 121

(96.85%) patients (65 on SOF+DCV [100%; 95% confidence interval (CI), 94.5% to 100%] and 56 on SOF+SMV [93.3%, 95% CI, 83.8% to 98.2%]; absolute difference, 6.6%; 95% CI, -15.0% to 0.0%). The most common adverse events were fatigue (n = 32 [25.6%]), headache (n = 27 [21.6%]), and mood swings (n = 24 [19.2%]). No patients discontinued. **CONCLUSION:** The overall SVR rate was 96.9%; SOF+DCV (100%) was higher than that of SOF+SMV (93.3%). Despite no statistically significant intergroup difference in SVR12 rates, the non-inferiority of SOF+SMV to SOF+DCV could not be established since the difference in efficacy was clinically relevant.

Hepatitis C Testing, Status and Treatment among Marginalized People Who Use Drugs in an Inner City Setting: An Observational Cohort Study.

Boucher LM1,2, Bayoumi AM3,4, Mark AE5, et al. *Subst Use Misuse*. 2018 Jun 22:1-13. doi: 10.1080/10826084.2018.1485699. [Epub ahead of print]

BACKGROUND: Chronic hepatitis C virus (HCV) infection is common among people who inject drugs (PWID) and is associated with morbidity and premature death. Although HCV can be cured, treatment may be inaccessible. We studied HCV testing, status and treatment among marginalized people who use drugs in Ottawa, Canada, a setting with universal insurance coverage for physician services. **METHODS:** We analyzed data from the Participatory Research in Ottawa: Understanding Drugs study, a cross-sectional, peer-administered survey of people who use drugs from 2012 to 2013. We linked responses to population-based health administrative databases and used multivariable Poisson regression to identify factors independently associated with self-reported HCV testing, self-reported positive HCV status, and database-determined engagement in HCV treatment. **RESULTS:** Among 663 participants, 562 (84.8%) reported testing for HCV and 258 (45.9%) reported HCV-positive status. In multivariable analysis, HCV-positive status was associated with female gender (RR 1.27; 95%CI 1.04 to 1.55), advancing age (RR 1.03/year; 95%CI 1.02 to 1.04), receiving disability payments (RR 1.42; 95%CI 1.06 to 1.91), injecting drugs (RR 5.11; 95%CI 2.64 to 9.91), ever injecting with a used needle (RR 1.30; 95%CI 1.12 to 1.52), and ever having taken methadone (RR 1.26; 95%CI 1.05 to 1.52). Of HCV positive participants, 196 (76%) were engaged in primary care but only 23 (8.9%) had received HCV therapy. **CONCLUSIONS/IMPORTANCE:** Although HCV testing and positive status rates are high among PWID in our study, few have received HCV treatment. Innovative initiatives to increase access to HCV treatment for PWID are urgently needed.

Psychiatric and functional neuroimaging abnormalities in chronic hepatitis C virus patients: Is vasculitis a contributing factor?

Zayed HS1, Amin A2, Alsirafy S2, Elsayed ND2, Abo Elfadl S3, Nasreldin M4, Enaba D4, Nawito Z5. *Arab J Gastroenterol*. 2018 Jun 20. pii: S1687-1979(18)30048-0. doi: 10.1016/j.ajg.2018.06.003. [Epub ahead of print]

BACKGROUND AND STUDY AIMS: Central nervous system (CNS) involvement in hepatitis C virus (HCV) infection has different facets such as anxiety, depression, cognitive impairment and vasculitis. We were interested in detecting subclinical CNS involvement in chronic HCV infected subjects with and without systemic vasculitis. **PATIENTS AND METHODS:** Nineteen patients (15 females and 4 males) with chronic HCV infection (mean age 46.5 ± 7 and mean duration since diagnosis of HCV infection 4.7 ± 4 years, including 6 (32%) Child-Pugh class A cirrhotic patients) and 30 age, sex and education matched healthy control subjects were studied. Thirteen patients had associated vasculitis. Patients and control subjects were assessed using the

block design and comprehension subtests of Wechsler Bellevue Adult Intelligence Scale, Wechsler Memory scale (WMS), Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). Brain HMPAO Single Photon Emission Computed Tomography (SPECT) was performed for HCV patients. **RESULTS:** Patients with HCV had lower scores on the block design test compared to control subjects (8.37 ± 1.89 versus 10.37 ± 1.47 , $p < 0.001$), lower total WMS scores (43.15 ± 10.49 versus 60.27 ± 8.08 , $p < 0.001$) and higher anxiety and depression scores (16.94 ± 10.46 and 37.17 ± 10.38 versus 10.3 ± 4.67 and 28.9 ± 5.99 , $p = 0.004$ and 0.001 , respectively). Total WMS were lower in HCV patients with vasculitis compared to those without vasculitis (39.14 ± 9.3 versus 51.17 ± 8.3 , $p = 0.019$) while the block design and comprehension tests, BAI and BDI were not significantly different between both groups. The block design and comprehension tests, WMS, BAI and BDI were not significantly different between cirrhotic and non-cirrhotic patients. Seven patients had different patterns of cerebral hypoperfusion on SPECT, and all of them had associated vasculitis. Abnormal SPECT was associated with lower total WMS scores (35.87 ± 10.8 versus 46.79 ± 8.6 in those with normal SPECT, $p = 0.049$). **CONCLUSIONS:** Vasculitis may contribute to the development of neuropsychiatric involvement in HCV patients.

[Change in hepatic profile in hepatitis C virus genotype 4 patients with compensated cirrhosis receiving ombitasvir, paritaprevir, and ritonavir plus ribavirin: a subanalysis of the AGATE-II study.](#) Waked I1, Esmat G2, Fouad R2, Allam N1, et al. J Med Virol. 2018 Jun 13. doi: 10.1002/jmv.25243. [Epub ahead of print]

BACKGROUND: In AGATE-II, treatment with ombitasvir co-formulated with paritaprevir/ritonavir plus ribavirin (RBV) in Egyptians infected with hepatitis C virus genotype 4 (HCV GT4) resulted in high rates of sustained virologic response at Post-Treatment Week 12. This subanalysis examined the effects of treatment in AGATE-II on liver biomarkers in patients with compensated cirrhosis. **METHODS:** AGATE-II was a phase 3, open-label, partly randomized trial of once-daily ombitasvir/paritaprevir/ritonavir with weight-based RBV in treatment-naïve or treatment-experienced patients. Patients without cirrhosis received treatment for 12 weeks and patients with compensated cirrhosis were randomized 1:1 to the same regimen for either 12 weeks or 24 weeks. **RESULTS:** Sixty patients with compensated cirrhosis were randomized to treatment for 12 weeks ($n=31$) or 24 weeks ($n=29$). In the 12-week arm, significant improvements were observed in biomarkers of liver injury (alanine aminotransferase: -53.7 U/L, $p < 0.001$; aspartate aminotransferase: -35.9 U/L, $p < 0.001$) and liver fibrosis (aspartate aminotransferase to platelet ratio index: -0.987 , $p < 0.001$; fibrosis-4 index: -1.165 , $p < 0.001$). Similar results were reported in the 24-week arm. **CONCLUSION:** Treatment with ombitasvir/paritaprevir/ritonavir plus RBV in HCV GT4-infected Egyptians with compensated cirrhosis resulted in improvements in certain biomarkers of liver synthetic function, injury, and fibrosis, independent of treatment duration. This article is protected by copyright. All rights reserved.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[miR-215 Enhances HCV Replication by Targeting TRIM22 and Inactivating NF- \$\kappa\$ B Signaling.](#) Tian H#1, He Z#2. Yonsei Med J. 2018 Jun;59(4):511-518. doi: 10.3349/ymj.2018.59.4.511.

PURPOSE: Hepatitis C virus (HCV) infection is a major cause of liver disease. Several miRNAs have been found to be associated with HCV infection. This study aimed to investigate the functional roles and possible molecular mechanisms of miR-215 in HCV replication. **MATERIALS AND METHODS:** The expression levels of miR-215 and TRIM22 were detected by quantitative real-time PCR (qRT-PCR) and western blot analysis in Con1b subgenomic genotype 1b HCV replicon cells (Con1b cells) and JFH1 full genome infecting Huh7.5.1 cells (Huh7.5.1 cells). HCV RNA levels were measured by qRT-PCR. The protein levels of NS3, NS5A, p65 subunit of NF- κ B (p65), and phosphorylated p65 (p-p65) were determined by western blot analysis. The relationship between miR-215 and TRIM22 were explored by target prediction and luciferase reporter analysis. **RESULTS:** miR-215 overexpression enhanced HCV replication in Con1b cells, while miR-215 knockdown suppressed HCV replication in Huh7.5.1 cells. TRIM22 was confirmed to be a direct target of miR-215. TRIM22 upregulation resulted in a decline in HCV replication, while TRIM22 inhibition led to enhancement of HCV replication. Additionally, exogenous expression of TRIM22 reversed the facilitating effect of miR-215 on HCV replication, while TRIM22 downregulation counteracted the inhibitory effect of miR-215 knockdown on HCV replication. Furthermore, miR-215 targeted TRIM22 to block the NF- κ B pathway, and exerted a positively regulatory role on HCV replication. **CONCLUSION:** miR-215 facilitated HCV replication via inactivation of the NF- κ B pathway by inhibiting TRIM22, providing a novel potential target for HCV infection.

[Role of T-Helper 9 Cells in Chronic Hepatitis C-Infected Patients.](#) Ali ME1, El-Badawy O2, Afifi NA3, Eldin AS4, Hassan EA5, Halby HM6, El-Mokhtar MA7. *Viruses*. 2018 Jun 24;10(7). pii: E341. doi: 10.3390/v10070341.

Hepatitis C virus is a hepatotropic virus that is transmitted parenterally. Viral infections are usually associated with modulations of the immune cells, leading to enhanced viral survival and spreading, and accordingly, life-threatening complications. Recently, it has been proposed that a new subset of T-helper, named T-helper 9, is involved in the pathogenesis of different immunopathological conditions, such as allergies, tumors, and viral infections. Some studies reported a protective role, and others described a pathogenic potential for the T-helper 9 cells. Here, we present evidence that T-helper 9 cells are dynamically increased with increasing the pathogenic strategy for hepatitis C virus (HCV). Furthermore, viral clearance is associated with a decrease in T-helper 9. The increase in T-helper 9 was paralleled with an increase in its receptor expression. Taken together, our data suggest that T-helper 9 cells play an important role in the pathogenesis of HCV, and is directly associated with HCV-related complications.

[Differential modulation of hepatitis C virus replication and innate immune pathways by synthetic calcitriol-analogs.](#) Saleh M1, Welsch C1, Cai C1, et al. *J Steroid Biochem Mol Biol*. 2018 Jun 7. pii: S0960-0760(18)30202-4. doi: 10.1016/j.jsbmb.2018.06.008. [Epub ahead of print]

BACKGROUND AND AIMS: Vitamin D signaling is involved in infectious and non-infectious liver diseases, yet the natural vitamin D metabolites are suboptimal therapeutic agents. In the present study, we therefore aimed to explore the potential and mechanism of selected calcitriol analogs to regulate the hepatocellular transcriptome and to inhibit hepatitis C virus (HCV) in comparison with calcitriol. **METHODS:** Human hepatoma cell lines and primary human macrophages were stimulated with calcitriol and selected calcitriol analogs. The effect of

calcitriol and its derivatives on hepatocellular gene expression and vitamin D receptor (VDR) signaling as well as on replication of HCV were assessed by quantitative PCR, microarray analyses and in silico analyses of ligand-VDR complexes. **RESULTS:** The structurally related vitamin D analogs calcipotriol and tacalcitol, but not calcitriol itself, suppressed HCV replication in a VDR-dependent manner. Using a residue-interaction network approach we outline structural and functional differences between VDR-ligand complexes. In particular we find characteristics in the VDR structure bound to calcipotriol with distinct local residue interaction patterns that affect key functional residues that pertain to the VDR charge clamp, H397 and F422, a VDR regulatory element for interaction with co-activators and -repressors. As a consequence, we show calcipotriol in comparison to calcitriol to induce stronger regulatory actions on the transcriptome of hepatocytes and macrophages including key antimicrobial peptides. **CONCLUSION:** Calcipotriol induces local structure rearrangements in VDR that could possibly translate into a superior clinical potential to execute important non-classical vitamin D effects such as inhibition of HCV replication.

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

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

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

Taken together, our findings clearly demonstrate that targeting OPN may provide opportunities for therapeutic intervention of HCV pathogenesis.

[A near full-length open reading frame next generation sequencing assay for genotyping and identification of resistance-associated variants in hepatitis C virus.](#)

Pedersen MS1, Fahnøe U2, Hansen TA3, Pedersen AG4, Jenssen H5, Bukh J2, Schønning K6. J Clin Virol. 2018 Jun 1;105:49-56. doi: 10.1016/j.jcv.2018.05.012. [Epub ahead of print]

BACKGROUND: The current treatment options for hepatitis C virus (HCV), based on direct acting antivirals (DAA), are dependent on virus genotype and previous treatment experience. Treatment failures have been associated with detection of resistance-associated substitutions (RASs) in the DAA targets of HCV, the NS3, NS5A and NS5 B proteins. **OBJECTIVE:** To develop a next generation sequencing based method that provides genotype and detection of HCV NS3, NS5A, and NS5 B RASs without prior knowledge of sample genotype. **STUDY DESIGN:** In total, 101 residual plasma samples from patients with HCV covering 10 different viral subtypes across 4 genotypes with viral loads of 3.84-7.61 Log IU/mL were included. All samples were de-identified and consequently prior treatment status for patients was unknown. Almost full open reading frame amplicons (~ 9 kb) were generated using RT-PCR with a single primer set. The resulting amplicons were sequenced with high throughput sequencing and analysed using an in-house developed script for detecting RASs. **RESULTS:** The method successfully amplified and sequenced 94% (95/101) of samples with an average coverage of 14,035; four of six failed samples were genotype 4a. Samples analysed twice yielded reproducible nucleotide frequencies across all sites. RASs were detected in 21/95 (22%) samples at a 15% threshold. The method identified one patient infected with two genotype 2b variants, and the presence of subgenomic deletion variants in 8 (8.4%) of 95 successfully sequenced samples. **CONCLUSIONS:** The presented method may provide identification of HCV genotype, RASs detection, and detect multiple HCV infection without prior knowledge of sample genotype.

HIV/HCV COINFECTION

[Hepatitis C Virus Elimination in the Human Immunodeficiency Virus-Coinfected Population: Leveraging the Existing Human Immunodeficiency Virus Infrastructure.](#)

Clement ME1, Collins LF2, Wilder JM3, Mugavero M4, Barker T5, Naggie S6. Infect Dis Clin North Am. 2018 Jun;32(2):407-423. doi: 10.1016/j.idc.2018.02.005.

The objective of this review is to consider how existing human immunodeficiency virus (HIV) infrastructure may be leveraged to inform and improve hepatitis C virus (HCV) treatment efforts in the HIV-HCV coinfecting population. Current gaps in HCV care relevant to the care continuum are reviewed. Successes in HIV treatment are then applied to the HCV treatment model for coinfecting patients. Finally, the authors give examples of HCV treatment strategies for coinfecting patients in both domestic and international settings.

[Adverse Effects of Direct Acting Antivirals in HIV/HCV Coinfected Patients: A 4-Year Experience in Miami, Florida.](#)

Gonzales Zamora JA1. Diseases. 2018 Jun 19;6(2). pii: E51. doi: 10.3390/diseases6020051.

INTRODUCTION: The new direct acting antivirals (DAA) have demonstrated low rates of adverse effects in controlled studies. However, real world-studies have disclosed emerging

toxicities and drug-drug interactions in special populations. **METHODS:** We conducted a retrospective review of HIV/HCV coinfecting patients who were treated with DAA at Jackson Memorial Hospital from 2014 to 2017. Our aim was to determine the adverse effects (AE) and factors that are associated with AE in HIV/HCV individuals who are treated with DAA.

RESULTS: There were 78 coinfecting patients treated with DAA. AE that were secondary to DAA were reported by 21 (26.9%) patients. The most common AE were fatigue (47.6%), gastrointestinal symptoms (38.1%), anemia (14.3%), and headache (14.3%). In comparison with the rest of the study cohort, the patients who developed AE were more often Caucasian (33.3% vs. 10.5%, $p = 0.017$) and were more frequently treated with PrOD/Ribavirin (9.5% vs. 0%, $p = 0.018$). In terms of antiretroviral therapy (ART), there was a trend towards a more frequent use of TDF/FTC + NNRTI (33.3% vs. 14%, $p = 0.055$). **CONCLUSIONS:** These findings demonstrated good tolerability of DAAs in HIV/HCV coinfecting patients. More real-world studies are needed to explore the variables that are associated with AE.

[Real-World Clinical Efficacy and Tolerability of Direct-Acting Antivirals in Hepatitis C Monoinfection Compared to Hepatitis C/HIV Coinfection in a Community Care Setting.](#)

Vijay G1, Rajib HM1, Mazin K1, et al. Gut Liver. 2018 Jun 22. doi: 10.5009/gnl18004. [Epub ahead of print]

BACKGROUND/AIMS: Limited data exist comparing the safety and efficacy of direct-acting antivirals (DAAs) in hepatitis C virus (HCV) monoinfected and HCV/human immunodeficiency virus (HIV) coinfecting patients in the real-world clinic practice setting. **METHODS:** All HCV monoinfected and HCV/HIV coinfecting patients treated with DAAs between January 2014 and October 2017 in community clinic settings were retrospectively analyzed. Pretreatment baseline patient characteristics, treatment efficacy, factors affecting sustained virologic response at 12 weeks (SVR 12) after treatment, and adverse reactions were compared between the groups.

RESULTS: A total of 327 patients were included in the study, of which 253 were HCV monoinfected, and 74 were HCV/HIV coinfecting. There was a statistically significant difference observed in SVR 12 when comparing HCV monoinfection and HCV/HIV coinfection (94% and 84%, respectively, $p=0.005$). However, there were no significant factors identified as a predictor of a reduced response. The most common adverse effect was fatigue (27%). No significant drug interaction was observed between DAA and antiretroviral therapy. None of the patients discontinued the treatment due to adverse events. **CONCLUSIONS:** In a real-world setting, DAA regimens have lower SVR 12 in HCV/HIV coinfection than in HCV monoinfection. Further studies involving a higher number of HCV/HIV coinfecting patients are needed to identify real predictors of a reduced response.

[Incidence of Acute Kidney Injury in Patients Coinfected with HIV and Hepatitis C Virus Receiving Tenofovir Disoproxil Fumarate and Ledipasvir/Sofosbuvir in a Real-World,](#)

[Urban.](#) Ryan White Clinic. Michal JL1, Rab S2, Patel M2, Kyle AW3, Miller LS4, Easley KA5, Kalapila AG6. AIDS Res Hum Retroviruses. 2018 Jun 19. doi: 10.1089/AID.2017.0271. [Epub ahead of print]

Ledipasvir/sofosbuvir (LDV/SOF), an antiviral treatment for hepatitis C virus (HCV), and tenofovir disoproxil fumarate (TDF), an antiretroviral for treating human immunodeficiency virus (HIV), may be coadministered in patients coinfecting with these viruses. A drug interaction between LDV and TDF could increase TDF-associated nephrotoxicity rates; however, there is minimal clinical evidence describing acute kidney injury (AKI) rates in this population. This

study was conducted at a Ryan White-funded facility in Atlanta, Georgia, that cares for over 5,000 patients with AIDS. This retrospective cohort used chart review to assess occurrence of and risk factors for AKI in HIV/HCV-coinfected patients receiving LDV/SOF and antiretroviral therapy (ART). AKI rates were compared between TDF-containing and non-TDF-containing ART groups according to Kidney Disease Improving Global Outcomes (KDIGO) criteria. Additional evaluated risk factors for AKI included chronic kidney disease and use of boosted protease inhibitor-based ART. In the 117 included patients, the overall incidence of AKI was 27.3%. AKI occurred more frequently in the non-TDF group (13/86, 15.1% vs. 19/31, 61.3%, $p < .001$). All AKI was KDIGO stage 1. From multivariable logistic regression, the only independent predictor of AKI was treatment with non-TDF relative to TDF (adjusted odds ratio 6.51, 95% confidence interval 2.34-18.10, $p < .001$). In this real-world cohort of HIV/HCV-coinfected patients, KDIGO-defined AKI was common, but occurred less frequently in patients receiving TDF-based ART. Our study suggests that patients with normal baseline renal function can be safely treated with TDF and LDV/SOF without significant nephrotoxicity if renal function is closely monitored.

[HIV/HCV Co-infection: Burden of Disease and Care Strategies in Appalachia.](#) Moorman JP1,2, Krolikowski MR3, Mathis SM4,5, Pack RP4,5. Curr HIV/AIDS Rep. 2018 Jun 21. doi: 10.1007/s11904-018-0404-1. [Epub ahead of print]

PURPOSE OF REVIEW: The purpose of this review is to address infection with HIV and hepatitis C in the Appalachian region of the USA and the driving forces underlying this epidemic. We seek to discuss epidemiology of disease and the possible interventions to reduce incidence and burden of disease in this resource-limited area. **RECENT FINDINGS:** The rise of the opioid crisis has fueled a rise in new hepatitis C infection, and a rise in new HIV infection is expected to follow. Injection drug use has directly contributed to the epidemic and continues to remain a risk factor. Men who have sex with men remains a significant risk factor for HIV acquisition as well. Progress has been made in the battle against HIV and, to a lesser extent, hepatitis C, but much more can be done. Limited data on co-infection with HIV/HCV are currently available for this at-risk region, but it is clear that Appalachia is highly vulnerable to co-infection outbreaks. A multipronged approach that includes advances in assessment of co-infection and education for both patients and clinicians can help to recognize, manage, and ideally prevent these illnesses.

[Implementing Treatment of Opioid-Use Disorder in Rural Settings: a Focus on HIV and Hepatitis C Prevention and Treatment.](#) Havens JR1, Walsh SL2, Korthuis PT3, Fiellin DA4,5. Curr HIV/AIDS Rep. 2018 Jun 9. doi: 10.1007/s11904-018-0402-3. [Epub ahead of print]

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

the rural U.S. will require a concerted effort to implement effective treatments according to national standards.

[Integrated Models of Care for Individuals with Opioid Use Disorder: How Do We Prevent HIV and HCV?](#)

Rich KM1, Bia J2, Altice FL1,3, Feinberg J4. *Curr HIV/AIDS Rep.* 2018 Jun;15(3):266-275. doi: 10.1007/s11904-018-0396-x.

PURPOSE OF REVIEW: To describe models of integrated and co-located care for opioid use disorder (OUD), hepatitis C (HCV), and HIV. **RECENT FINDINGS:** The design and scale-up of multidisciplinary care models that engage, retain, and treat individuals with HIV, HCV, and OUD are critical to preventing continued spread of HIV and HCV. We identified 17 models within primary care (N = 3), HIV specialty care (N = 5), opioid treatment programs (N = 6), transitional clinics (N = 2), and community-based harm reduction programs (N = 1), as well as two emerging models. Key components of such models are the provision of (1) medication-assisted treatment for OUD, (2) HIV and HCV treatment, (3) HIV pre-exposure prophylaxis, and (4) behavioral health services. Research is needed to understand differences in effectiveness between co-located and fully integrated care, combat the deleterious racial and ethnic legacies of the "War on Drugs," and inform the delivery of psychiatric care. Increased access to harm reduction services is crucial.

[Challenges Facing a Rural Opioid Epidemic: Treatment and Prevention of HIV and Hepatitis C.](#)

Schranz AJ1, Barrett J2, Hurt CB3, Malvestutto C2, Miller WC4. *Curr HIV/AIDS Rep.* 2018 Jun;15(3):245-254. doi: 10.1007/s11904-018-0393-0.

PURPOSE OF REVIEW: This article reviews recent epidemiologic trends in HIV and hepatitis C virus (HCV) and strategies for treatment and prevention of these infections as they relate to the opioid epidemic. **RECENT FINDINGS:** Among people who inject drugs (PWID) in the United States (US), HIV diagnoses are decreasing, while HCV is increasing. Care for HIV and HCV relies heavily on specialist infrastructure, which is lacking in rural areas. Antiretrovirals for HIV and direct-acting antivirals for HCV are effective among PWID, yet multiple barriers make it difficult for rural injectors to access these treatments. Similarly, access to syringe service programs, medication-assisted therapy for opioid addiction, and pre-exposure prophylaxis for HIV are all limited in rural areas. Previous research on HIV and HCV among PWID has focused on urban or international populations, yet the US opioid epidemic is moving away from metropolitan centers. Increasing rurality of opioid injection brings unique challenges in treatment and prevention. Research into the care of HIV, HCV, and opioid use disorder among rural populations is urgently needed.

[Modeling NAFLD Disease Burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030.](#) Estes C1, Anstee QM2, Arias-Loste MT3, et al. J Hepatol. 2018 Jun 7. pii: S0168-8278(18)32121-4. doi: 10.1016/j.jhep.2018.05.036. [Epub ahead of print]

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) with resulting nonalcoholic steatohepatitis (NASH) are increasingly a cause of cirrhosis and hepatocellular carcinoma (HCC) globally. This burden is expected to increase as epidemics of obesity, diabetes and metabolic syndrome continue to grow. The goal of this analysis was to use a Markov model to forecast NAFLD disease burden using currently available data. **METHODS:** A model was used to estimate NAFLD and NASH disease progression in 8 countries based on data for adult prevalence of obesity and type 2 diabetes mellitus (DM). Published estimates and expert consensus were used to build and validate the model projections. **RESULTS:** If obesity and DM level off in the future, we project a modest growth in total NAFLD cases (0-30%), between 2016-2030, with the highest growth in China as result of urbanization and the lowest growth in Japan as result of a shrinking population. However, at the same time, NASH prevalence will increase 15-56%, while liver mortality and advanced liver disease will more than double as result of an aging/increasing population. **CONCLUSIONS:** NAFLD and NASH represent a large and growing public health problem and efforts to understand this epidemic and to mitigate the disease burden are needed. If obesity and DM continue to increase at current and historical rates, both NAFLD and NASH prevalence are expected to increase. Since both are reversible, public health campaigns to increase awareness and diagnosis, and to promote diet and exercise can help manage the growth in future disease burden. **LAY SUMMARY:** Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) can lead to advanced liver disease, and are occurring in increasing numbers in tandem with epidemics of obesity and diabetes. A mathematical model was built to understand how the disease burden associated with NAFLD and NASH will change over time. Results suggest increasing numbers of cases of advanced liver disease and liver-related mortality in the coming years.

[Five Questions Concerning Managing Hepatitis C in the Justice System: Finding Practical Solutions for Hepatitis C Virus Elimination.](#) Spaulding AC1, Adee MG2, Lawrence RT3, Chhatwal J4, von Oehsen W5. Infect Dis Clin North Am. 2018 Jun;32(2):323-345. doi: 10.1016/j.idc.2018.02.014.

An estimated 30% of Americans with hepatitis C virus (HCV) pass through a jail or prison annually. One in 7 incarcerated persons is viremic. Screening and treatment is cost-effective and beneficial to society as a whole. Yet at current (2018) levels of funding for HCV management, prisons are not aggressively seeking cases; few incarcerated persons with HCV actually receive treatment. This article explores barriers to screening for and treating hepatitis C in state prisons, and ways that states may overcome these barriers, such as nominal pricing. While high prices for direct-acting antivirals discourage treatment, potential strategies exist to lower prices.

[A Guide to the Economics of Hepatitis C Virus Cure in 2017.](#) Linas BP1, Nolen S2. Infect Dis Clin North Am. 2018 Jun;32(2):447-459. doi: 10.1016/j.idc.2018.02.013.

This commentary reviews the core principals of cost-effectiveness and applies them to the rapidly evolving context of hepatitis C virus treatment in the United States. The article provides a foundation of evidence that hepatitis C virus treatment provides good economic value, even though it is expensive, and even when treating people who inject drugs who are at high risk for hepatitis C virus reinfection. The price of medications has decreased, but the high price continues to limit access to care. This wedge between cost effectiveness and affordability stands front and center as one of the leading obstacles to elimination.

[Depression, fatigue and neurocognitive deficits in chronic hepatitis C.](#) Yeoh SW1, Holmes ACN2, Saling MM3,4,5, Everall IP2,6,7, Nicoll AJ8,9. *Hepatology Int.* 2018 Jun 21. doi: 10.1007/s12072-018-9879-5. [Epub ahead of print]

Patients with chronic hepatitis C virus (HCV) infection experience a range of symptoms including depression, fatigue and neurocognitive deficits, impairing quality of life. Depression, in particular, may be reactive to increased psychosocial stress, and the physical symptoms of advanced HCV or associated comorbidities. However, even patients at an early stage of HCV infection, with minimal hepatic inflammation or comorbidities, report more depressive symptoms and fatigue than the general population. Similarly, specific neurocognitive deficits occur in early stage HCV infection and are independent of the presence of depression or encephalopathy. Therefore, intracerebral neurobiological changes associated with HCV may potentially explain these symptoms. These changes may arise from infiltration of the brain by peripherally induced cytokines, as well as direct neuropathic effects of HCV viral particles penetrating the blood-brain barrier. These phenomena parallel those reported in human immunodeficiency virus (HIV) infection. HCV-associated intracerebral changes include upregulated inflammatory responses, altered neurotransmitter levels, hormonal dysregulation, and release of neurotoxic substances. These may subsequently lead to abnormal neuronal conduction and function in areas of the brain governing affective responses, emotional processing, motivation, attention and concentration. Although direct-acting antiviral medications lead to high rates of HCV clearance, intracerebral changes may not be subsequently reversed and symptoms of depression, fatigue and neurocognitive deficits may persist. There is an ongoing role for multidisciplinary care and pharmacotherapy to manage these symptoms in HCV patients. Furthermore, there may be opportunities for future therapies to specifically target and ameliorate HCV-associated intracerebral changes.

[Development of a Comprehensive Dataset of Hepatitis C Patients and Examination of Disease Epidemiology in the United States, 2013-2016.](#) Chirikov VV1, Marx SE2, Manthana SR3, Strezewski JP3, Saab S4. *Adv Ther.* 2018 Jun 9. doi: 10.1007/s12325-018-0721-1. [Epub ahead of print]

INTRODUCTION: Chronic infection with hepatitis C virus (HCV) is a leading cause of liver disease and infectious disease deaths. While recent and emerging treatment options for HCV patients have enabled higher rates of sustained virologic response (SVR), the demographic, clinical, geographic, and payer characteristics of the estimated 3.4 million chronic HCV patients in the USA are poorly understood. The goal of this study was to create a dataset describing the current HCV patient landscape in the USA. **METHODS:** Data from two large national laboratory companies representing the majority of US patients screened for HCV antibody and/or tested for HCV RNA from 2013 through 2016 were organized into the present study dataset. Age, gender, payer channel, 3-digit ZIP code and ordering physician specialty, and 3-digit ZIP

code information were available for all patients. Among RNA-positive patients, additional clinical characteristics included HCV genotype, fibrosis stage, renal function, and HIV status. Initiating treatment and attaining cure were imputed using data-driven algorithms based on successive RNA viral load measurements. **RESULTS:** The number of RNA-positive HCV patients increased from 200,066 patients in 2013 to 469,550 in 2016. The availability of clinical data measurements and rates of treatment initiation increased over the study period, indicating improved care engagement for HCV patients. Treatment and cure rates varied by age, disease severity, geographic location, and payer channel. Sensitivity and specificity of the cure prediction algorithms were consistently above 0.90, validating the robustness of the data imputation approach. **CONCLUSION:** This is the largest, most comprehensive dataset available to describe the current US HCV patient landscape. Our results highlight that the epidemiology of HCV is evolving with an increasing number of patients who are younger and have milder disease than described in previous years. Results of this study should help guide efforts toward the elimination of HCV in this country. Future work will focus on factors associated with varying treatment and cure patterns and describing recent changes in the HCV patient landscape. **FUNDING:** AbbVie. Plain language summary available for this article.

[Long-Term Liver Disease, Treatment, and Mortality Outcomes Among 17,000 Persons Diagnosed with Chronic Hepatitis C Virus Infection: Current Chronic Hepatitis Cohort Study Status and Review of Findings.](#) Moorman AC1, Rupp LB2, Gordon SC2, et al. Infect Dis Clin North Am. 2018 Jun;32(2):253-268. doi: 10.1016/j.idc.2018.02.002.

Chronic Hepatitis Cohort Study (CHeCS) publications using data from "real-world" patients with hepatitis C virus (HCV) have described demographic disparities in access to care; rates of advanced liver disease, morbidity, and mortality (2.5%-3.5% per year during 2006-10, although only 19% of all CHeCS decedents, and just 30% of those with deaths attributed to liver disease, had HCV listed on death certificate); substantial comorbidities, such as diabetes, advanced liver fibrosis (29% prevalence), renal disease, and depression, and partial reversal of all these with successful antiviral therapy; patient risk behaviors; and use of noninvasive markers to assess liver disease.

[New Treatments Have Changed the Game: Hepatitis C Treatment in Primary Care.](#)

Facente SN1, Burk K2, Eagen K3, Mara ES4, Smith AA2, Lynch CS5. Infect Dis Clin North Am. 2018 Jun;32(2):313-322. doi: 10.1016/j.idc.2018.02.012.

In the pre-direct-acting antiviral era, hepatitis C virus (HCV) treatments were complex and largely managed by hepatologists, gastroenterologists, and infectious disease physicians. As direct-acting antivirals have driven up demand for treatment, the relative scarcity of these specialists has created a bottleneck effect, resulting in only a fraction of HCV-infected individuals offered treatment. The San Francisco Health Network is a safety net system of care. Its intervention was designed to be sustainable and scalable; with minimal time commitments for training providers, primary care-based HCV treatment increased 3-fold in a period of just over 3 years.

[Hepatitis C Care in the Department of Veterans Affairs: Building a Foundation for Success.](#) Belperio PS1, Chartier M2, Gonzalez RI3, Park AM4, Ross DB2, Morgan TR5, Backus LI6. Infect Dis Clin North Am. 2018 Jun;32(2):281-292. doi: 10.1016/j.idc.2018.02.011.

The Department of Veterans Affairs (VA) has made significant progress in treating hepatitis C virus, experiencing more than a 75% reduction in veterans remaining to be treated since the availability of oral direct-acting antivirals. Hepatitis C Innovation Teams use lean process improvement and system redesign, resulting in practice models that address gaps in care. The key to success is creative improvements in veteran access to providers, including expanded use of nonphysician providers, video telehealth, and electronic technologies. Population health management tools monitor and identify trends in care, helping the VA tailor care and address barriers.

[Localized US Efforts to Eliminate Hepatitis C](#). Gaudino A1, Gay B1, Garmon C2, et al. *Infect Dis Clin North Am*. 2018 Jun;32(2):293-311. doi: 10.1016/j.idc.2018.02.009.

The United States has national plans for the elimination of hepatitis C virus but much of US health care is organized on the state level and requires local solutions. This article describes the plans developed by New York, Massachusetts, and the city/county of San Francisco for hepatitis C virus elimination. Coalitions capitalize on existing resources and advocate for new resources to address barriers in hepatitis C virus care. Although each coalition has distinct plans, all share a commitment to groups that are disproportionately affected and are at risk for being excluded from advances in hepatitis C virus treatment and cure.

HEPATOCELLULAR (LIVER) CANCER

[Interaction Between Hepatocellular Carcinoma and Hepatitis C Eradication With Direct-acting Antiviral Therapy](#). Konjeti VR1, John BV2. *Curr Treat Options Gastroenterol*. 2018 Jun;16(2):203-214. doi: 10.1007/s11938-018-0178-y.

PURPOSE OF REVIEW: The approval of direct-acting antiviral (DAA) therapy has revolutionized hepatitis C virus (HCV) treatment. However, the publication of a study from Barcelona in 2016 raised concern for an increased risk of recurrence of hepatocellular carcinoma (HCC) after potentially curative therapy in patients receiving DAAs. This article reviews the current literature on the interaction between HCC and hepatitis C eradication with DAAs.

RECENT FINDINGS: Following publication of the initial observation in 2016, a number of studies have looked at the impact of active HCC on the success of antiviral therapy, as well as that of treatment with DAAs on both the occurrence and recurrence of HCC. The presence of active HCC decreases sustained virologic response (SVR) rates with DAAs. However, SVR rates improve in patients who have achieved complete radiological response or are treated post transplantation. With respect to occurrence of HCC after DAAs, many small single-center studies without a control group have documented high incidence. The rates are also higher when compared to those of historical controls treated with interferon, but these patients are not comparable because DAA-treated population is more likely to have advanced fibrosis or decompensation. In large studies that have included a control group (patients treated concurrently who did not achieve SVR), a decrease in the occurrence of HCC has been demonstrated. With regard to recurrence of HCC, while smaller single-center studies have shown an increase, larger studies with control group have not replicated those findings. However, methodological limitations in the published studies limit our ability to make a firm conclusion on both the occurrence and recurrence of HCC after DAA therapy. The presence of active HCC decreases treatment success rates with DAAs. Therefore, it is recommended that treatment of HCV in patients with HCC be deferred till there is complete radiological response. Though there

are major limitations with the currently published studies, the data does not support an increase in the occurrence or recurrence of HCC after DAA therapy.

Rapidly growing hepatocellular carcinoma recurrence during direct-acting antiviral treatment for chronic hepatitis C.

Yamashita N1, Tanimoto H2, Shimoda S3, Komori A4, Nomura H2. Clin J Gastroenterol. 2018 Jun 11. doi: 10.1007/s12328-018-0876-y. [Epub ahead of print]

We herein report the case of a woman in her 80s with a recurrent hepatocellular carcinoma (HCC) tumor that rapidly increased in size during direct-acting antiviral (DAA) treatment. She suffered from HCC at her initial visit to our department and underwent hepatectomy. Thereafter, she underwent DAA treatment for chronic hepatitis C; however, her alpha-fetoprotein (AFP) level rapidly increased, and a liver tumor of > 1 cm in diameter was observed that had not been seen immediately before DAA treatment. She underwent hepatectomy again and moderate to poorly differentiated HCC was diagnosed. The patient's AFP level showed a rapid increase immediately after the start of DAA treatment; however, the increase ceased after the first month, and the influence from the surrounding environment of the tumor was considered to be temporary.

Dual effects of the Nrf2 inhibitor for inhibition of hepatitis C virus and hepatic cancer cells.

Murakami Y1, Sugiyama K2, Ebinuma H3, et al. BMC Cancer. 2018 Jun 25;18(1):680. doi: 10.1186/s12885-018-4588-y.

BACKGROUND: We previously showed that knockdown of nuclear factor E2-related factor 2 (Nrf2) resulted in suppression of hepatitis C virus (HCV) infection. In this study, whether brusatol, an Nrf2 inhibitor, has dual anti-HCV and anticancer effects was explored. **METHODS:** The anti-HCV effect of brusatol was investigated by analyzing HCV RNA and proteins in a hepatic cell line persistently-infected with HCV, HPI cells, and by analyzing HCV replication in a replicon-replicating hepatic cell line, OR6 cells. Then, dual anti-HCV and anticancer effects of brusatol and enhancement of the effects by the combination of brusatol with anticancer drugs including sorafenib, which has been reported to have the dual effects, were then investigated. **RESULTS:** Brusatol suppressed the persistent HCV infection at both the RNA and protein levels in association with a reduction in Nrf2 protein in the HPI cells. Analysis of the OR6 cells treated with brusatol indicated that brusatol inhibited HCV persistence by inhibiting HCV replication. Combination of brusatol with an anticancer drug not only enhanced the anticancer effect but also, in the case of the combination with sorafenib, strongly suppressed HCV infection. **CONCLUSIONS:** Brusatol has dual anti-HCV and anticancer effects and can enhance the comparable effects of sorafenib. There is therefore the potential for combination therapy of brusatol and sorafenib for HCV-related hepatocellular carcinoma.

Late Development of Hepatocellular Carcinoma After Viral Clearance in Chronic Hepatitis C Patients: A Need for Continual Surveillance.

Tong MJ1,2, Theodoro CF3, Salvo RT1. J Dig Dis. 2018 Jun 11. doi: 10.1111/1751-2980.12615. [Epub ahead of print]

BACKGROUND & AIMS: Successful eradication of chronic hepatitis C (CHC) infection decreases the incidence of hepatocellular carcinoma (HCC), but a risk remains. We investigated factors associated with HCC development in CHC patients who had sustained virologic response (SVR) after antiviral therapies. **METHODS:** We retrospectively compared CHC patients achieving SVR to antiviral treatments between 1996 and 2016 who did and did not develop

HCC. Their median follow-up period was 8.01 years. **RESULTS:** Compared to 164 non-HCC SVR patients, 22 who developed HCC were older in age at SVR (59 vs. 52.1 years, $p=0.032$), had a higher incidence of diabetes (27% vs. 8%, $p=0.013$), and more had fibrosis Stage 3 and cirrhosis (77% vs. 38%, $p=0.0009$). In addition, their pre-antiviral treatment alpha-fetoprotein (AFP) levels were higher (109.9ng/ml vs. 78.6ng/ml, $p=0.016$) and more were anti-HBc positive (65% vs. 29%, $p=0.006$). Eight of 22 (36%) patients developed HCC 4 to 10 years after SVR, while another seven (32%) developed HCC 10 years after SVR. The longest duration from SVR to HCC was 18.7 years. By multivariate analysis, independent factors associated with HCC development were anti-HBc positivity (hazard ratio [HR] 5.57, 95% CI 1.45-21.39, $p=0.012$), age at SVR (HR 1.08, 95% CI 1.02-1.14, $p=0.014$), higher pre-antiviral treatment AFP levels (HR 1.01, 95% CI 1.00-1.02, $p=0.01$), and Hispanic compared to Caucasian patients (HR 12.9, 95% CI 2.54-65.49, $p=0.082$). The risk for HCC was significantly less in genotype 2 (HR 0.2, 95% CI 0.05-0.78, $p=0.02$) compared to genotype 1 patients, and in those with higher pre-antiviral treatment albumin levels (HR 0.33, 95% CI 0.10-1.09 $p=0.04$). **CONCLUSIONS:** The risk for HCC still exists in a subset of CHC patients after SVR and may occur up to 18 years after viral clearance. Therefore, indefinite HCC surveillance may be necessary in SVR patients with other risk factors. This article is protected by copyright. All rights reserved.

[An unfortunate failure: multifocal hepatocellular carcinoma in a non-cirrhotic patient with chronic hepatitis C treated with ledipasvir/sofosbuvir.](#) Soliman MS1, Soliman YY1, Ahmad Q1, Yarlagadda R1. J Community Hosp Intern Med Perspect. 2018 Jun 12;8(3):167-169. doi: 10.1080/20009666.2018.1473702. eCollection 2018.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the third highest cause of cancer mortality worldwide. Risk factors include chronic liver disease and cirrhosis of various causes including chronic hepatitis B and C. In cases of chronic hepatitis C virus (HCV), HCC usually does not manifest unless the liver has become cirrhotic. Fortunately, novel treatments for hepatitis C including ledipasvir/sofosbuvir can cure patients from their disease and as a result, may never develop cirrhosis and therefore, be at much lower risk of developing HCC. We present a patient with chronic HCV genotype 1a who was successfully treated with ledipasvir/sofosbuvir with documented sustained viral response, but 6 months later was found to have multifocal HCC with virus reactivation with no evidence of cirrhosis on imaging or biochemical testing. While novel antiviral agents for HCV lead to >90% cure rate, cure is defined as sustained viral response of only 12 weeks. This brings to light a new patient population who may require further follow-up than 3 months to ensure viral clearance. Furthermore, this patient developed HCC despite initial viral clearance and no evidence of cirrhosis, indicating possible oncogenic potential of HCV that is independent of cirrhosis that necessitates further investigation.

[Should we cure HCV in patients with hepatocellular carcinoma while treating cancer?](#) Cabibbo G1, Celsa C1, Cammà C1, Craxì A1. Liver Int. 2018 Jun 23. doi: 10.1111/liv.13918. [Epub ahead of print]

Direct acting antivirals (DAAs) stabilize or improve liver function in the majority of patients with HCV cirrhosis. Hepatic decompensation is the main driver of death of patients with early, successfully treated HCC superimposed to cirrhosis. Treatment with DAAs could improve the prognosis of these subjects, independently from the subsequent course of HCC, if the efficacy in obtaining viral clearance is as high as in patients without a history of HCC, and if the risk of

HCC recurrence is unaffected. When dealing with HCC patients, DAAs can be indicated in two different settings: a) subjects in which HCC has been already successfully treated ("cured" HCC), or b) subjects whose HCC is still untreated or untreatable ("active" HCC). While there are abundant data on "cured" HCC, evidence supporting treatment decisions in patients with "active" HCC is at best scarce and controversial, since these patients as well as patients with HCC listed for liver transplantation (LT) are usually excluded from treatment. This article is protected by copyright. All rights reserved.