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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Retreatment with sofosbuvir, ledipasvir, and add-on ribavirin for patients who failed daclatasvir and asunaprevir combination therapy. Suda G1, Ogawa K1, Yamamoto Y2, et al. J Gastroenterol. 2017 Mar 18. doi: 10.1007/s00535-017-1328-z. [Epub ahead of print]
BACKGROUND: The optimal retreatment regimen for patients with hepatitis C virus (HCV) infection who failed interferon-free, direct-acting antiviral (DAA) therapy is undetermined. In this study, we aimed to evaluate the efficacy and safety of 12-week retreatment with ledipasvir (LDV) and sofosbuvir (SOF) with add-on ribavirin (RBV) for patients who previously failed to respond to HCV-NS5A inhibitor, daclatasvir (DCV), and HCV-NS3 inhibitor, asunaprevir (ASV), therapy. **METHODS:** This multicenter, prospective study enrolled 15 patients with genotype-1 HCV infection who failed DCV/ASV combination therapy. They were retreated with SOF, LDV, and RBV for 12 weeks and underwent physical examinations and blood tests at baseline, during treatment, and after therapy. At baseline and relapse, NS3/NS5A and NS5B resistance-associated variants (RAVs) were evaluated. **RESULTS:** Of the 15 enrolled patients, 73.3% (11/15), 86.7% (13/15), and 0% (0/15) had RAVs in NS3 D168A/V/T/E, NS5A L31I/M/F/V plus Y93H, and NS5B S282T, respectively. Overall, 86.7% (13/15) of patients achieved a sustained viral response, and all patients completed therapy. No patients experienced severe adverse events. Two patients who failed to respond to SOF, LDV, and RBV combination therapy were elderly women, had the IL28B non-TT genotype, and NS5A RAVs in L31I/Y93H or NS5A A92 K at baseline. **CONCLUSIONS:** This study revealed that SOF, LDV, and RBV combination therapy was effective and well-tolerated for patients with genotype-1 HCV infection who failed DCV and ASV combination therapy. Thus, RBV added to DAA therapy for difficult-to-treat patients might improve treatment outcomes.

Improvement of liver stiffness in patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response.
Tada T1, Kumada T1, Toyoda H1, Mizuno K1, Sone Y2, Kataoka S3, Hashinokuchi S3. J Gastroenterol Hepatol. 2017 Mar 15. doi: 10.1111/jgh.13788. [Epub ahead of print]
BACKGROUND AND AIM: There is insufficient research on whether direct-acting antiviral (DAA) therapy can improve liver fibrosis in patients with chronic hepatitis C virus (HCV). We evaluated sequential changes in liver stiffness using shear wave elastography (SWE) in patients with HCV who received DAA therapy. **METHODS:** A total of 210 patients with HCV who

received daclatasvir and asunaprevir therapy and achieved sustained virological response (SVR) were analyzed. Liver stiffness, as evaluated by SWE, and laboratory data were assessed before treatment (baseline), at end of treatment (EOT), and at 24 weeks after EOT (SVR24). **RESULTS:** Alanine aminotransferase (ALT) levels decreased over time, and there were significant differences between baseline and EOT and between EOT and SVR24. Although platelet counts did not significantly differ between baseline and EOT, they increased significantly from EOT to SVR24. The median (interquartile range) liver stiffness values at baseline, EOT, and SVR24 were 10.2 (7.7-14.7), 8.8 (7.1-12.1), and 7.6 (6.3-10.3) kPa, respectively ($p < 0.001$, baseline versus EOT; $p < 0.001$, EOT versus SVR24). Additionally, in patients with ALT levels ≤30 (indicating low necroinflammatory activity in the liver) and FIB-4 index >2.0 (n = 75), the liver stiffness values at baseline, EOT, and SVR24 were 9.6 (7.7-15.2), 9.2 (7.3-12.1), and 7.7 (6.3-10.1) kPa, respectively ($p < 0.001$, baseline versus EOT; $p < 0.001$, EOT versus SVR24). **CONCLUSION:** These results suggest that early improvement of liver stiffness starts during the administration of DAAs in patients who achieve SVR, and this effect is particularly pronounced in patients with progressive liver fibrosis.

Patient engagement and study design of PROP UP: A multi-site patient-centered prospective observational study of patients undergoing hepatitis C treatment. Evon DM1, Golin CE2, Stewart P3, et al. Contemp Clin Trials. 2017 Mar 22. pii: S1551-7144(16)30312-3. doi: 10.1016/j.cct.2017.03.013. [Epub ahead of print]
BACKGROUND: New highly efficacious direct-acting antiviral (DAA) therapies are available to treat chronic hepatitis C viral (HCV) infection. Real-world, patient-centered data on harms and benefits associated with these therapies are needed. **METHODS:** PROP UP is a multi-center prospective observational study that plans to enroll 1600 patients starting treatment with recently-approved DAA regimens. Informed by extensive input from a HCV patient engagement group who prioritized outcomes most important to them, patient-reported outcomes will be characterized using surveys at five time points: Baseline (T1), treatment week 4 (T2), end of treatment (T3), 12weeks post-treatment (T4), 12months post-treatment (T5). **OUTCOMES:** (1) Changes in side effects, functioning, pre-existing conditions, and out-of-pocket costs during therapy (T1 vs T2/T3); (2) Medication adherence in relation to a history of mental health/substance abuse, treatment regimens, pill burden, reasons for missed doses, and cure rates; (3) Short term impact of cure on functioning and amelioration of symptoms (T1 vs T4); (4) Long-term treatment harms or benefits of cure on symptoms, side effects, pre-existing conditions, and functioning (T1 vs T5). Similarities between regimens will be examined where comparisons are appropriate and meaningful. **CONCLUSION:** PROP UP complements previous clinical trials by focusing on patient-reported outcomes in a representative sample of patients treated in clinical practice, by collaborating with a patient engagement group, by characterizing the experiences of vulnerable subgroups, and by investigating long-term harms and benefits of treatments. PROP UP is designed to provide novel and detailed information to support informed decision-making for patients and providers contemplating HCV treatment (PCORI CER-1408-20,660; NCT02601820).

Eight- or 12-Week Treatment of Hepatitis C with Ledipasvir/Sofosbuvir: Real-World Experience in a Large Integrated Health System. Lai JB1,2, Witt MA1, Pauly MP2, Ready J2, Allerton M1, Seo S2, Witt DJ3. Drugs. 2017 Mar;77(3):313-318. doi: 10.1007/s40265-016-0684-y.

BACKGROUND: Second-generation direct-acting antiviral agents are integral to treatment of hepatitis C (HCV) infection. Eight-week courses of ledipasvir/sofosbuvir (LDV/SOF) have been supported in some studies, but data are limited on efficacy in real-world use. Controversy exists regarding applicability of clinical trials to real-world effectiveness. We report virologic responses of patients with HCV genotype 1 infection receiving LDV/SOF for 8 or 12 weeks in a large integrated healthcare system. **METHODS:** All patients receiving LDV/SOF, without ribavirin, were identified from pharmacy records, and outcomes are reported. Only treatment-naïve patients without evidence of cirrhosis and hepatitis C viral load less than 6 million IU/ml were candidates for 8-week therapy. Treatment was at clinician discretion, but delivered by a multidisciplinary team and reviewed for appropriateness and adherence to these criteria by one of the authors, all experienced in hepatitis C treatment. Sustained viral response at 12 weeks (SVR 12) was contrasted between those receiving 8 and those receiving 12 weeks of treatment. **RESULTS:** Completed prescriptions for LDV/SOF, without ribavirin, as of 30 September 2015 were identified in 1021 patients. Five patients discontinued therapy due to medical reasons and 35 had incomplete follow-up viral load data, thus there were 981 evaluable patients: 377 treated for 8 weeks and 604 treated for 12 weeks. SVR 12 was virtually identical at 93.6 and 93.5%, respectively. Baseline characteristics differed between the two groups, as only treatment-naïve, non-cirrhotic, non-HIV-infected patients were eligible for an 8-week course of therapy. **CONCLUSIONS:** Eight-week courses of LDV/SOF are comparable to 12-week courses in real-world use among selected patients supported by a multidisciplinary team.

[Improving Support and Education of Low Income Baby Boomers Diagnosed with Chronic Hepatitis C Virus Infection through Universal Screening.](#) Turner BJ1,2, Craig K3, Makanji VS3, Flores BE2,4, Hernandez L2. J Clin Nurs. 2017 Mar 15. doi: 10.1111/jocn.13806. [Epub ahead of print]

AIMS AND OBJECTIVES: The objective of this study was to identify support needs of low income baby boomers recently diagnosed with chronic hepatitis C virus infection. **BACKGROUND:** The United States Preventive Services Task Force has endorsed one-time screening of all baby boomers (born 1945 to 1965) for hepatitis C because 75% of the estimated 2 to 3 million persons with chronic infection are in this age range. We hypothesized that persons diagnosed by routine screening would have significant psycho-emotional, cognitive, and health care challenges that need to be met by collaborative care and services from nurses and other health care personnel. **DESIGN:** Qualitative descriptive study of data from three focus groups with predominantly minority participants (N=16). Data were analyzed using qualitative content analysis, transcribed data were categorized by 3 domains in a previously developed model and a new domain identified in this study. Frequencies of unique participants' comments about each theme were calculated. **RESULTS:** Elucidated domains were: 1) psycho-emotional effects due to social stigma, shame, fear, dealing with risky behaviors; 2) social effects due to concerns about infecting others; and 3) cognitive deficits because of poor understanding about HCV infection and its care. A new domain related to health care emerged reflecting the following themes: poor access to care, barriers to costly treatment, and navigating complex care for comorbidities. Despite these challenges, participants strongly endorsed universal baby boomer hepatitis C virus screening. **CONCLUSION:** This study describes psycho-emotional and social challenges of people dealing with a hepatitis C diagnosis that are compounded by poor knowledge and barriers to supportive care.

Increased mortality among persons with chronic hepatitis C with moderate or severe liver disease: a cohort study. Cepeda JA1, Thomas DL2, Astemborski J3, Sulkowski MS2, Kirk GD2,3, Mehta SH3. Clin Infect Dis. 2017 Mar 10. doi: 10.1093/cid/cix207. [Epub ahead of print]

BACKGROUND: Despite the availability of curative treatment for hepatitis C virus (HCV) infection, because of cost, treatment is often denied until liver fibrosis has progressed to at least moderate fibrosis and in some cases cirrhosis. That practice is justified on assumptions that there are no medical consequences to having moderate disease and that disease stage transitions can be anticipated. **METHODS:** We performed transient elastography on 964 people chronically infected with HCV with a history of injection drug use living in Baltimore, Maryland. Liver stiffness was evaluated semiannually from 2006 to 2014 using validated cutoffs for moderate fibrosis (8.0 - 12.3 kPa) and severe fibrosis/cirrhosis (>12.3 kPa). **RESULTS:** Among 964 persons, 62%, 23% and 15% had baseline measurements suggestive of no/mild fibrosis, moderate fibrosis and severe fibrosis/cirrhosis, respectively. All-cause and non-accidental mortality were elevated in persons with moderate fibrosis (adjusted hazard ratio [aHR]: 1.42, 95% CI: 0.96 - 2.11; aHR: 1.66, 95%CI: 1.06 - 2.59, respectively) after adjustment for sociodemographics, substance use, and HIV status. Despite the increased risk of mortality among those with moderate fibrosis, no combination of demographic, behavioral, clinical factors, nor changes in stiffness measurements themselves could predict the transition from mild to moderate fibrosis with sufficiently high diagnostic accuracy (C-statistic =0.72 for best performing model). **CONCLUSIONS:** Delaying treatment for anyone chronically infected with HCV regardless of fibrosis stage may be detrimental given the increased risk of mortality even for those with moderate disease and the inability to predict the transition from mild to moderate disease.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Non-neutralizing epitopes induce robust HCV-specific antibody-dependent CD56+ NK cell responses in chronic HCV-infected patients. Long L1,2, Jia M3, Fan X2, Liang H3, Wang J4, Zhu L2, Xie Z2, Shen T2. Clin Exp Immunol. 2017 Mar 20. doi: 10.1111/cei.12962. [Epub ahead of print]

NK cell-mediated antibody-dependent cellular cytotoxicity (NK-ADCC) is of considerable interest in viral infection. However, little is known about NK-ADCC responses in chronic hepatitis C virus (HCV) infection. In this study, impaired nonspecific antibody-dependent CD56+ NK cell responses were observed in chronic HCV infection, as shown by decreased degranulation (extracellular CD107a expression) and IFN-γ production in response to antibody-bound P815 cells. A peptide pool composed of epitopes recognized by anti-HCV-E1/E2 antibodies could induce pronounced HCV-specific antibody-dependent NK cell responses in sera from approximately half of the chronic HCV carriers. Additionally, HCV-specific epitopes with the capacity to induce robust NK-ADCC activity were identified. Five linear NK-ADCC epitopes (aa211-aa217, aa384-aa391, aa464-aa475, aa544-aa551, and aa648-aa659 of the HCV envelope) were identified and do not overlap with putative linear neutralizing epitopes. This study revealed the dysfunctional characteristics of antibody-dependent CD56+ NK cell responses in chronic HCV carriers. The key non-neutralizing NK-ADCC epitopes identified in this study may act as new targets for immunologic intervention. This article is protected by copyright. All rights reserved.

IFNL4 polymorphism effects on outcome of simeprevir, peginterferon, and ribavirin therapy for older patients with genotype 1 chronic hepatitis C. Mori N1, Imamura M2, Kawakami Y2, et al. Hepatol Res. 2017 Mar;47(3):E5-E13. doi: 10.1111/hepr.12715. Epub 2016 Apr 21.

AIM: Older patients with chronic hepatitis C have a lower virological response to interferon (IFN)-based treatments compared to younger patients. A single nucleotide polymorphism in the IFN-λ-4 (IFNL4) gene has a potent predictive effect on treatment response to IFN-based treatments. The efficacy of simeprevir (SMV) plus pegylated-IFN (PEG-IFN) and ribavirin therapy and the predictive value of IFNL4 on the outcome of therapy for older patients have not been addressed. **METHODS:** This retrospective multicenter study included 234 consecutive Japanese patients with genotype 1 chronic hepatitis C. We assessed the predictive factors for sustained virological response (SVR) to SMV, PEG-IFN, and ribavirin triple therapy in 170 younger (<70 years) and 64 older (≥70 years) patients. IFNL4 polymorphism ss469415590 was analyzed by Invader assay. **RESULTS:** The SVR rate for older patients was similar to that for younger patients (63.9% and 72.0%, respectively). The SVR rate for the IFNL4 TT/TT group was significantly higher than the IFNL4 TT/ΔG or ΔG/ΔG group both in younger (93.6% and 46.1%, respectively, P < 0.01) and older patients (84.4% and 33.3%, respectively, P < 0.001). In multivariate regression analysis, IFNL4 TT/TT genotype, response to previous treatment and IFNL4 TT/TT genotype were identified as independent predictive factors for SVR in older and younger patients, respectively. Decrease in hemoglobin level was similar between the two groups. **CONCLUSION:** The virological response to SMV triple therapy in older patients was similar to that of younger patients. Analysis of IFNL4 polymorphisms is a valuable predictor in both younger and older patients.

In vitro selection of resistance to sofosbuvir in HCV replicons of genotype 1 to 6. Xu S1, Doehle B1, Rajyaguru S1, et al. Antivir Ther. 2017 Mar 1. doi: 10.3851/IMP3149. [Epub ahead of print]

BACKGROUND: Sofosbuvir is a nucleoside analog inhibitor of the hepatitis C virus (HCV) NS5B polymerase approved for treatment of HCV-infected patients in combination with ribavirin or with other antivirals. It has activity against all genotypes of HCV. Resistance to sofosbuvir in genotype 1 and 2 HCV is conferred by the S282T substitution in NS5B. **METHODS:** To begin to define the correlates of resistance to sofosbuvir in other genotypes, we performed selection experiments in cell culture using cell lines containing subgenomic replicons derived from genotypes 1b, 2a, 3a, and 4a, or chimeric replicons in a genotype 1b background but encoding genotype 2b, 5a, and 6a NS5B polymerase. **RESULTS:** In every case, S282T was selected following passage in the presence of increasing concentrations of sofosbuvir for 10 to 15 weeks. When introduced as a site-directed mutant, S282T conferred reductions in sofosbuvir susceptibility of between 2.4 and 19.4-fold. Other substitutions observed during the selections had relatively less impact on susceptibility, such as N237S in genotype 6a (2.5-fold). Replication capacity was affected by the introduction of S282T in all genotypes to variable extents (3.2% to 22% of wild-type). **CONCLUSIONS:** These results confirm that S282T is the primary sofosbuvir resistance-associated substitution and that replication capacity is reduced when it is present in all genotypes of HCV.

[Augmentation of HCV specific immunity and Sustained virological response (SVR).](#)
Shrivastava S1, Wilson E1, Poonia B1, Tang L1, Osinusi A2, Kohli A3, Kottilil S1. J Viral Hepat. 2017 Mar 7. doi: 10.1111/jvh.12702. [Epub ahead of print]

BACKGROUND: Treatment for chronic hepatitis C virus (HCV) infection has rapidly evolved into interferon-free directly acting antiviral regimens (DAA) that result in high sustained-virologic-response. DAAs primarily work by suppressing HCV replication and rely less on the immune system than interferon-based therapies. However it is unclear whether the immune system recovers with suppression of HCV replication and contributes to HCV clearance with DAA therapy. We previously demonstrated HCV clearance is associated with increased HCV-specific-immunity in CHCV-GT-1 infected patients during treatment with sofosbuvir (SOF)+ribavirin (RBV). Here, we aimed to analyze changes in HCV-specific immunologic responses associated with viral clearance with combination DAA therapy of SOF+ledipasvir (LDV) for 12 weeks in CHCV-GT1 (N=14) patients who relapsed without augmentation of HCV-specific-immunity during treatment with SOF+RBV. **METHODS:** Phenotypic and functional changes within the T-cell compartment of PBMCs pre- and post-treatment were analyzed. **RESULTS:** Retreatment of relapsers with LDV/SOF resulted in all patients attaining SVR12 . Suppression of HCV was associated with a decline in T-cell exhaustion markers (CD57; Tim3; PD1) along with augmented of HCV-specific T-cell IFN-gamma responses post-treatment. **CONCLUSIONS:** Addition of LDV to SOF was associated with augmentation of HCV-specific-immunity and SVR in patients who previously failed SOF+RBV therapy without increased immunity. These findings demonstrate a novel effect of DAA in inducing host immune responses to aid HCV clearance and achieve SVR. This article is protected by copyright. All rights reserved.

[Improved full-length killer cell immunoglobulin-like receptor transcript discovery in Mauritian cynomolgus macaques.](#) Prall TM1, Graham ME2, Karl JA2, et al. Immunogenetics. 2017 Mar 25. doi: 10.1007/s00251-017-0977-7. [Epub ahead of print]

Killer cell immunoglobulin-like receptors (KIRs) modulate disease progression of pathogens including HIV, malaria, and hepatitis C. Cynomolgus and rhesus macaques are widely used as nonhuman primate models to study human pathogens, and so, considerable effort has been put into characterizing their KIR genetics. However, previous studies have relied on cDNA cloning and Sanger sequencing that lack the throughput of current sequencing platforms. In this study, we present a high throughput, full-length allele discovery method utilizing Pacific Biosciences circular consensus sequencing (CCS). We also describe a new approach to Macaque Exome Sequencing (MES) and the development of the Rhexome1.0, an adapted target capture reagent that includes macaque-specific capture probe sets. By using sequence reads generated by whole genome sequencing (WGS) and MES to inform primer design, we were able to increase the sensitivity of KIR allele discovery. We demonstrate this increased sensitivity by defining nine novel alleles within a cohort of Mauritian cynomolgus macaques (MCM), a geographically isolated population with restricted KIR genetics that was thought to be completely characterized. Finally, we describe an approach to genotyping KIRs directly from sequence reads generated using WGS/MES reads. The findings presented here expand our understanding of KIR genetics in MCM by associating new genes with all eight KIR haplotypes and demonstrating the existence of at least one KIR3DS gene associated with every haplotype.

HIV/HCV COINFECTION

Prevalence and predictors for compensated Advanced Chronic Liver Disease (c-ACLD) in patients with chronic Hepatitis Delta Virus (HDV) infection. Couto I1, Victoria M1, Veloso VG2, Rodrigues L1, Grinsztejn B2, Lacerda M3,4, Victoria F1, Perazzo H2. PLoS One. 2017 Mar 22;12(3):e0174453. doi: 10.1371/journal.pone.0174453. eCollection 2017.

OBJECTIVE: The study aimed to evaluate the prevalence and predictor factors for compensated advanced chronic liver disease (c-ACLD) in patients with hepatitis Delta virus (HDV) infection. **METHODS:** This cross-sectional study included consecutive HDV-infected patients defined by positive anti-HDV. Patients with hepatitis C coinfection, liver transplantation or presence of conditions that limit liver (LSM) or spleen stiffness measurement (SSM) were excluded. Blood tests, abdominal ultrasound, SSM and LSM by transient elastography (FibroScan®) were performed at the same day. Alcohol consumption was quantified using the AUDIT score and c-ACLD was defined by LSM ≥ 15 kPa performed by an experimented operator blinded for clinical and laboratory data. **RESULTS:** 101 patients were eligible and few patients were excluded due to negative anti-HDV (n = 7), hepatitis C coinfection (n = 2), liver transplantation (n = 10) and limitation for LSM or SSM (n = 5). Therefore, 77 patients [61% male, age = 43 (IQR,36-52) years] were included. The prevalence of c-ACLD was 57% (n = 44/77). Patients with c-ACLD had a higher rate of detectable HBV viral load (p = 0.039), higher levels of transaminases, GGT, alkaline phosphatases, total bilirubin and INR (p<0.001 for all), as well as lower platelet count and albumin levels (p>0.001 for both) compared to those without c-ACLD. Patients with c-ACLD had higher SSM [65.2 (IQR,33.8-75.0) vs 21.8 (16.5-32.0) kPa; p<0.001] and higher splenic volume [475 (IQR,311-746) vs 154 (112-283) cm3; p<0.001] compared to those without. Detectable HBV viral load (>10 UI/ml), alkaline phosphatase (per IU/L) and GGT levels (per IU/L) were independently associated with c-ACLD in all multivariate models. Splenic volume [per cm3,OR = 1.01 (95%CI,1.01-1.02);p = 0.002], SSM [per kPa, OR = 1.04 (1.01-1.07);p = 0.012] and splenomegaly [yes vs no,OR = 28.45 (4.42-182.95);p<0.001] were independently associated with c-ACLD. **CONCLUSIONS:** The prevalence of c-ACLD was high in patients with chronic HDV infection in western Amazon basin. HBV viral load, liver enzymes and splenic features can be used to predict severe liver disease in HDV-infected patients.

TURQUOISE-I Part 1b: Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Ribavirin for Hepatitis C Virus Infection in HIV-1 Coinfected Patients on Darunavir. Wyles D1, Saag M2, Viani RM3, et al. J Infect Dis. 2017 Mar 14. doi: 10.1093/infdis/jiw597. [Epub ahead of print]

BACKGROUND: Ombitasvir/paritaprevir/ritonavir with dasabuvir (OBV/PTV/r + DSV) ± ribavirin (RBV) is approved for hepatitis C virus (HCV) genotype 1 (GT1) treatment in HIV-1 coinfected patients. In healthy controls, coadministration of OBV/PTV/r + DSV + darunavir (DRV) lowered DRV trough concentration (Ctrough) levels. To assess the clinical significance of this change, TURQUOISE-I, Part 1b, evaluated the efficacy and safety of OBV/PTV/r + DSV + RBV in coinfected patients on stable, DRV-containing antiretroviral therapy (ART). **METHODS:** Patients were HCV treatment-naive or interferon-experienced, had CD4+ lymphocyte count ≥200 cells/μL or ≥14%, and plasma HIV-1 RNA suppression on once-daily (QD) DRV-containing ART at screening. Patients were randomized to maintain DRV 800 mg QD or switch to twice-daily (BID) DRV 600 mg; all received OBV/PTV/r + DSV + RBV for 12 weeks. **RESULTS:** Twenty-two patients were enrolled and achieved SVR12. No adverse events

led to discontinuation. Coadministration had minimal impact on DRV maximum observed plasma concentration and area under the curve; DRV Ctrough levels were slightly lower with DRV QD and BID. No patient experienced plasma HIV-1 RNA >200 copies/mL during treatment. **CONCLUSIONS:** HCV GT1/HIV-1 coinfected patients on stable DRV-containing ART achieved 100% SVR12 while maintaining plasma HIV-1 RNA suppression. Despite DRV exposure changes, episodes of intermittent HIV-1 viremia were infrequent.

[**Reactivation of occult HBV infection in an HIV/HCV Co-infected patient successfully treated with sofosbuvir/ledipasvir: a case report and review of the literature.**](#) Fabbri G1, Mastrorosa I2, Vergori A2, et al. BMC Infect Dis. 2017 Mar 1;17(1):182. doi: 10.1186/s12879-017-2287-y.

BACKGROUND: Reactivation of occult or inactive Hepatitis B virus (HBV) infection during immunosuppressant treatments is well known and widely described in literature. The same observation has been made in Hepatitis C (HCV)-infected patients previously exposed to HBV and treated with interferon-free DAA treatments. Because of common transmission routes, persons may have been exposed to HCV, HBV and HIV, but few cases have been reported in this scenario to date. Frequency of HBV reactivation in HIV/HCV co-infected patients previously exposed to HBV and treated with DAA remains unclear. Herein, we report an episode of HBV reactivation in an HIV/HCV co-infected patient prescribed with sofosbuvir/ledipasvir for HCV. **CASE PRESENTATION:** The patient is a Caucasian 54-years old female, with HIV/HCV co-infection (genotype 4), and a previous exposure to HBV, documented by negativity of HBsAg and positivity of HBsAb and HBcAb. Her medical history included: myocardial infarct, chronic kidney disease stage 3, chronic obstructive pulmonary disease, and mild pulmonary hypertension. HCV had not been treated with interferon (IFN)-based regimens and liver stiffness was 10.5 KPa (Metavir stage F3) at hepatic elastography. Because of CKD, she was prescribed with a nucleoside reverse transcriptase (NRTI)-sparing regimen including darunavir/ritonavir plus etravirine, and thereafter with sofosbuvir/ledipasvir for 12 weeks. Four weeks after DAA termination, the patient was hospitalized with symptoms of acute hepatitis. Blood tests showed HCV RNA <12 IU/ml, but positivity of HBAg, HBeAg, and of anti-core antibodies (IgM and IgG), while anti-HBs and anti-HBe antibodies were negative. HBV DNA was 6.06 Log10 IU/ml. Entecavir was started obtaining resolution of symptoms, normalization of liver enzymes, as well as reduction of HBV DNA and of quantitative HBV surface antigen. **CONCLUSIONS:** This case-report highlights the risk of HBV reactivation with interferon-free DAA treatment in HIV/HCV co-infected patients previously exposed to HBV and who have contraindications for treatment with nucleoside/nucleotide reverse transcriptase Inhibitors because of comorbid conditions. In the setting of HIV infection, clinicians prescribing DAA should be aware of this risk, and HBV assessment at treatment start as well as virological monitoring during DAA treatment is recommended. Large epidemiological and virological studies are needed to investigate reactivation of occult HBV infection more in depth.

[**Perceived health and alcohol use in individuals with HIV and Hepatitis C who use drugs.**](#) Elliott JC1, Hasin DS2, Des Jarlais DC3. Addict Behav. 2017 Mar 10;72:21-26. doi: 10.1016/j.addbeh.2017.03.004. [Epub ahead of print]

BACKGROUND: Individuals who use illicit drugs are at heightened risk for HIV and/or Hepatitis C Virus (HCV). Despite the medical consequences of drinking for drug-using individuals with these infections, many do drink. In other studies, how individuals perceive their

health relates to their engagement in risk behaviors such as drinking. However, among drug-using individuals with HIV and HCV, whether perceived health relates to drinking is unknown. **OBJECTIVE:** We examine the association between perceived health and drinking among drug-using individuals with HIV and/or HCV. **METHODS:** In a large, cross-sectional study, we utilized samples of individuals with HIV (n=476), HCV (n=1145), and HIV/HCV co-infection (n=180), recruited from drug treatment centers from 2005 to 2013. In each sample, we investigated the relationship between perceived health and drinking, using ordinal logistic regressions. We present uncontrolled models as well as models controlled for demographic characteristics. **RESULTS:** ong samples of drug using individuals with HIV and with HCV, poorer perceived health was associated with risky drinking only when demographic characteristics were taken into account (Adjusted Odds Ratios: 1.32 [1.05, 1.67] and 1.16 [1.00, 1.34], respectively). In the smaller HIV/HCV co-infected sample, the association of similar magnitude was not significant (AOR=1.32 [0.90, 1.93]). **CONCLUSIONS:** Drug using patients with HIV or HCV with poor perceived health are more likely to drink heavily, which can further damage health. However, when demographics are not accounted for, these effects can be masked. Patients' reports of poor health should remind providers to assess for health risk behaviors, particularly heavy drinking.

[Real-World Efficacy of Daclatasvir and Sofosbuvir, With and Without Ribavirin, in HIV/HCV Co-Infected Patients With Advanced Liver Disease in a French Early-Access Cohort.](#) Lacombe K1, Fontaine H, Dhiver C, et al. J Acquir Immune Defic Syndr. 2017 Mar 6. doi: 10.1097/QAI.0000000000001342. [Epub ahead of print]
BACKGROUND: Efficacious, well-tolerated direct antiviral agents have drastically changed the prognosis of hepatitis C virus (HCV) disease, but real-world data for oral treatments are limited in key populations such as human immunodeficiency virus (HIV)/HCV co-infection with advanced liver disease. Daclatasvir (DCV) efficacy and safety was assessed in the French "Autorisation Temporaire d'Utilisation" (ATU) program providing DCV ahead of market authorization to patients with advanced HCV disease without other treatment options. **METHODS:** This was a sub-analysis of HIV/HCV co-infected ATU patients treated with DCV plus sofosbuvir (SOF). Recommended duration was 24 weeks; addition of ribavirin (RBV) and/or shorter treatment was at physician's discretion. Primary efficacy analysis was sustained virologic response at post-treatment week 12 (SVR12; modified intention-to-treat). Safety was assessed by spontaneous adverse event reporting. **RESULTS:** The efficacy population (N=407) was mostly cirrhotic (72%, of whom 18% were decompensated), HCV treatment-experienced (82%), and infected with genotypes 1 (69%), 3 (12%), or 4 (19%). Median CD4 was 555 cells/mm; 95% had HIV-RNA <50 copies/mL. Most (74%) were treated for 24 weeks; 14% received RBV. SVR12 was 92% overall (95% confidence interval: 88.6% to 94.0%); 90% (86.4% to 93.2%) in patients with cirrhosis; 95% (88.9% to 97.5%) in patients without cirrhosis. SVR12 was consistent across HCV genotypes and antiretroviral regimens. Among 617 patients with safety data, seven discontinued for an adverse event and 10 died. **CONCLUSIONS:** DCV+SOF±RBV achieved high SVR12 and was well tolerated in this large real-world cohort of HIV/HCV co-infected patients with advanced liver disease.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

[High prevalence of willingness to use direct-acting antiviral-based regimens for hepatitis C virus (HCV) infection among HIV/HCV coinfected people who use drugs.](#) Socías ME1,2, Ti L1,2, Dong H1, Shoveller J1,3, Kerr T1,2, Montaner J1,2, Milloy MJ1,2. HIV Med. 2017 Mar 13. doi: 10.1111/hiv.12501. [Epub ahead of print]

OBJECTIVES: Despite the high burden of hepatitis C virus (HCV)-related morbidity and mortality among HIV-positive people who use illicit drugs (PWUD), uptake of interferon-based treatments for HCV infection has been negligible among this group. Direct-acting antiviral (DAA) therapies offer an opportunity to expand treatment access among this population. The aim of this study was to explore willingness to use DAA-based regimens among HIV/HCV-coinfected PWUD in Vancouver, Canada. **METHODS:** Data were drawn from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), a prospective cohort of HIV-positive PWUD. Using logistic regression analyses, we investigated factors associated with willingness to use DAA-based regimens among HIV/HCV-coinfected participants. **RESULTS:** Of 418 HIV/HCV-coinfected PWUD surveyed between June 2014 and May 2015, 295 (71%) were willing to use DAA-based regimens. In multivariable analysis, participants enrolled in methadone maintenance therapy [adjusted odds ratio (AOR) 1.61; 95% confidence interval (CI) 1.04-2.51], those with a recent assessment by an HCV specialist (AOR 2.02; 95% CI 1.28-3.19) and those who perceived that HCV infection was affecting their health (AOR 2.49; 95% CI 1.41-4.37) were more likely to be willing to use DAA-based regimens. **CONCLUSIONS:** Overall, this study found a high prevalence of willingness to use DAA-based regimens among HIV/HCV-coinfected PWUD in Vancouver. Importantly, enrolment in methadone maintenance therapy was positively associated with willingness, suggesting that integrated models of HIV, HCV and addiction care should be explored as a way to address HCV-related morbidity and mortality among HIV/HCV-coinfected PWUD.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

[Herbal approach in the treatment of pancytopenia.](#) Bagwe SM, Kale PP, Bhatt LK, Prabhavalkar KS. J Complement Integr Med. 2017 Mar 1;14(1). pii: /j/jcim.2017.14.issue-1/jcim-2016-0053/jcim-2016-0053.xml. doi: 10.1515/jcim-2016-0053.

Pancytopenia is a health condition in which there is a reduction in the amount of leucocytes, erythrocytes and thrombocytes. If more than one of the blood cells is low then the condition is called as bicytopenia. The pancytopenic condition is observed in treatment of diseased conditions like thalassemia and hepatitis C. Iatrogenically pancytopenia is caused by some antibiotics and anti-HCV drugs. Medical conditions like aplastic anaemia, lymphoma, copper deficiency, and so forth can also cause pancytopenia. Pancytopenia can in turn decrease the immunity of the person and thereby can be fatal. Current therapies for pancytopenia include bone marrow stimulant drugs, blood transfusion and bone marrow transplant. The current therapies are very excruciating and have long-term side-effects. Therefore, treating these condition using herbal drugs is very important. Herbs like wheatgrass, papaya leaves and garlic are effective in treating single lineage cytopenias. The present review is focused on the potential effects of natural herbs for the treatment of pancytopenia.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir: Drug Interactions With Antiretroviral Agents and Drugs forSubstance Abuse. King JR1, Menon RM1. Clin Pharmacol Drug Dev. 2017 Mar;6(2):201-205. doi: 10.1002/cpdd.327.

AbbVie's 3 direct-acting antiviral (3D) regimen containing ombitasvir, paritaprevir, ritonavir, and dasabuvir with and without ribavirin is approved for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection. Safe and efficacious antiviral regimens resulting in minimal to no drug-drug interactions (DDIs) with antiretrovirals are needed to ensure that patients coinfected with HCV and the human immunodeficiency virus (HIV) achieve 12-week sustained virologic response rates similar to HCV-monoinfected patients. Also, the prevalence of injection drug use history is high in both monoinfected and HIV/HCV-coinfected patients. This review summarizes results from phase 1 DDI studies of the 3D regimen and antiretrovirals or drugs to treat substance abuse. Data suggest the 3D regimen is a viable option for HIV/HCV-coinfected patients on antiretroviral therapy containing tenofovir/emtricitabine, abacavir/lamivudine, dolutegravir, raltegravir, or atazanavir. HCV-infected patients receiving medications for substance abuse, particularly methadone or buprenorphine/naloxone, can also be treated with the 3D regimen.

Cost-effectiveness of combination daclatasvir-sofosbuvir for the treatment of genotype 3 chronic hepatitis c infection in the United States. Saint-Laurent Thibault C1, Moorjaney D2, Ganz ML3, Sill B4, Hede S5, Yuan Y5, Gorsh B6. J Med Econ. 2017 Mar 15:1-20. doi: 10.1080/13696998.2017.1307204. [Epub ahead of print]

BACKGROUND: A phase III trial evaluated the efficacy and safety of Daklinza (daclatasvir or DCV) in combination with sofosbuvir (SOF) for treatment of genotype (GT) 3 hepatitis C virus (HCV) patients. **AIM:** This study evaluated the cost-effectiveness of DCV+SOF versus SOF in combination with ribavirin (RBV) over a 20-year time horizon from the payer perspective in the United States (US). **METHODS:** A published Markov model was adapted to reflect US demographic characteristics, treatment patterns, costs of drug acquisition, monitoring, disease and adverse event management, and mortality risks. Clinical inputs came from the ALLY-3 and VALENCE trials. The primary cost-effectiveness outcome was the incremental cost-utility ratio. Life-years, incidence of complications, number of patients achieving sustained virological response (SVR), and the total cost per SVR were secondary outcomes. Costs (2014 USD) and quality-adjusted life years (QALYs) were discounted at 3% per year. Deterministic (DSA), probabilistic (PSA), and scenario sensitivity analyses were conducted. **RESULTS:** DCV+SOF was associated with lower costs and better effectiveness than SOF+RBV in the base case and in almost all scenarios (ie, treatment-experienced, non-cirrhotic, time horizons of 5, 10, and 80 years). DCV+SOF was less costly but also slightly less effective than SOF+RBV in the cirrhotic and treatment-naïve population scenarios. Results were sensitive to variations in the probability of achieving SVR for both treatment arms. DCV+SOF costs less than $50,000 per QALY gained in 79% of all iterations compared with SOF+RBV. **CONCLUSION:** DCV+SOF is a dominant option compared with SOF+RBV in the US for the overall GT3 HCV patient population.

Transformation of hepatitis C antiviral treatment in a national healthcare system following the introduction of direct antiviral agents. Moon AM1, Green PK2, Berry K2, Ioannou GN1,2,3. Aliment Pharmacol Ther. 2017 Mar 8. doi: 10.1111/apt.14021. [Epub ahead of print]

BACKGROUND: Highly effective direct antiviral agents (DAAs) for hepatitis C virus (HCV) were introduced recently. Their utilisation has been limited by high cost and low access to care.

AIM: To describe the effect of DAAs on HCV treatment and cure rates in the United States Veterans Affairs (VA) national healthcare system. **METHODS:** We identified all HCV antiviral treatment regimens initiated from 1 January 1999 to 31 December 2015 (n = 105 369) in the VA national healthcare system, and determined if they resulted in sustained virological response (SVR). **RESULTS:** HCV antiviral treatment rates were low (1981-6679 treatments/year) in the interferon era (1999-2010). The introduction of simeprevir and sofosbuvir in 2013 and ledipasvir/sofosbuvir and paritaprevir/ombitasvir/ritonavir/dasabuvir in 2014 were followed by increases in annual treatment rates to 9180 in 2014 and 31 028 in 2015. The number of patients achieving SVR was 1313 in 2010, the last year of the interferon era, and increased 5.6-fold to 7377 in 2014 and 21-fold to 28 084 in 2015. The proportion of treated patients who achieved SVR increased from 19.2% in 1999 and 36.0% in 2010 to 90.5% in 2015. Within 2015, monthly treatment rates ranged from 727 in July to 6868 in September correlating with the availability of funds for DAAs. **CONCLUSIONS:** DAAs resulted in a 21-fold increase in the number of patients achieving HCV cure. Treatment rates in 2015 were limited primarily by the availability of funds. Further increases in funding and cost reductions of DAAs in 2016 suggest that the VA could cure the majority of HCV-infected Veterans in VA care within the next few years.

[Optimizing hepatitis C virus treatment through pharmacist interventions: Identification and management of drug-drug interactions.](#) Langness JA1, Nguyen M1, Wieland A1, Everson GT1, Kiser JJ1. World J Gastroenterol. 2017 Mar 7;23(9):1618-1626. doi: 10.3748/wjg.v23.i9.1618.

AIM: To quantify drug-drug-interactions (DDIs) encountered in patients prescribed hepatitis C virus (HCV) treatment, the interventions made, and the time spent in this process. **METHODS:** As standard of care, a clinical pharmacist screened for DDIs in patients prescribed direct acting antiviral (DAA) HCV treatment between November 2013 and July 2015 at the University of Colorado Hepatology Clinic. HCV regimens prescribed included ledipasvir/sofosbuvir (LDV/SOF), paritaprevir/ritonavir/ombitasvir/dasabuvir (OBV/PTV/r + DSV), simeprevir/sofosbuvir (SIM/SOF), and sofosbuvir/ribavirin (SOF/RBV). This retrospective analysis reviewed the work completed by the clinical pharmacist in order to measure the aims identified for the study. The number and type of DDIs identified were summarized with descriptive statistics. **RESULTS:** Six hundred and sixty four patients (83.4% Caucasian, 57% male, average 56.7 years old) were identified; 369 for LDV/SOF, 48 for OBV/PTV/r + DSV, 114 for SIM/SOF, and 133 for SOF/RBV. Fifty-one point five per cent of patients were cirrhotic. Overall, 5217 medications were reviewed (7.86 medications per patient) and 781 interactions identified (1.18 interactions per patient). The number of interactions were fewest for SOF/RBV (0.17 interactions per patient) and highest for OBV/PTV/r + DSV (2.48 interactions per patient). LDV/SOF and SIM/SOF had similar number of interactions (1.28 and 1.48 interactions per patient, respectively). Gastric acid modifiers and vitamin/herbal supplements commonly caused interactions with LDV/SOF. Hypertensive agents, analgesics, and psychiatric medications frequently caused interactions with OBV/PTV/r + DSV and SIM/SOF. To manage these interactions, the pharmacists most often recommended discontinuing the medication (28.9%), increasing monitoring for toxicities (24.1%), or separating administration times (18.2%). The pharmacist chart review for each patient usually took approximately 30 min, with additional time for more complex patients. **CONCLUSION:** DDIs are common with HCV medications and management can require medication adjustments and increased monitoring. An interdisciplinary team including a clinical pharmacist can optimize patient care.

[Outcomes of Pharmacy-Led Hepatitis C Direct-Acting Antiviral Utilization Management at a Veterans Affairs Medical Center.](#) Yang S1, Britt RB1, Hashem MG1, Brown JN1. J Manag Care Spec Pharm. 2017 Mar;23(3):364-369. doi: 10.18553/jmcp.2017.23.3.364.

BACKGROUND: The Veterans Affairs Health (VA) Administration has reported hepatitis C virus (HCV) infection rates among veterans to be twice that of the general U.S population. New HCV direct-acting antiviral (DAA) treatment options offer superior sustained virologic response (SVR) rates, improved side-effect profiles, and shortened treatment courses; yet, these new HCV DAAs are expensive, and utilization management strategies are needed to optimize use and improve clinical outcomes. A VA medical center uses pharmacist-led HCV DAA utilization management strategies that includes clinical guidance, optimizing operational flow, budget tracking and forecasting, and patient outcomes tracking. **OBJECTIVE:** To assess the economic and clinical outcomes of pharmacy-led HCV DAA utilization management in a VA medical center. **METHODS:** This was a single-center, retrospective cohort study. Patient electronic health records and the hepatitis C DAA outcomes tracking database were reviewed at a VA medical center. Patients with an HCV DAA prior authorization drug request and therapy initiated between October 1, 2014, and September 30, 2015, were included. The primary endpoint was the ratio of drug spend to cure rate calculated as the total dollars spent to the number of patients achieving SVR at least 12 weeks from end of treatment. Secondary endpoints included economic, clinical, and safety outcomes. **RESULTS:** A total of 372 patients were included in the study. The overall cost ratio of total drug spend to cure rate was \$40,135.22. The overall cure rate was 94.1%, with no discontinuations due to treatment failure. The ratio of drug spend to cure rate was \$41,907.35 and \$38,430.77 in cirrhotic and noncirrhotic patients, respectively, and \$39,481.62 and \$39,178.74 in treatment-experienced and naive patients, respectively. Ten patients discontinued therapy because of the adverse effects of anemia, nausea, vomiting, and anxiety. The medication possession ratio was 98.7% ($\pm$ 0.13) for all patients included in the study. **CONCLUSIONS:** This study suggests that pharmacist-led HCV DAA utilization management is an important factor in costs and cure rates. Utilization management strategies are valuable to help adequately manage patients with chronic hepatitis C (CHC) and may allow practitioners to maximize available funding for CHC, while maintaining high efficacy and safety. **DISCLOSURES:** No outside funding supported this research. The authors have no conflicts of interest to report. Study concept and design were contributed primarily by Britt, along with Hashem, Brown, and Yang. Yang took the lead in data collection, along with Britt, and data interpretation was performed by all the authors. The manuscript was written and revised by Yang, Britt, Brown, and Hashem.

[Evaluation of the new cobas® HCV genotyping test based on real-time PCRs of three different HCV genome regions.](#) Stelzl E, Appel HM, Mehta R, Marins EG, Berg J, Paar C, Zurl H, Santner BI, Kessler HH. Clin Chem Lab Med. 2017 Mar 1;55(4):517-521. doi: 10.1515/cclm-2016-0620.

BACKGROUND: Determination of the hepatitis C virus (HCV) genotype and discrimination between HCV subtypes 1a and 1b is still mandatory prior to anti-HCV treatment initiation. The aim of this study was to evaluate the performance of the recently introduced cobas® HCV GT assay (Roche) and to compare it to two comparator assays. **METHODS:** The cobas® HCV GT assay is based on primer-specific real-time polymerase chain reaction (PCR). For comparison, the TRUGENE® HCV 5'NC Genotyping Kit (Siemens) and the VERSANT® HCV Genotype

2.0 Assay (Siemens) were employed. Accuracy of the new assay was determined using proficiency panels. For clinical evaluation, 183 residual clinical samples obtained from patients with chronic hepatitis C infection were included. **RESULTS:** When accuracy was tested, panel members containing HCV subtypes 1a, 1b, and 3a were identified as expected; however, the new assay failed to identify low titer panel members containing HCV subtype 5a correctly. Of 183 clinical samples, 160 gave concordant results. For seven samples, an indeterminate result was reported with the cobas® HCV GT assay and the remaining 16 samples were found discordant with one of the comparator assays. When time-to-results of the assays were compared, the new assay showed shorter total time and similar hands-on time per sample. **CONCLUSIONS:** The cobas® HCV GT assay showed a good performance and proved to be suitable for use in the routine diagnostic laboratory. Due to the high level of automation, fast and reliable results are obtained with short hands-on time.

[Linking hepatitis C virus infection to pre-1994 blood transfusions in female patients.](#)
Ramos Flores C1, Echeagaray E2, Castañeda G3, Vargas ML4, Montes-González R4, Luna S5, Díaz L5, Torres O4. Medwave. 2017 Mar 15;17(2):e6886. doi: 10.5867/medwave.2017.02.6886. **INTRODUCTION:** Most blood transfusions occur in female patients. The introduction of serologic screening practices by blood banks reduced the transfusion-related rate of infection with hepatitis C virus (HCV). In Mexico patients with pre-1994 transfusion history are at high risk of being detected with HCV infection. We aimed at establishing an interrelationship between two variables: pre-1994 transfusion history and rate of infection in women treated in the Guadalajara Metropolitan Area hospitals, in Mexico. **METHODS:** Analytical observational case-control study which included both non-infected women and patients diagnosed with hepatitis C virus infection, in whom the pre-1994 transfusion history was determined. The cases were 150 women with confirmed hepatitis C virus serologic diagnosis. The controls were 150 women whose hepatitis C virus-detection serologic tests had yielded negative results. **RESULTS:** An odds ratio of 9.07 (95% CI: 5.37 – 15.3; p< 0.001) was found where the rate of infection for the case group was 0.72 while the control group had a ratio of 0.22; population attributable risk (PAR) was 0.64 (95% CI: 0.53 – 0.73), while etiologic fraction was 0.88 (95% CI: 0.81 – 0.93). **CONCLUSIONS:** Among women, having been exposed to pre-1994 blood transfusion means a risk 9.07 times higher than not being exposed to blood transfusion in the same time frame.

[Does a Primary Health Clinic for Formerly Incarcerated Women Increase Linkage to Care?](#) Morse DS1, Wilson JL2, McMahon JM3, Dozier AM4, Quiroz A2, Cerulli C5. Womens Health Issues. 2017 Mar 13. pii: S1049-3867(17)30065-8. doi: 10.1016/j.whi.2017.02.003. [Epub ahead of print]
OBJECTIVE: This study examined a primary care-based program to address the health needs of women recently released from incarceration by facilitating access to primary medical, mental health, and substance use disorder (SUD) treatment. **STUDY DESIGN:** Peer community health workers recruited women released from incarceration within the past 9 months into the Women's Initiative Supporting Health Transitions Clinic (WISH-TC). Located within an urban academic medical center, WISH-TC uses cultural, gender, and trauma-specific strategies grounded in the self-determination theory of motivation. Data abstracted from intake forms and medical charts were examined using bivariate and multivariable regression analyses. **RESULTS:** Of the 200 women recruited, 100 attended the program at least once. Most (83.0%) did not have a primary

care provider before enrollment. Conditions more prevalent than in the general population included psychiatric disorders (94.0%), substance use (90.0%), intimate partner violence (66.0%), chronic pain (66.0%), and hepatitis C infection (12.0%). Patients received screening and vaccinations (65.9%-87.0%), mental health treatment (91.5%), and SUD treatment (64.0%). Logistic regression revealed that receipt of mental health treatment was associated with number of psychiatric (adjusted odds ratio [AOR], = 4.09; p < .01), and social/behavioral problems (AOR, 2.67; p = .04), and higher median income (AOR, 1.07; p = .05); African American race predicted lower receipt of SUD treatment (AOR, 0.08; p < .01). **CONCLUSIONS:** An innovative primary care transitions program successfully helped women recently released from incarceration to receive medical, mental health, and SUD treatment. Primary care settings with specialty programs, including community health workers, may provide a venue to screen, assess, and help recently incarcerated women access needed care.

[Daclatasvir and asunaprevir treatment in patients with severe liver fibrosis by HCV genotype 1b infection: Real world data.](#) Ishigami M1, Hayashi K1, Honda T1, et al. J Gastroenterol Hepatol. 2017 Mar 4. doi: 10.1111/jgh.13779. [Epub ahead of print]
BACKGROUNDS AND AIMS: In this study, we investigated the real-world data of the first approved interferon free regimen in Japan; daclatasvir as asunaprevir in chronic hepatitis C patients with severe fibrosis. **PATIENTS AND METHODS:** Among 924 patients registered in our multicenter study, 535 patients were defined as having severe fibrosis with Fib-4 index≧3.25, and were included in this study. We investigated anti-viral effect and factors associated with SVR12, and the additional effects on serum AFP and albumin levels by eradicating virus in patients who attained SVR were investigated. In statistical analysis, P<0.05 was considered as significant levels. **RESULTS:** Anti-viral effect was lower in patients with severe fibrosis at 8 and 12 weeks after start of the treatment (96.3%, 97.1% with severe fibrosis vs 99.5%, 99.2% without severe fibrosis, P=0.002 and P=0.036, respectively), and more early relapse (SVR4; 90.4% with severe fibrosis vs 95.4% without fibrosis, P=0.008) were seen in patients with severe fibrosis, however, there were no differences in SVR12 and SVR24. In the safety profiles, discontinuation rate due to liver injury (2.8% with severe fibrosis vs 3.3% without severe fibrosis) or other causes of discontinuation was not different between two groups. Serum AFP significantly decreased and serum albumin levels significantly increased as early as 4 weeks after the start of treatment. **CONCLUSIONS:** Though the anti-viral effect was slightly lower in patients with severe fibrosis compared with those without, treatment with daclatasvir and asunaprevir is basically an effective, and well-tolerable treatment in these populations.

[Variation in the Viral Hepatitis and HIV Policies and Practices of Methadone Maintenance Programs.](#) Jessop AB1, Hom JK, Burke M. J Addict Med. 2017 Mar 1. doi: 10.1097/ADM.0000000000000296. [Epub ahead of print]
OBJECTIVE: Patients prescribed methadone maintenance treatment (MMT) demonstrate elevated prevalence of hepatitis B virus (HBV), hepatitis C virus, and HIV. Government agencies recommend testing for these infections in MMT programs, but uptake is limited. **METHODS:** We audited infection-related policies and practices of all 14 MMT programs in Philadelphia, Pennsylvania, in 2015. Results were tabulated and compared with the results from a 2010 audit of 10 of 12 MMT programs. The audit focused on which patients are tested, timing

and frequency, specific tests ordered, vaccination, and communication of test results.
RESULTS: Written policies were nonspecific, offering little guidance on appropriate testing. The principal change in policy between 2010 and 2015 involved adding clearer guidance for communication of results to patients. In 2010 and 2015, all MMT programs tested new patients for hepatitis C virus antibodies, although retesting of existing patients varied. HBV testing increased from 2010 to 2015, though it was not uniform, with 5 programs testing for HBV surface antibodies and 10 programs testing for HBV surface antigens. Six programs assessed hepatitis vaccination status, but only 1 administered vaccines. In 2010, city-sponsored HIV antibody testing was available at all MMT programs. Without this program in 2015, few MMT programs conducted HIV testing. **CONCLUSIONS:** Despite limited hepatitis and HIV screening in MMT programs nationally, this study shows that testing can be incorporated into routine procedures. MMT programs are positioned to play an integral role in the identification of patients with chronic infections, but additional guidance and resources are required to maximize their impact.

Is response to anti-hepatitis C virus treatment predictive of mortality in hepatitis C virus/HIV-positive patients? Hepatitis C Working Group for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. AIDS. 2017 Mar 13;31(5):661-668. doi: 10.1097/QAD.0000000000001378.
BACKGROUND: Long-term clinical outcomes after hepatitis C virus (HCV) treatment of HIV/HCV patients are not well described. We aimed to compare the risk of all-cause and liver-related death (LRD) according to HCV treatment response in HIV/HCV patients in the multicohort study Collaboration of Observational HIV Epidemiological Research in Europe. **METHODS:** All patients who had started pegylated interferon+ribavirin (baseline) and followed for at least 72 weeks after baseline were included. Patients were categorized into three response groups depending on treatment duration and HCV-RNA measured in the window 24-72 weeks after baseline. Patients who received at least 24 weeks of therapy were defined as responders if their last HCV-RNA measured between 24 and 72 weeks after baseline was negative, and having 'unknown response' if HCV-RNA was unknown. Nonresponders were treated for less than 24 weeks or were HCV-RNA+ between 24 and 72 weeks after baseline. Mortality rates were compared using survival analysis, and Cox regression was used to compare hazard ratios of death between response groups. **RESULTS:** A total of 3755 patients were included: 1031 (27.5%) responders, 1639 (43.6%) nonresponders and 1085 (28.9%) with unknown response. Rates [per 1000 person-years of follow-up, 95% confidence interval (CI)] of all-cause death were 17.59 (14.88-20.78), 10.43 (7.62-14.28) and 11.00 (8.54-14.23) for nonresponders, responders and unknown responders, respectively. After adjustment, the relative hazard (nonresponders vs. responders) for all-cause death, LRD and nonliver-related death was 1.53 (95% CI 1.06-2.22), 3.39 (95% CI 1.32-8.75) and 1.22 (95% CI 0.80-1.84), respectively. **CONCLUSION:** HIV/HCV patients with a favourable virological response to pegylated interferon+ribavirin had reduced risk of all-cause and LRD, whereas there was no difference in risk of nonliver-related death when comparing responders and nonresponders.

International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. Zignego AL1, Ramos-Casals M2, Ferri C3, et al. Autoimmun Rev. 2017 Mar 7. pii: S1568-9972(17)30057-5. doi: 10.1016/j.autrev.2017.03.004. [Epub ahead of print]

Hepatitis C virus (HCV) is both hepatotrophic and lymphotropic virus that causes liver as well extrahepatic manifestations including cryoglobulinemic vasculitis, the most frequent and studied condition, lymphoma, and neurologic, cardiovascular, endocrine-metabolic or renal diseases. HCV-extrahepatic manifestations (HCV-EHMs) may severely affect the overall prognosis, while viral eradication significantly reduces non-liver related deaths. Different clinical manifestations may coexist in the same patient. Due to the variety of HCV clinical manifestations, a multidisciplinary approach along with appropriate therapeutic strategies are required. In the era of interferon-free anti-HCV treatments, international recommendations for the therapeutic management of HCV-EHMs are needed. This implies the need to define the best criteria to use antivirals and/or other therapeutic approaches. The present recommendations, based on qualified expert experience and specific literature, will focus on etiological (antiviral) therapies and/or traditional pathogenetic treatments that still maintain their therapeutic utility.

Liver Disease and Fibrosis Assessment in Substance Use-Related Disorders. Zeremski M1, Martinez A2. Clin Pharmacol Drug Dev. 2017 Mar;6(2):164-168. doi: 10.1002/cpdd.312. Substance users have the highest prevalence of hepatitis C virus (HCV) infection but have rarely been treated, largely because of their mistrust of the health care system, misconceptions about the consequences of the infection, and concerns regarding interferon-related side effects. With the development of highly efficacious, interferon-free therapeutic regimens without significant side effects, the concept of colocating HCV and substance use treatment would appear to be highly feasible. This process has been further facilitated by widespread clinical adaptation of noninvasive assays for fibrosis assessment, which could be performed routinely in substance use treatment facilities. The most commonly used noninvasive fibrosis assessment methods are serum marker indexes and transient elastography, both of which are very accurate in detecting cirrhosis or the absence of fibrosis, but much less successful in identifying intermediate fibrosis stages. The effect of drugs of abuse on the liver is not completely understood or sufficiently studied. There are no indications that heroin and cocaine affect fibrosis progression, but some recreational drugs (eg, alcohol and cannabis) can induce hepatic injury. In addition, knowledge gaps exist on the effect of impaired liver function on metabolism or transport of agents used to treat substance disorders as well as their interactions with HCV antivirals.

Enduring Consequences From the War on Drugs: How Policing Practices Impact HIV Risk Among People Who Inject Drugs in Baltimore City. Flath N1, Tobin K1, King K1, Lee A1, Latkin C1. Subst Use Misuse. 2017 Mar 20:1-8. doi: 10.1080/10826084.2016.1268630. [Epub ahead of print]
BACKGROUND: Neighborhood-level characteristics, including police activity, are associated with HIV and Hepatitis C injection risk-behaviors among people who inject drugs (PWID). However, the pathways through which these neighborhood perceptions shape individual-level HIV risk behaviors are unclear. This study helps to explain perceived behaviors between perceived neighborhood police activity and HIV injection risk behavior (i.e., injection syringe/tool sharing in the previous 6 months). **METHODS:** A sample of (n = 366) PWIDs who self-reported recent use were recruited using community-based outreach methods in Baltimore, Maryland. Neighborhood police perceptions were assessed by asking participants whether they would (1) be more likely to ask others to share injection tools in the context of heightened police activity and (2) be less likely to carry syringes with them due to fear of arrest. Poisson regression

with robust variance was used to identify statistical relationships. Recent police encounters, frequency of heroin injection, and sociodemographic characteristics were controlled for in the model. **RESULTS:** Neighborhood police perceptions shaped injection-risk behavior. Half of the sample (49%) reported an aversion of carrying personal syringes, due to fear of arrest. Those who agreed they would be more likely to ask others to share injection equipment in the context of heightened police activity were more likely to share syringes (21% vs. 3%, p <.01). Adjusted models showed that syringe sharing was independently associated with asking to borrow equipment in neighborhoods with perceived heightened police activity (aPR: 2.22, 95% confidence interval (CI): 1.7, 3.0). **CONCLUSION:** This study sheds light on how police perceptions may influence injection risk behavior. While these relationships require further elucidation, this study suggests that public health interventions aiming to reduce HIV risk would benefit from improving community-police relationships.

Considerations on bringing warehoused HCV patients into active care following interferon-free, direct-acting antiviral drug approval. Palak A1, Livoti C1, Audibert C1. Postgrad Med. 2017 Mar 15:1-5. doi: 10.1080/00325481.2017.1304795. [Epub ahead of print]
OBJECTIVES: Until recently, lack of efficacious and tolerable hepatitis C virus (HCV) treatments prompted patient warehousing until better treatment options became available. We investigated whether the introduction of ledipasvir/sofosbuvir precipitated patient return to clinics, thereby changing HCV clinic dynamics. **METHODS:** Online questionnaire responses indicated the volume of HCV patients followed, the proportion of warehoused patients and those who were proactively offered new options, methods for identifying and contacting patients, and insurance authorization/reimbursement-related information. **RESULTS:** Of 168 practices surveyed, 19% indicated no patient warehousing in the previous 3 years; 81% had warehoused 40% of patients; 92% were able to handle their patient load; and 82% had not changed practices to accommodate more HCV patients in the previous 12 months. Of the 35% of patients who were ledipasvir/sofosbuvir-eligible, 50% already completed/are completing therapy, 21% were not treated due to insurance denial, and 19% were awaiting responses from insurance companies. **CONCLUSIONS:** Launch of a new treatment did not overburden HCV practices. Patients eligible to receive new treatments were being treated, but pre-authorization processes and reimbursement denials reduced the numbers of treated patients.

"Where's My Choice?" An Examination of Veteran and Provider Experiences With Hepatitis C Treatment Through the Veteran Affairs Choice Program. Tsai J1, Yakovchenko V, Jones N, Skolnik A, Noska A, Gifford AL, McInnes DK. Med Care. 2017 Mar 3. doi: 10.1097/MLR.0000000000000706. [Epub ahead of print]
BACKGROUND: The Department of Veterans Affairs (VA) is the country's largest provider for chronic hepatitis C virus (HCV) infection. The VA created the Choice Program, which allows eligible veterans to seek care from community providers, who are reimbursed by the VA. **OBJECTIVES:** This study aimed to examine perspectives and experiences with the VA Choice Program among veteran patients and their HCV providers. **RESEARCH DESIGN:** Qualitative study based on semistructured interviews with veteran patients and VA providers. Interview transcripts were analyzed using rapid assessment procedures based in grounded theory. **SUBJECTS:** A total of 38 veterans and 10 VA providers involved in HCV treatment across 3 VA medical centers were interviewed. **MEASURES:** Veterans and providers were asked open-

ended questions about their experiences with HCV treatment in the VA and through the Choice Program, including barriers and facilitators to treatment access and completion.

RESULTS: Four themes were identified: (1) there were difficulties in enrollment, ongoing upport, and billing with third-party administrators; (2) veterans experienced a lack of choice in location of treatment; (3) fragmented care led to coordination challenges between VA and community providers; and (4) VA providers expressed reservations about sending veterans to community providers. **CONCLUSIONS:** The Choice Program has the potential to increase veteran access to HCV treatment, but veterans and VA providers have described substantial problems in the initial years of the program. Enhancing care coordination, incorporating shared decision-making, and establishing a wide network of community providers may be important areas for further development in designing community-based specialist services for needy veterans.

HEPATOCELLULAR (LIVER) CANCER

HCV core inhibits hepatocellular carcinoma cell replicative senescence through downregulating microRNA-138 expression. Shiu TY[1], Shih YL[1], Feng AC[2], Lin HH[1], Huang SM[3], Huang TY[1], Hsieh CB[2], Chang WK[1], Hsieh TY[4]. J Mol Med (Berl). 2017 Mar 3. doi: 10.1007/s00109-017-1518-4. [Epub ahead of print]

Hepatitis C virus (HCV) infection is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). HCV core protein is considered as a positive regulator of telomerase activity. In this study, we focused on the deregulated microRNA-138 (miR-138) in HCV-associated HCC. Differential expression of miR-138 was determined by TaqMan quantitative real-time PCR. The target gene of miR-138 was verified by luciferase reporter assay, quantitative real-time PCR, and Western blotting. Moreover, three assays based on telomerase activity, cell proliferation, and senescence-associated β-galactosidase activity were performed. The correlation analysis revealed a significantly negative correlation between miR-138 and telomerase reverse transcriptase (TERT) mRNA expression in HCC. Further, we showed that mature HCV core protein of 173 amino acids, but not full-length form of 191 amino acids, suppressed miR-138 expression. TERT was verified as a direct target of miR-138 in HCC cells. Furthermore, TERT-targeting miR-138 supplementation can prevent HCV core protein from repressing HCC cell replicative senescence. Collectively, HCV core protein can enhance TERT protein expression through downregulating TERT-targeting miR-138 expression, which in turn inhibits HCC cell replicative senescence. This study may further help our understanding on the pathogenic mechanisms of HCV core protein in HCV-associated HCC development. KEY MESSAGE: miR-138 is downregulated in HCV-associated HCC. Mature HCV core protein plays a pathogenic role in suppressing miR-138 expression. Telomerase reverse transcriptase represents a direct target of miR-138 in HCC cells. miR-138 promotes HCC cell senescence, suggesting potential for HCC treatment.

Liver Transplant (LT) recipients with Nonalcoholic Steatohepatitis (NASH) Have Lower Risk Hepatocellular Carcinoma (HCC). Lewin SM1, Mehta N1, Kelley RK2, Roberts JP3, Yao FY1, Brandman D1. Liver Transpl. 2017 Mar 24. doi: 10.1002/lt.24764. [Epub ahead of print]

BACKGROUND: Liver transplantation is a well-established treatment for HCC in carefully selected patients. Risk factors for tumors with poor prognostic features on explant have not been

well described in a national cohort. **METHODS:** We performed a retrospective cohort study of adult LT recipients with HCC transplanted from 4/8/12 (when explant pathology in UNOS became available) until 9/30/2014. We evaluated the association between listing diagnosis and other demographic factors with tumor features on explant using logistic regression. High-risk tumor features included: >3 tumors, largest tumor >5 cm, presence of vascular invasion, presence of metastases, and poor differentiation of tumor. **RESULTS:** 3733 LT recipients with HCC who had complete explant data in UNOS were included. The median age was 60, 78% were male and 68% were white. 2608 (70%) had hepatitis C (HCV), 271 (7%) had NASH, 246 (7%) had alcoholic cirrhosis, and 189 (5%) had hepatitis B (HBV) as the primary non-HCC listing diagnosis. 1140 (31%) had evidence of ≥1 high-risk explant feature(s). The presence of ≥1 high-risk explant feature(s) was associated with HCC recurrence post-transplant (OR 5.00; p<0.001). Compared to HCV-associated HCC transplant recipients, individuals with NASH had lower likelihood of high-risk explant features (OR 0.71, p=0.02) after adjusting for covariables. Women were more likely to have high-risk explant features (OR 1.23, p=0.04). Diabetes mellitus was not associated with high-risk explant features. **CONCLUSION:** LT recipients with NASH-associated HCC had fewer high-risk tumor features on explant compared to HCV-associated HCC, despite having higher rates of DM and other potential risk factors for the development of HCC. Women had a higher likelihood of high-risk tumor features. Further study is warranted whether these differences are due to disease-specific or gender-specific influences on tumor biology or due to selection criteria for transplant. This article is protected by copyright. All rights reserved.

[**Global Trends and Predictions in Hepatocellular Carcinoma Mortality.**](#) Bertuccio P1, Turati F1, Carioli G1, Rodriguez T2, La Vecchia C3, Malvezzi M4, Negri E5. J Hepatol. 2017 Mar 20. pii: S0168-8278(17)30145-9. doi: 10.1016/j.jhep.2017.03.011. [Epub ahead of print]
BACKGROUND: Hepatocellular carcinoma (HCC) has been one of the few cancers showing upward trends over recent decades in most countries, and is the third cause of cancer death worldwide. **PATIENTS AND METHODS:** We updated global trends in HCC mortality to 2014, and predicted trends in rates in the EU, USA and Japan to 2020, using data from the World Health Organization database. **RESULTS:** In EU men, mortality rates were stable in the last decade around 3.5/100,000. HCC mortality tended to increase in northern and central Europe and to decrease in southern Europe. In the USA, HCC mortality increased by 35% between 2002 and 2012, to reach 3.1/100,000 men in 2012, and is predicted to remain stable to 2020. Substantial falls were observed in eastern Asia, though the rates remained around 10-24/100,000 men. In Japan, HCC mortality is predicted to decrease (5.4/100,000 men in 2020). Trends were favorable in the young, while unfavorable in middle aged, except in eastern Asia. Rates were 3-5 fold lower in women than in men in most areas, but trends were similar. **CONCLUSIONS:** Control of hepatitis B (HBV) and hepatitis C (HCV) virus infections mainly explains HCC mortality falls in eastern Asia and southern Europe. The unfavorable trends in other areas of the world are due to HCV (and HBV) epidemics between the 60s and 80s, changes in alcohol consumption, and increased overweight/obesity, and consequently diabetes. Improvements in the management of cirrhosis and in HCC diagnosis and treatment account for part of the mortality trends worldwide. **LAY SUMMARY:** HCC is one of the few major cancer sites showing unfavorable trends in several areas of the world over the last few decades. In this work, we updated worldwide mortality trends from HCC from 1990 to 2014, and predicted its trends for selected major countries to 2020. We observed unfavorable trends in the EU, North and Latin America.

Substantial declines were registered in eastern Asia, where however rates were two- to five-fold higher than most European countries and the Americas. Steady declines to 2020 are predicted for eastern Asia but not for Europe and the Americas.

[Features of hepatocellular carcinoma in Hispanics differ from African Americans and non-Hispanic Whites.](#) Venepalli NK1, Modayil MV1, Berg SA1, et al. World J Hepatol. 2017 Mar 8;9(7):391-400. doi: 10.4254/wjh.v9.i7.391.
AIM: To compare features of hepatocellular carcinoma (HCC) in Hispanics to those of African Americans and Whites. **METHODS:** Patients treated for HCC at an urban tertiary medical center from 2005 to 2011 were identified from a tumor registry. Data were collected retrospectively, including demographics, comorbidities, liver disease characteristics, tumor parameters, treatment, and survival (OS) outcomes. OS analyses were performed using Kaplan-Meier method. **RESULTS:** One hundred and ninety-five patients with HCC were identified: 80.5% were male, and 22% were age 65 or older. Mean age at HCC diagnosis was 59.7 ± 9.8 years. Sixty-one point five percent of patients had Medicare or Medicaid; 4.1% were uninsured. Compared to African American (31.2%) and White (46.2%) patients, Hispanic patients (22.6%) were more likely to have diabetes ($P = 0.0019$), hyperlipidemia ($P = 0.0001$), nonalcoholic steatohepatitis (NASH) ($P = 0.0021$), end stage renal disease ($P = 0.0057$), and less likely to have hepatitis C virus ($P < 0.0001$) or a smoking history ($P < 0.0001$). Compared to African Americans, Hispanics were more likely to meet criteria for metabolic syndrome ($P = 0.0491$), had higher median MELD scores ($P = 0.0159$), ascites ($P = 0.008$), and encephalopathy ($P = 0.0087$). Hispanic patients with HCC had shorter OS than the other racial groups ($P = 0.020$), despite similarities in HCC parameters and treatment. **CONCLUSION:** In conclusion, Hispanic patients with HCC have higher incidence of modifiable metabolic risk factors including NASH, and shorter OS than African American and White patients.

[Prediction of recurrence following hepatectomy in patients with hepatitis C virus infection-related hepatocellular carcinoma who achieved a sustained virological response.](#) Okimoto S1, Kobayashi T1, Kuroda S1, et al. Hepatol Res. 2017 Mar 21. doi: 10.1111/hepr.12896. [Epub ahead of print]
AIM: The risk of hepatitis C virus infection-related hepatocellular carcinoma (HCC) is lower, with a better prognosis, in patients who achieve a sustained virological response (SVR) than in those who do not. We aimed to identify risk factors of post-hepatectomy HCC recurrence in patients who achieved a SVR. **METHODS:** This retrospective study included 349 HCC patients who underwent an initial radical hepatectomy at our institution between January 2005 and December 2014. Sixty-eight patients had achieved a SVR (the SVR group) and 281 patients had not (the non-SVR group). Clinical characteristics and long-term outcomes were compared between the groups. Univariate and multivariate analyses identified variables associated with recurrence-free survival in the SVR group. **RESULTS:** Post-hepatectomy overall and recurrence-free survival rates were significantly higher in the SVR group than the non-SVR group ($p < 0.01$ and $p < 0.05$, respectively). Univariate analysis of post-hepatectomy recurrence-free survival in the SVR group revealed multiple significant factors: aspartate aminotransferase, ≥25 IU/L ($p = 0.01$); indocyanine green retention rate at 15 minutes, ≤20.0% ($p < 0.05$); hepatic vascular invasion ($p < 0.05$), and an interval of ≤30 months between achieving a SVR and hepatectomy ($p < 0.01$). Multivariate analysis confirmed an interval of ≤30 months between achieving a SVR and hepatectomy as an independent prognostic factor of recurrence-free

survival (hazard ratio: 2.30, 95.0% confidence interval: 1.04-5.13; p < 0.05). **CONCLUSION:** The interval between achieving a SVR and hepatectomy is an important predictor of recurrence in hepatitis C virus infection-related HCC patients who achieved a SVR.

Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals.
Baumert TF1,2,3, Jühling F1,2, Ono A4,5, Hoshida Y6. BMC Med. 2017 Mar 14;15(1):52. doi: 10.1186/s12916-017-0815-7.
Hepatitis C virus infection is a major cause of hepatocellular carcinoma worldwide. Interferon has been the major antiviral treatment, yielding viral clearance in approximately half of patients. New direct-acting antivirals substantially improved the cure rate to above 90%. However, access to therapies remains limited due to the high costs and under-diagnosis of infection in specific subpopulations, e.g., baby boomers, inmates, and injection drug users, and therefore, hepatocellular carcinoma incidence is predicted to increase in the next decades even in high-resource countries. Moreover, cancer risk persists even after 10 years of viral cure, and thus a clinical strategy for its monitoring is urgently needed. Several risk-predictive host factors, e.g., advanced liver fibrosis, older age, accompanying metabolic diseases such as diabetes, persisting hepatic inflammation, and elevated alpha-fetoprotein, as well as viral factors, e.g., core protein variants and genotype 3, have been reported. Indeed, a molecular signature in the liver has been associated with cancer risk even after viral cure. Direct-acting antivirals may affect cancer development and recurrence, which needs to be determined in further investigation.

Hepatitis C virus NS3 protein enhances hepatocellular carcinoma cell invasion by promoting PPM1A ubiquitination and degradation. Zhou Y1, Zhao Y1, Gao Y1, et al. J Exp Clin Cancer Res. 2017 Mar 10;36(1):42. doi: 10.1186/s13046-017-0510-8.
BACKGROUND: Growing evidence suggests that hepatitis C virus (HCV) contributes to hepatocellular carcinoma (HCC) by directly modulating oncogenic signaling pathways. Protein phosphatase magnesium-dependent 1A (PPM1A) has recently emerged as an important tumor suppressor as it can block a range of tumor-centric signaling pathways through protein dephosphorylation. However, the role and regulatory mechanisms of PPM1A in HCV-infected cells have not been reported. **METHODS:** Total, cytoplasmic, and nuclear PPM1A protein after HCV infection or overexpression of HCV nonstructural protein 3 (NS3) were detected by western blotting. The expression of PPM1A in normal liver and HCV-related HCC tissues was quantified by immunohistochemistry. The effects of HCV infection and NS3 expression on the PPM1A protein level were systematically analyzed, and the ubiquitination level of PPM1A was determined by precipitation with anti-PPM1A and immunoblotting with either anti-ubiquitin or anti-PPM1A antibody. Finally, the roles of NS3 and PPM1A in hepatoma cell migration and invasion were assessed by wound healing and transwell assays, respectively. **RESULTS:** HCV infection and replication decreased PPM1A abundance, mediated by NS3, in hepatoma cells. Compared to normal liver tissues, the expression of PPM1A was significantly decreased in the HCC tumor tissues and adjacent non-tumor tissues. NS3 directly interacted with PPM1A to promote PPM1A ubiquitination and degradation, which was dependent on its protease domain. Blockade of PPM1A through small interfering RNA significantly promoted HCC cell migration, invasion, and epithelial mesenchymal transition (EMT), which were further intensified by TGF-β1 stimulation, in vitro. Furthermore, restoration of PPM1A abrogated the NS3-mediated promotion of HCC migration and invasion to a great extent, which was dependent on its protein phosphatase function. **CONCLUSIONS:** Our findings demonstrate that the HCV protein NS3

can downregulate PPM1A by promoting its ubiquitination and proteasomal degradation, which might contribute to the migration and invasion of hepatoma cells and may represent a new strategy of HCV in carcinogenesis.

Impact of Hepatitis C Virus Eradication on the Clinical Outcome of Patients with Hepatitis C Virus-Related Advanced Hepatocellular Carcinoma Treated with Sorafenib.
Kawaoka T, Aikata H, Teraoka Y, et al. Oncology. 2017 Mar 1. doi: 10.1159/000458532. [Epub ahead of print]
OBJECTIVE: To evaluate the impact of hepatitis C virus (HCV) eradication on the clinical outcome of patients with HCV-related advanced hepatocellular carcinoma (HCC) treated with sorafenib. **METHODS:** A total of 58 HCV-related advanced HCC patients with Child-Pugh grade A disease who were treated with sorafenib were enrolled in this retrospective cohort study. Of these, 27 patients were HCV RNA negative as a result of previous antiviral therapy (sustained viral response [SVR] group), while the remaining 31 were HCV RNA positive (non-SVR group). **RESULTS:** The response rate, disease control rate and median time to progression in the SVR group (6, 46.0%, and 3.8 months, respectively) were similar to those in the non-SVR group (3, 51.5%, and 2.7 months, respectively). On the other hand, the median time to treatment failure (TTTF), post-progression survival (PPS), and overall survival (OS) were significantly longer in the SVR group than in the non-SVR group (9.7, 8.5, and 15 months vs. 5.9, 5.2, and 9.3 months; $p = 0.023$, 0.02, and 0.014, respectively). On multivariate analysis, SVR was identified as a significant and independent determinant of PPS ($p = 0.009$), TTTF ($p = 0.028$), and OS ($p = 0.01$). **CONCLUSION:** HCV eradication before sorafenib treatment for HCV-related advanced HCC could prolong PPS and TTTF and improve OS.

Effectiveness of hepatitis c antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. Beste LA1, Green PK2, Berry K2, Kogut MJ3, Allison SK3, Ioannou GN4. J Hepatol. 2017 Mar 3. pii: S0168-8278(17)30126-5. doi: 10.1016/j.jhep.2017.02.027. [Epub ahead of print]
BACKGROUND & AIMS: Hepatitis C virus (HCV) treatment for patients with hepatocellular carcinoma (HCC) was uncommon before direct acting antiviral (DAA) medications. Real-world effectiveness of DAAs for HCV in patients with HCC is unclear. We describe rates of sustained virologic response (SVR) with DAA regimens by HCV genotype in patients with history of HCC. **METHODS:** We identified patients who initiated antiviral treatment between January 1, 2014 and June 30, 2015 in the national Veterans Affairs health care system. Regimens included sofosobuvir, ledipasvir/ sofosbuvir, and paritaprevir/ ritonavir/ ombitasvir and dasabuvir with or without ribavirin. HCC patients were divided into those who were treated with liver transplantation after HCC diagnosis ("HCC/LT" group) and those treated with other modalities prior to antiviral therapy ("HCC" group). **RESULTS:** Of 17,487 HCV treatment recipients, 624 (3.6%) had prior HCC, including 142 with HCC/LT and 482 with HCC. Overall SVR was 91.9% in non- HCC, 74.5% in HCC, and 93.4% in HCC/LT. Among HCC patients, genotype 1 had the highest SVR overall (79.0% in HCC and 96.0% in HCC/LT), and genotype 3 the lowest (47.0% in HCC and 88.9% in HCC/LT). After adjustment for confounders, the presence of HCC was associated with lower likelihood of SVR overall (AOR 0.38 [95%CI 0.29, 0.48], p<.001). **CONCLUSION:** HCV can be cured with DAAs in the majority of patients with prior HCC, and in virtually all HCC patients post-liver transplant. Deferral of HCV treatment until the post-transplant setting may be considered among HCC patients listed for transplantation.