



March & April, 2018

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Relationship of muscle cramps to quality of life and sleep disturbance in patients with chronic liver diseases: a nationwide study.](#) Iwasa M1, Karino Y2, Kawaguchi T3, et al. Liver Int. 2018 Mar 27. doi: 10.1111/liv.13745. [Epub ahead of print]

BACKGROUND & AIMS: Although muscle cramps frequently occur in patients with cirrhosis, the importance of muscle cramps remains unclear. The aims of this study were to investigate the relationship of muscle cramps with quality of life (QOL) and sleep disturbance. In addition, this multi-institutional collaborative study in Japan investigated factors associated with muscle cramps in patients with cirrhosis. **METHODS:** A total of 1,788 patients with chronic liver diseases including both non-cirrhosis and cirrhosis completed a questionnaire survey investigating: i) frequency of muscle cramps, ii) relationship of muscle cramps to poor QOL and sleep disturbance, iii) characteristics of patients who require therapeutic intervention, and iv) characteristics of patients prone to experiencing muscle cramps. **RESULTS:** This study revealed that 51.8% of patients with cirrhosis have experienced muscle cramps. People who experienced muscle cramps were more likely to have reduced QOL and sleep disturbance if muscle cramps had i) high frequency (occurring daily to a few times per week, $P < 0.01$); ii) long duration (between a few minutes and a few hours, $P < 0.01$); and iii) intense severity (visual analogue scale ≥ 4 , $P < 0.01$). Age, female sex, positive results for hepatitis C virus, low serum albumin concentration, and cirrhosis were independent factors related to the severity of muscle cramps. **CONCLUSION:** Muscle cramps occurred with great frequency and were associated with various factors such as age, sex, hepatitis C virus, and liver function. Many patients experience poor QOL (26.3%) due to muscle cramps, and therapeutic interventions are therefore needed.

[Integrated Resistance Analysis of CERTAIN-1 and CERTAIN-2 Studies in Hepatitis C Virus-Infected Patients Receiving Glecaprevir and Pibrentasvir in Japan.](#) Krishnan P1, Schnell G2, Tripathi R2, et al. Antimicrob Agents Chemother. 2018 Jan 25;62(2). pii: e02217-17. doi: 10.1128/AAC.02217-17. Print 2018 Feb.

Glecaprevir and pibrentasvir are hepatitis C virus (HCV) pangenotypic inhibitors targeting NS3/4A protease and NS5A, respectively. This once-daily, fixed-dose combination regimen demonstrated high sustained virologic response 12 weeks postdosing (SVR12) rates in CERTAIN-1 and CERTAIN-2 studies in Japanese HCV-infected patients, with a low virologic failure rate (1.2%). There were no virologic failures among direct-acting antiviral (DAA)-treatment-naive genotype 1a (GT1a) ($n = 4$)-, GT1b ($n = 128$)-, and GT2 ($n = 97$)-infected

noncirrhotic patients treated for 8 weeks or among GT1b (n = 38)- or GT2 (n = 20)-infected patients with compensated cirrhosis treated for 12 weeks. Two of 33 DAA-experienced and 2 of 12 GT3-infected patients treated for 12 weeks experienced virologic failure. Pooled resistance analysis, grouped by HCV subtype, treatment duration, prior treatment experience, and cirrhosis status, was conducted. Among DAA-naive GT1b-infected patients, the baseline prevalence of NS3-D168E was 1.2%, that of NS5A-L31M was 3.6%, and that of NS5A-Y93H was 17.6%. Baseline polymorphisms in NS3 or NS5A were less prevalent in GT2, with the exception of the common L/M31 polymorphism in NS5A. Among DAA-experienced GT1b-infected patients (30/32 daclatasvir plus asunaprevir-experienced patients), the baseline prevalence of NS3-D168E/T/V was 48.4%, that of NS5A-L31F/I/M/V was 81.3%, that of the NS5A P32deletion was 6.3%, and that of NS5A-Y93H was 59.4%. Common baseline polymorphisms in NS3 and/or NS5A had no impact on treatment outcomes in GT1- and GT2-infected patients; the impact on GT3-infected patients could not be assessed due to the enrollment of patients infected with diverse subtypes and the limited number of patients. The glecaprevir-pibrentasvir combination regimen allows a simplified treatment option without the need for HCV subtyping or baseline resistance testing for DAA-naive GT1- or GT2-infected patients. (The CERTAIN-1 and CERTAIN-2 studies have been registered at ClinicalTrials.gov under identifiers NCT02707952 and NCT02723084, respectively.).

Pharmacokinetic Interactions and Safety of Coadministration of Glecaprevir and Pibrentasvir in Healthy Volunteers. Lin CW1, Dutta S1, Zhao W1, Asatryan A2, Campbell A2, Liu W3. Eur J Drug Metab Pharmacokinet. 2018 Feb;43(1):81-90. doi: 10.1007/s13318-017-0428-8.

BACKGROUND AND OBJECTIVE: Glecaprevir and pibrentasvir are pangenotypic direct-acting antiviral agents for the treatment of chronic hepatitis C virus infection. The aim of the present study was to evaluate the drug-drug interaction and safety of glecaprevir and pibrentasvir coadministration in healthy volunteers. **METHODS:** In this open-label, randomized, multiple-dose, Phase 1 study in 72 subjects, glecaprevir (100-1200 mg once daily) and pibrentasvir (40-200 mg once daily) were administered alone for 7 days and then in combination for another 7 days. Intensive blood sampling was performed on Days 1, 7, 8, and 14, and pharmacokinetic interactions were assessed using a repeated measures analysis of glecaprevir and pibrentasvir maximum plasma concentration (C max) and area under the curve (AUC). **RESULTS:** Coadministration of glecaprevir 400 mg increased pibrentasvir 120 and 40 mg steady-state C max and AUC values to 2.9-6.3-fold, and coadministration of glecaprevir 700 mg increased pibrentasvir 160 mg steady-state C max and AUC₂₄ values to up to sevenfold of the values when pibrentasvir was administered alone. Glecaprevir C max and AUC values during coadministration were less than 1.5-fold of the values when glecaprevir was administered alone. The combination of glecaprevir and pibrentasvir at doses up to 400 mg was well tolerated by the healthy subjects in this study. High glecaprevir exposures at 700 and 1200 mg were associated with grade 2/3 elevations in alanine aminotransferase, aspartate aminotransferase, and/or bilirubin. **CONCLUSIONS:** Coadministration of pibrentasvir 120 mg with glecaprevir doses up to 400 mg resulted in increases in pibrentasvir exposures without significant changes in glecaprevir exposures in the absence of any clinically significant laboratory abnormalities. PMID: 28688001

[Predictors of functional benefit of hepatitis C therapy in a 'real-life' cohort.](#) Steinebrunner N1, Stein K2, Sandig C1, Bruckner T3, Stremmel W1, Pathil A4. World J Gastroenterol. 2018 Feb 21;24(7):852-861. doi: 10.3748/wjg.v24.i7.852.

AIM: To define predictors of functional benefit of direct-acting antivirals (DAAs) in patients with chronic hepatitis C virus (HCV) infection and liver cirrhosis. **METHODS:** We analysed a cohort of 199 patients with chronic HCV genotype 1, 2, 3 and 4 infection involving previously treated and untreated patients with compensated (76%) and decompensated (24%) liver cirrhosis at two tertiary centres in Germany. Patients were included with treatment initiation between February 2014 and August 2016. All patients received a combination regimen of one or more DAAs for either 12 or 24 wk. Predictors of functional benefit were assessed in a univariable as well as multivariable model by binary logistic regression analysis. **RESULTS:** Viral clearance was achieved in 88% (175/199) of patients. Sustained virological response (SVR) 12 rates were as follows: among 156 patients with genotype 1 infection the SVR 12 rate was 90% (n = 141); among 7 patients with genotype 2 infection the SVR 12 rate was 57% (n = 4); among 30 patients with genotype 3 infection the SVR 12 rate was 87% (n = 26); and among 6 patients with genotype 4 infection the SVR 12 rate was 67% (n = 4). Follow-up MELD scores were available for 179 patients. A MELD score improvement was observed in 37% (65/179) of patients, no change of MELD score in 41% (74/179) of patients, and an aggravation was observed in 22% (40/179) of patients. We analysed predictors of functional benefit from antiviral therapy in our patients beyond viral eradication. We identified the Child-Pugh score, the MELD score, the number of platelets and the levels of albumin and bilirubin as significant factors for functional benefit. **CONCLUSION:** Our data may contribute to the discussion of potential risks and benefits of antiviral therapy with individual patients infected with HCV and with advanced liver disease.

[Rationale, design, and methodology of a trial evaluating three models of care for HCV treatment among injection drug users on opioid agonist therapy.](#) Akiyama MJ1, Agyemang L1, Arnsten JH1, Heo M2, Norton BL1, Schackman BR3, Linas BP4, Litwin AH5,6,7. BMC Infect Dis. 2018 Feb 9;18(1):74. doi: 10.1186/s12879-018-2964-5.

BACKGROUND: People who inject drugs (PWID) constitute 60% of the approximately 5 million people in the U.S. infected with hepatitis C virus (HCV). Treatment of PWID is complex due to addiction, mental illness, poverty, homelessness, lack of positive social support, poor adherence-related skills, low motivation and knowledge, and poor access to and trust in the health care system. New direct-acting antiviral medications are available for HCV with high cure rates and few side effects. The life expectancy and economic benefits of new HCV treatments will not be realized unless we determine optimal models of care for the majority of HCV-infected patients. The purpose of this study is to evaluate the effectiveness of directly observed therapy and group treatment compared with self-administered individual treatment in a large, urban opioid agonist therapy clinic setting in the Bronx, New York. **METHODS/DESIGN:** In this randomized controlled trial 150 PWID with chronic HCV were recruited from opioid agonist treatment (OAT) clinics and randomized to one of three models of onsite HCV treatment in OAT: 1) modified directly observed therapy; 2) group treatment; or 3) control - self-administered individual treatment. Participants were age 18 or older, HCV genotype 1, English or Spanish speaking, treatment naïve (or treatment experienced after 12/3/14), willing to receive HCV treatment onsite, receiving methadone or buprenorphine at the medication window at least once per week, and able to provide informed consent. Outcomes of interest include adherence (as

measured by self-report and electronic blister packs), HCV treatment completion, sustained virologic response, drug resistance, and cost-effectiveness. **DISCUSSION:** This paper describes the design and rationale of a randomized controlled trial comparing three models of care for HCV therapy delivered in an opioid agonist treatment program. Our trial will be critical to rigorously identify models of care that result in high adherence and cure rates. Use of blister pack technology will help us determine the role of adherence in successful cure of HCV. Moreover, the trial methodology outlined here can serve as a template for the development of future programs and studies among HCV-infected drug users receiving opioid agonist therapy, as well as the cost-effectiveness of such programs. **TRIAL REGISTRATION:** This trial was registered with ClinicalTrials.gov (NCT01857245). Trial registration was obtained prospectively on May 20th, 2013.

[**Incidence of Drug Interactions Identified by Clinical Pharmacists in Veterans Initiating Treatment for Chronic Hepatitis C Infection.**](#) Ottman AA1, Townsend ML1, Hashem MG1, DiMondi VP2, Britt RB1. *Ann Pharmacother.* 2018 Mar 1;1060028018766507. doi: 10.1177/1060028018766507. [Epub ahead of print]

BACKGROUND: Many direct-acting antivirals (DAAs) have drug-drug interactions (DDIs) with the potential to affect efficacy and safety. **OBJECTIVE:** To describe the incidence and severity of DDIs with DAAs identified by the hepatitis C virus (HCV) clinical pharmacist within a Veterans Affairs health care system. **METHODS:** This single-center, retrospective cohort study evaluated patients with HCV treated with DAA therapy. Primary end points included the total number of identified DDIs, percentage of patients with at least 1 DDI, mean number of DDIs per patient, and the number of DDIs by severity category. Additional end points included characterization of interacting drugs, clinical consequence of interaction, intervention recommended, acceptance rate of actionable recommendations, and achievement of sustained virological response 12 weeks after treatment (SVR12). **RESULTS:** A total of 300 patients were included. There were 554 identified DDIs, and 80.3% of patients had at least 1 DDI, with an average of 1.85 DDIs per patient; 76% of the DDIs identified were categorized as either a potentially clinically significant or critical interaction. The most common DDIs involved acid suppression agents (20%). Patient monitoring was the most commonly recommended intervention (59%), followed by dose modification of the interacting medication (30%). There was no difference in SVR12 between patients with at least 1 DDI compared with those with no DDIs (94.8% vs 95.8%; $P = 0.73$). There were a total of 227 actionable recommendations, with an acceptance rate of 84.1%. **CONCLUSIONS:** This study suggests that DDIs are prevalent among patients treated with DAAs for HCV. A HCV clinical pharmacist can help optimize patient care by identifying DDIs and recommending interventions to providers.

[**Safety and efficacy of ledipasvir/sofosbuvir with or without ribavirin in hepatitis C genotype 1 patients including those with decompensated cirrhosis who failed prior treatment with simeprevir/sofosbuvir.**](#) Modi AA1, Nazario HE2, Gonzales GR3, Gonzalez SA1. *Aliment Pharmacol Ther.* 2018 Mar 23. doi: 10.1111/apt.14604. [Epub ahead of print]

BACKGROUND: Combination therapy of simeprevir (SIM)/sofosbuvir (SOF) is an approved treatment for hepatitis C genotype (gen) 1 with overall SVR12 rate of 85%-95%. The single tablet fixed-dose combination of ledipasvir (LDV)/SOF is also approved for gen 1 with sustained virologic response at 12 weeks (SVR12) rates $\geq 95\%$. No data are available on the efficacy of retreatment with LDV/SOF in patients who failed initial treatment with SIM/SOF. **AIM:** Our

aim was to evaluate the efficacy of retreatment with LDV/SOF ± ribavirin (RBV) in gen 1 patients who had previously failed treatment with SIM/SOF. **METHODS:** Data from a combined treatment cohort of 2 hepatology centres, which included patients previously treated with SIM/SOF ± RBV for 12 weeks but failed to achieve SVR and then underwent retreatment with LDV/SOF ± RBV, were analysed (n = 30). LDV/SOF ± RBV was administered for 12-24 weeks based on the discretion of the treating hepatologist. **RESULTS:** Of the 30 patients, 23 (77%) were male, 77% were Caucasian and 26 (87%) were gen 1a. 26 (86%) had cirrhosis, of which 16 (62%) had decompensated, Child's class B or C cirrhosis. Three patients were liver transplant recipients with recurrent hepatitis C. Overall, 27/30 (90%) achieved SVR. Treatment was well tolerated with 37% reporting no adverse events. The most common adverse events were fatigue, headache, insomnia and nausea. Two patients with Child's B cirrhosis required hospitalization during treatment for variceal haemorrhage and abdominal pain respectively. However, no treatment discontinuations or deaths occurred. **CONCLUSION:** Single tablet fixed-dose combination LDV/SOF ± RBV is efficacious and well tolerated in patients who previously failed treatment with SIM/SOF, including those with decompensated cirrhosis and recurrent hepatitis C following liver transplantation.

Fatty liver in hepatitis C patients post-sustained virological response with direct-acting antivirals. Noureddin M1, Wong MM2, Todo T3, Lu SC4, Sanyal AJ5, Mena EA2. World J Gastroenterol. 2018 Mar 21;24(11):1269-1277. doi: 10.3748/wjg.v24.i11.1269.

AIM: To determine steatosis and fibrosis prevalence in hepatitis C patients after a sustained virological response achieved with direct-acting antivirals. **METHODS:** Transient elastography with controlled attenuation parameter (CAP) was used to assess hepatic steatosis post-sustained virological response (SVR); the CAP technology was not available in the United States at study initiation. Liver stiffness/fibrosis was measured before and 47 wk after treatment completion. Patients with genotype 3 and patients with cirrhosis were excluded. **RESULTS:** One hundred and one patients were included in the study. Post-SVR there were decreases from baseline in alanine aminotransferase (ALT) (63.1 to 17.8 U/L), aspartate aminotransferase (51.8 to 21.5 U/L) and fibrosis score (7.4 to 6.1 kPa) (P < 0.05). Post-SVR, 48 patients (47.5%) had steatosis on CAP; of these, 6.25% had advanced fibrosis. Patients with steatosis had higher body mass index (29.0 vs 26.1 kg/m²), glucose (107.8 vs 96.6 mg/dL), ALT (20.4 vs 15.3 mg/dL), CAP score (296.3 vs 212.4 dB/m) and fibrosis score (7.0 vs 5.3 kPa); P < 0.05. Interestingly, compared to baseline, both patients with and without steatosis had change in fibrosis score post-SVR (7.7 kPa vs 7.0 kPa and 7.0 kPa vs 5.3 kPa); alternatively, (P < 0.05) and therefore patients with steatosis continued to have clinically significant stiffness (≥ 7 kPa). **CONCLUSION:** Fatty liver is very common in hepatitis C virus (HCV) patients post-SVR. These patients continue to have elevated mean fibrosis score (≥ 7 kPa) compared to those without fatty liver; some have advanced fibrosis. Long term follow up is needed to assess steatosis and fibrosis in HCV patients post-SVR.

No Difference in Effectiveness of 8 vs 12 Weeks of Ledipasvir and Sofosbuvir for Treatment of Hepatitis C in Black Patients. Marcus JL1, Hurley LB2, Chamberland S3, et al. Clin Gastroenterol Hepatol. 2018 Mar 10. pii: S1542-3565(18)30255-6. doi: 10.1016/j.cgh.2018.03.003. [Epub ahead of print]

BACKGROUND & AIMS: Treatment with the combination of ledipasvir and sofosbuvir for 12 weeks has been approved by the Food and Drug Administration for patients with genotype 1

hepatitis C virus (HCV) infection; some patients can be treated with an 8-week course. Guidelines recommend a 12-week treatment course for black patients, but studies have not compared the effectiveness of 8 vs 12 weeks in black patients who are otherwise eligible for an 8-week treatment regimen. **METHODS:** We conducted an observational study of Kaiser Permanente Northern California members with HCV genotype 1 infection who were eligible for 8 weeks of treatment with ledipasvir and sofosbuvir (treatment-naïve, no cirrhosis, no HIV infection, level of HCV RNA <6 million IU/mL) and were treated for 8 or 12 weeks from October 2014 through December 2016. We used χ^2 analyses to compare sustained virologic response 12 weeks after the end of treatment (SVR12) among patients treated for 8 vs 12 weeks, and adjusted Poisson models to identify factors associated with receipt of 12 weeks of therapy among patients eligible for 8 weeks. **RESULTS:** Of 2653 patients eligible for 8 weeks of treatment with ledipasvir and sofosbuvir, 1958 (73.8%) received 8 weeks of treatment and 695 (26.2%) received 12 weeks; the proportions of patients with SVR12 were 96.3% and 96.3%, respectively ($P=.94$). Among 435 black patients eligible for the 8-week treatment regimen, there was no difference in the proportions who achieved an SVR12 following 8 vs 12 weeks' treatment (95.6% vs 95.8%; $P=.90$). Male sex, higher transient elastography or FIB-4 scores, higher INR and level of bilirubin, lower level of albumin, obesity, diabetes, and ≥ 15 alcohol drinks consumed/week were independently associated with receiving 12 weeks of treatment among patients eligible for the 8-week treatment regimen, but were not associated with reduced SVR12 after 8 weeks of treatment. **CONCLUSION:** In an observational study of patients who received ledipasvir and sofosbuvir treatment for HCV genotype 1 infection, we found that contrary to guidelines, 8-week and 12-week treatment regimens do not result in statistically significant differences in SVR12 in black patients. Patient characteristics were associated with receipt of 12-week regimens among patients eligible for 8 weeks, but were not associated with reduced SVR12 after 8 weeks. Shorter treatment courses might therefore be more widely used without compromising treatment effectiveness.

[Retreatment With Sofosbuvir Plus Grazoprevir/Elbasvir Plus Ribavirin of Patients With Hepatitis C Virus Genotype 1 or 4 Who Previously Failed an NS5A- or NS3-Containing Regimen: The ANRS HC34 REVENGE Study.](#) de Ledinghen V1,2, Laforest C3, Hézode C4, et al. Clin Infect Dis. 2018 Mar 19;66(7):1013-1018. doi: 10.1093/cid/cix916.

BACKGROUND: Failure to achieve sustained virological response (SVR) with hepatitis C virus (HCV) direct-acting antiviral (DAA)-based regimens is commonly associated with emergence of resistance-associated substitutions (RASs). Retreatment of patients who failed prior DAAs remains challenging. The aim of this prospective and randomized study was to evaluate the efficacy (primary endpoint: SVR 12 weeks after end of treatment [SVR12]) and safety of sofosbuvir + grazoprevir/elbasvir + ribavirin for 16 or 24 weeks in patients who had failed to achieve SVR on previous NS5A- or NS3-based therapy and with evidence of RASs at failure. **METHODS:** Patients were chronically infected with HCV genotype 1 or 4. Most of them had advanced fibrosis or compensated cirrhosis (liver stiffness 5.8-48.8 kPa). **RESULTS:** All patients achieved HCV RNA below the lower limit of quantification (either target detected [unquantifiable] or target not detected) during treatment. SVR12 was achieved by 25 of 26 patients. The only patient who did not reach SVR was a patient who died, but HCV RNA was negative at this time (5 weeks after stopping treatment). No patient discontinued treatment because of adverse events or virological failure. Globally, treatment was well tolerated. **CONCLUSIONS:** Our findings support the concept of retreating with sofosbuvir +

grazoprevir/elbasvir + ribavirin, for 16 weeks, genotype 1 or 4 DAA-experienced patients with proven NS5A or NS3 RASs.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Transmission genetics of drug-resistant hepatitis C virus.](#) van Buuren N1, Tellinghuisen TL2, Richardson CC3, Kirkegaard K1. *Elife*. 2018 Mar 28;7. pii: e32579. doi: 10.7554/eLife.32579. [Epub ahead of print]

Antiviral development is plagued by drug resistance and genetic barriers to resistance are needed. For HIV and hepatitis C virus (HCV), combination therapy has proved life-saving. The targets of direct-acting antivirals for HCV infection are NS3/4A protease, NS5A phosphoprotein and NS5B polymerase. Differential visualization of drug-resistant and -susceptible RNA genomes within cells revealed that resistant variants of NS3/4A protease and NS5A phosphoprotein are cis-dominant, ensuring their direct selection from complex environments. Confocal microscopy revealed that RNA replication complexes are genome-specific, rationalizing the non-interaction of wild-type and variant products. No HCV antivirals yet display the dominance of drug susceptibility shown for capsid proteins of other viruses. However, effective inhibitors of HCV polymerase exact such high fitness costs for drug resistance that stable genome selection is not observed. Barriers to drug resistance vary with target biochemistry and detailed analysis of these barriers should lead to the use of fewer drugs.

[Glycine Zipper Motifs in Hepatitis C Virus Nonstructural Protein 4B Are Required for the Establishment of Viral Replication Organelles.](#) Paul D1, Madan V2, Ramirez O3, Bencun M2, Stoeck IK2, Jirasko V4, Bartenschlager R1. *J Virol*. 2018 Jan 30;92(4). pii: e01890-17. doi: 10.1128/JVI.01890-17. Print 2018 Feb 15.

Hepatitis C virus (HCV) RNA replication occurs in tight association with remodeled host cell membranes, presenting as cytoplasmic accumulations of single-, double-, and multimembrane vesicles in infected cells. Formation of these so-called replication organelles is mediated by a complex interplay of host cell factors and viral replicase proteins. Of these, nonstructural protein 4B (NS4B), an integral transmembrane protein, appears to play a key role, but little is known about the molecular mechanisms of how this protein contributes to organelle biogenesis. Using forward and reverse genetics, we identified glycine zipper motifs within transmembrane helices 2 and 3 of NS4B that are critically involved in viral RNA replication. Foerster resonance energy transfer analysis revealed the importance of the glycine zippers in NS4B homo- and heterotypic self-interactions. Additionally, ultrastructural analysis using electron microscopy unraveled a prominent role of glycine zipper residues for the subcellular distribution and the morphology of HCV-induced double-membrane vesicles. Notably, loss-of-function NS4B glycine zipper mutants prominently induced single-membrane vesicles with secondary invaginations that might represent an arrested intermediate state in double-membrane vesicle formation. These findings highlight a so-far-unknown role of glycine residues within the membrane integral core domain for NS4B self-interaction and functional as well as structural integrity of HCV replication organelles. **IMPORTANCE:** Remodeling of the cellular endomembrane system leading to the establishment of replication organelles is a hallmark of positive-strand RNA viruses. In the case of HCV, expression of the nonstructural proteins induces the accumulation of double-membrane vesicles that likely arise from a concerted action of viral and coopted cellular factors. However, the underlying molecular mechanisms are incompletely understood. Here, we identify glycine

zipper motifs within HCV NS4B transmembrane segments 2 and 3 that are crucial for the protein's self-interaction. Moreover, glycine residues within NS4B transmembrane helices critically contribute to the biogenesis of functional replication organelles and, thus, efficient viral RNA replication. These results reveal how glycine zipper motifs in NS4B contribute to structural and functional integrity of the HCV replication organelles and, thus, viral RNA replication.

[Interactions between the Hepatitis C Virus Nonstructural 2 Protein and Host Adaptor Proteins 1 and 4 Orchestrate Virus Release.](#) Xiao F1, Wang S1, Barouch-Bentov R1, et al. MBio. 2018 Mar 13;9(2). pii: e02233-17. doi: 10.1128/mBio.02233-17.

Hepatitis C virus (HCV) spreads via secreted cell-free particles or direct cell-to-cell transmission. Yet, virus-host determinants governing differential intracellular trafficking of cell-free- and cell-to-cell-transmitted virus remain unknown. The host adaptor proteins (APs) AP-1A, AP-1B, and AP-4 traffic in post-Golgi compartments, and the latter two are implicated in basolateral sorting. We reported that AP-1A mediates HCV trafficking during release, whereas the endocytic adaptor AP-2 mediates entry and assembly. We demonstrated that the host kinases AAK1 and GAK regulate HCV infection by controlling these clathrin-associated APs. Here, we sought to define the roles of AP-4, a clathrin-independent adaptor; AP-1A; and AP-1B in HCV infection. We screened for interactions between HCV proteins and the μ subunits of AP-1A, AP-1B, and AP-4 by mammalian cell-based protein fragment complementation assays. The nonstructural 2 (NS2) protein emerged as an interactor of these adaptors in this screening and by coimmunoprecipitations in HCV-infected cells. Two previously unrecognized dileucine-based motifs in the NS2 C terminus mediated AP binding and HCV release. Infectivity and coculture assays demonstrated that while all three adaptors mediate HCV release and cell-free spread, AP-1B and AP-4, but not AP-1A, mediate cell-to-cell spread. Live-cell imaging revealed HCV cotrafficking with AP-1A, AP-1B, and AP-4 and that AP-4 mediates HCV trafficking in a post-Golgi compartment. Lastly, HCV cell-to-cell spread was regulated by AAK1 and GAK and thus susceptible to treatment with AAK1 and GAK inhibitors. These data provide a mechanistic understanding of HCV trafficking in distinct release pathways and reveal a requirement for APs in cell-to-cell viral spread. **IMPORTANCE:** HCV spreads via cell-free infection or cell-to-cell contact that shields it from antibody neutralization, thereby facilitating viral persistence. Yet, factors governing this differential sorting remain unknown. By integrating proteomic, RNA interference, genetic, live-cell imaging, and pharmacological approaches, we uncover differential coopting of host adaptor proteins (APs) to mediate HCV traffic at distinct late steps of the viral life cycle. We reported that AP-1A and AP-2 mediate HCV trafficking during release and assembly, respectively. Here, we demonstrate that dileucine motifs in the NS2 protein mediate AP-1A, AP-1B, and AP-4 binding and cell-free virus release. Moreover, we reveal that AP-4, an adaptor not previously implicated in viral infections, mediates cell-to-cell spread and HCV trafficking. Lastly, we demonstrate cell-to-cell spread regulation by AAK1 and GAK, host kinases controlling APs, and susceptibility to their inhibitors. This study provides mechanistic insights into virus-host determinants that facilitate HCV trafficking, with potential implications for pathogenesis and antiviral agent design.

[Authentic Patient-Derived Hepatitis C Virus Infects and Productively Replicates in Primary CD4+ and CD8+ T Lymphocytes In Vitro.](#) Skardasi G1, Chen AY1, Michalak TI2. J Virol. 2018 Jan 17;92(3). pii: e01790-17. doi: 10.1128/JVI.01790-17. Print 2018 Feb 1.

Accumulated evidence indicates that immune cells can support the replication of hepatitis C virus (HCV) in infected patients and in culture. However, there is a scarcity of data on the degree to which individual immune cell types support HCV propagation and on characteristics of virus assembly. We investigated the ability of authentic, patient-derived HCV to infect in vitro two closely related but functionally distinct immune cell types, CD4+ and CD8+ T lymphocytes, and assessed the properties of the virus produced by these cells. The HCV replication system in intermittently mitogen-stimulated T cells was adapted to infect primary human CD4+ or CD8+ T lymphocytes. HCV replicated in both cell types although at significantly higher levels in CD4+ than in CD8+ T cells. Thus, the HCV RNA replicative (negative) strand was detected in CD4+ and CD8+ cells at estimated mean levels \pm standard errors of the means of $6.7 \times 10^2 \pm 3.8 \times 10^2$ and $1.2 \times 10^2 \pm 0.8 \times 10^2$ copies/ μ g RNA, respectively ($P < 0.0001$). Intracellular HCV NS5a and/or core proteins were identified in 0.9% of CD4+ and in 1.2% of CD8+ T cells. Double staining for NS5a and T cell type-specific markers confirmed that transcriptionally competent virus replicated in both cell types. Furthermore, an HCV-specific protease inhibitor, telaprevir, inhibited infection in both CD4+ and CD8+ cells. The emergence of unique HCV variants and the release of HCV RNA-reactive particles with biophysical properties different from those of virions in plasma inocula suggested that distinct viral particles were assembled, and therefore, they may contribute to the pool of circulating virus in infected patients. **IMPORTANCE:** Although the liver is the main site of HCV replication, infection of the immune system is an intrinsic characteristic of this virus independent of whether infection is symptomatic or clinically silent. Many fundamental aspects of HCV lymphotropism remain uncertain, including the degree to which different immune cells support infection and contribute to virus diversity. We show that authentic, patient-derived HCV productively replicates in vitro in two closely related but functionally distinct types of T lymphocytes, CD4+ and CD8+ cells. The display of viral proteins and unique variants, the production of virions with biophysical properties distinct from those in plasma serving as inocula, and inhibition of replication by an antiviral agent led us to ascertain that both T cell subtypes supported virus propagation. Infection of CD4+ and CD8+ T cells, which are central to adaptive antiviral immune responses, can directly affect HCV clearance, favor virus persistence, and decisively influence the development and progression of hepatitis C.

[Rapid Changes in Serum Lipid Profiles during Combination Therapy with Daclatasvir and Asunaprevir in Patients Infected with Hepatitis C Virus Genotype 1b.](#) Chida T1,2, Kawata K1, Ohta K1,2, et al. Gut Liver. 2018 Mar 15;12(2):201-207. doi: 10.5009/gnl17179.

BACKGROUND/AIMS: Changes in lipid profiles in patients infected with hepatitis C virus (HCV) during direct-acting antiviral therapy have been reported in recent years. However, the clinical aspects of disturbed lipid metabolism in chronic HCV infection have not been fully elucidated. **METHODS:** Dynamic changes in serum total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and apolipoprotein levels in patients infected with HCV genotype 1b were examined during combination therapy with daclatasvir (DCV) and asunaprevir (ASV). **RESULTS:** Total, LDL-, and HDL-cholesterol levels increased rapidly and persistently after week 4. Apolipoprotein (apo) A-I, apo B, apo C-II, and apo C-III levels were significantly higher at week 4 than at week 0. In contrast, apo A-II and apo E levels were significantly lower. The differences in LDL- and HDL-cholesterol levels were positively correlated with those of apo B and apo A-I, respectively. Interestingly, in patients with non-sustained virological response, these cholesterol levels decreased rapidly after viral breakthrough or viral relapse. Furthermore, similar changes were observed for apo A-I, apo B and apo C-III

levels. **CONCLUSIONS:** Clearance of HCV using combination therapy with DCV and ASV results in rapid changes in serum lipid profiles, suggesting an influence of HCV infection on disturbed lipid metabolism.

HIV/HCV COINFECTION

[Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Co-infected with Hepatitis C Virus and Human Immunodeficiency Virus-1: the EXPEDITION-2 Study.](#) Rockstroh JK1, Lacombe K2, Viani RM3, et al. Clin Infect Dis. 2018 Mar 16. doi: 10.1093/cid/ciy220. [Epub ahead of print]

BACKGROUND: Once-daily glecaprevir coformulated with pibrentasvir (glecaprevir/pibrentasvir) has demonstrated high rates of sustained virologic response 12 weeks post-treatment (SVR12) in patients with hepatitis C virus (HCV) genotype 1-6 infection. This phase 3 study evaluated the efficacy and safety of glecaprevir/pibrentasvir in patients with chronic HCV genotype 1-6 and HIV-1 co-infection, including patients with compensated cirrhosis. **METHODS:** EXPEDITION-2 was a phase 3, multicenter, open-label study evaluating glecaprevir/pibrentasvir (300 mg/120 mg) in HCV genotype 1-6/HIV-1 co-infected adults without and with compensated cirrhosis for 8 and 12 weeks, respectively. Patients were either HCV treatment-naïve or experienced with sofosbuvir, ribavirin or interferon, and antiretroviral therapy (ART)-naïve or on a stable ART regimen for at least 8 weeks. Treatment-experienced genotype 3-infected patients were excluded. The primary endpoint was the proportion of patients with SVR12. **RESULTS:** In total, 153 patients were enrolled, including 16 (10%) with cirrhosis. The SVR12 rate was 98% (150/153; 95% CI 95.8-100), with no virologic failures in the 137 patients treated for 8 weeks. One genotype 3-infected patient with cirrhosis had on-treatment virologic failure. Most adverse events were mild in severity; four patients (2.6%) had serious adverse events, all deemed by investigator unrelated to glecaprevir/pibrentasvir. Treatment discontinuation was rare (<1%). All patients treated with ART maintained HIV-1 suppression (below 200 copies/mL) during treatment. **CONCLUSIONS:** Glecaprevir/pibrentasvir for 8 weeks in non-cirrhotic and 12 weeks in cirrhotic patients is a highly efficacious and well-tolerated treatment for HCV/HIV-1 co-infection, regardless of baseline HCV viral load or prior treatment with interferon or sofosbuvir.

[Infection by HTLV-1 Is Associated With High Levels of Proinflammatory Cytokines in HIV-HCV-Coinfected Patients.](#) Brites C1, Abrahão M2, Bozza P3, Netto EM1, Lyra A1, Bahia F1. J Acquir Immune Defic Syndr. 2018 Feb 1;77(2):230-234. doi: 10.1097/QAI.0000000000001576.

OBJECTIVES: HIV, hepatitis C virus (HCV), and human T-cell lymphotropic virus type 1 (HTLV-1) share the same routes of infection, making coinfection by these viruses a frequent finding in endemic areas. However, there is scarce information on the clinical/immunological consequences of triple infection. Coinfection by HTLV-1 is able to modulate cytokine's production in patients with HIV, but there are no data on the immune response of HIV-HCV-HTLV-1-infected patients. **METHODS:** We compared the plasma levels of 25 different cytokines in patients with HIV-HCV, according to their serostatus to HTLV-1 infection. Eligible patients should be on stable highly active antiretroviral therapy and have undetectable HIV-1 plasma viral load for, at least, 12 months. Cytokines levels were also evaluated by CD4 cells count, rates of sustained virological response (SVR) to previous HCV treatment, frequency of

spontaneous HCV clearance, and HCV/IFN- λ 3 genotypes. **RESULTS:** Twenty-five patients (15 coinfecting by HIV and HCV, 10 coinfecting by HIV, HCV, and HTLV-1) were evaluated. Among the triply infected group, 3 had undetectable HCV viremia (spontaneous clearance). All but one remaining patients were previously treated for HCV, with similar SVR rates (~29%). Cytokines levels did not differ per HCV/IFN- λ 3 genotypes, mean CD4 cells count, age, sex, or SVR. However, patients coinfecting by HTLV-1 showed significantly higher levels of IL-1b, IL-2, TNF- α , IFN- γ , MIP-1 α , RANTES, and interferon-induced protein 10 (IP-10) than HIV-HCV-coinfecting ones. Patients presenting HCV spontaneous clearance had the highest levels of cytokines. **CONCLUSIONS:** Coinfection by HTLV-1 increases the plasma levels of proinflammatory cytokines of patients with HIV-HCV and can influence the outcomes of coinfecting patients.

[Risk of Complications After THA Increases Among Patients Who Are Coinfecting With HIV and Hepatitis C](#), Mahure SA1, Bosco JA, Slover JD, Vigdorichik J, Iorio R, Schwarzkopf R. Clin Orthop Relat Res. 2018 Feb;476(2):356-369. doi: 10.1007/s11999-0000000000000025.

BACKGROUND: Individuals coinfecting with both hepatitis C virus (HCV) and HIV represent a unique and growing population of patients undergoing orthopaedic surgical procedures. Data regarding complications for HCV mono-infection or HIV mono-infection are robust, but there are no data available, to our knowledge, on patients who have both HCV and HIV infections.

QUESTIONS/PURPOSES: We sought to determine whether patients with coinfection differed in terms of baseline demographics and comorbidity burden as compared with patients without coinfection and whether these potential differences were translated into varying levels of postoperative complications, mortality, and hospital readmission risk. Specifically, we asked: (1) Are there demonstrable differences in baseline demographic variables between patients infected with HCV and HIV and those who do not have those infections (age, sex, race, and insurance status)? (2) Do patients with HCV and HIV infection differ from patients without those infections in terms of other medical comorbidities? (3) Do patients with HCV/HIV coinfection have a higher incidence of early postoperative complications and mortality than patients without coinfection? (4) Is the frequency of readmission greater for patients with HCV/HIV coinfection than those without? **METHODS:** The New York Statewide Planning and Research Cooperative System (SPARCS) database was used to identify patients undergoing THA between 2010 and 2014. The SPARCS database is particularly useful because it captures 100% of all New York State inpatient admissions while providing detailed demographic and comorbidity data for a large, heterogeneous patient population with long-term followup. Patients were stratified into four groups based on HCV/HIV status: control patients without disease, HCV mono-infection, HIV mono-infection, and coinfection. We sought to determine whether patients coinfecting with HCV and HIV would differ in terms of demographics from patients without those infections and whether patients with HCV and HIV would have a greater risk of complications, longer length of stay, and hospital readmission. A total of 80,722 patients underwent THA between 2010 and 2014. A total of 98.55% (79,554 of 80,722) of patients did not have either HCV or HIV, 0.66% (530 of 80,722) had HCV mono-infection, 0.66% (534 of 80,722) HIV mono-infection, and 0.13% (104 of 80,722) were coinfecting with both HCV and HIV. Multivariate analysis was performed controlling for age, sex, insurance, residency status, diagnosis, and comorbidities to allow for an equal comparison between groups. **RESULTS:** Patients with coinfection were more likely to be younger, male (odds ratio [OR], 2.90; 95% confidence interval [CI], 2.20-3.13; $p < 0.001$), insured by Medicaid (OR, 6.43; 4.41-7.55; $p < 0.001$), have a history of avascular necrosis (OR,

8.76; 7.20-9.53; $p < 0.001$), and to be homeless (OR, 6.95; 5.31-7.28; $p < 0.001$) as compared with patients without HIV or HCV. Additionally, patients with coinfection had the highest proportion of alcohol abuse, drug abuse, and tobacco use along with a high proportion of psychiatric disorders, including depression. HCV and HIV coinfection were independent risk factors for increased length of stay (OR, 1.97; 95% CI, 1.29-3.01; $p < 0.001$), having two or more in-hospital complications (OR, 1.64; 1.01-2.67; $p < 0.001$), and 90-day readmission rates (OR, 2.97; 1.86-4.77; $p < 0.001$). **CONCLUSIONS:** As the prevalence of HCV and HIV coinfectivity continues to increase, orthopaedic surgeons will encounter a greater number of these patients. Awareness of the demographic and socioeconomic factors leading to increased complications after THA will allow physicians to consider interventions such as in-hospital psychiatric counseling, advanced discharge planning, and coordination with social work and collaboration with HCV/HIV infectious disease specialists to improve patient health status to improve outcomes and reduce costs. **LEVEL OF EVIDENCE:** Level III, therapeutic study.

[Ledipasvir-Sofosbuvir for 8 Weeks in Non-Cirrhotic Patients with Previously Untreated Genotype 1 HCV Infection ± HIV-1 Co-Infection.](#)

Isakov V1, Gankina N2, Morozov V3, et al. Clin Drug Investig. 2018 Mar;38(3):239-247. doi: 10.1007/s40261-017-0606-0.

BACKGROUND AND OBJECTIVES: The efficacy of < 12 weeks of hepatitis C virus (HCV) treatment in patients co-infected with HCV and human immunodeficiency virus type 1 (HIV-1) has not been established. We assessed the efficacy and safety of ledipasvir-sofosbuvir for 8 weeks in HCV mono-infected and HCV/HIV-1 co-infected patients. **METHODS:** We enrolled patients mono-infected with genotype 1 HCV or co-infected with HCV and HIV-1 who were HCV treatment-naïve and did not have cirrhosis. HCV/HIV-1 co-infected patients were either not receiving antiretroviral treatment and had a CD4 T-cell count > 500 cells/mm³ or were receiving a protocol-approved antiretroviral regimen for ≥ 8 weeks (or ≥ 6 months for abacavir-containing regimens) and had HIV-1 RNA < 50 copies/mL and a CD4 T-cell count > 200 cells/mm³. Patients received ledipasvir-sofosbuvir (90/400 mg) once daily for 8 weeks. The primary efficacy endpoint was sustained virologic response 12 weeks after treatment discontinuation (SVR12). **RESULTS:** The SVR12 rate was 100% (67/67) for HCV mono-infected patients and 97% (57/59) for HCV/HIV-1 co-infected patients. Two patients relapsed by the week 4 post-treatment visit. Overall, the most common adverse events were headache (52%) and upper abdominal pain (26%). There were no serious adverse events or treatment discontinuations due to adverse events. No HCV/HIV-1 co-infected patients receiving antiretroviral treatment experienced HIV virologic rebound, and no clinically meaningful changes in CD4 T-cell counts were observed in any co-infected patient. **CONCLUSIONS:** Non-cirrhotic, treatment-naïve patients with genotype 1 HCV mono-infection and HCV/HIV-1 co-infection achieved high rates of SVR12 with 8 weeks of treatment with ledipasvir/sofosbuvir.

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

Rossi C1, Saeed S1, Cox J2, et al. AIDS. 2018 Mar 27;32(6):751-759. doi: 10.1097/QAD.0000000000001750.

OBJECTIVE: To examine the impact of sustained virologic response (SVR) and illicit (injection and noninjection) drug use on kidney function among hepatitis C virus (HCV) and HIV co-infected individuals. **DESIGN:** Longitudinal observational cohort study of HCV-HIV co-infected patients. **METHODS:** Data from 1631 patients enrolled in the Canadian Co-

Infection Cohort between 2003 and 2016 were analyzed. Patients who achieved SVR were matched 1:2 with chronically infected patients using time-dependent propensity scores. Linear regression with generalized estimating equations was used to model differences in estimated glomerular filtration rates (eGFR) between chronic HCV-infected patients and those achieving SVR. The relationship between illicit drug use and eGFR was explored in patients who achieved SVR. **RESULTS:** We identified 384 co-infected patients who achieved SVR (53% treated with interferon-free antiviral regimens) and 768 propensity-score matched patients with chronic HCV infection. Most patients were men (78%) and white (87%), with a median age of 51 years (interquartile range: 45-56). During 1767 person-years of follow-up, 4041 eGFR measurements were available for analysis. Annual rates of decline in eGFR were similar between patients with SVR [-1.32(ml/min per 1.73m)/year, 95% confidence interval (CI) -1.75 to -0.90] and chronic infection [-1.19(ml/min per 1.73m) per year, 95% CI -1.55 to -0.84]. Among SVR patients, recent injection cocaine use was associated with rapid eGFR decline [-2.16(ml/min per 1.73 m)/year, 95% CI -4.17 to -0.16]. **CONCLUSION:** SVR did not reduce the rate of kidney function decline among HCV-HIV co-infected patients. Increased risk of chronic kidney disease in co-infection may not be related to persistent HCV replication but to ongoing injection cocaine use.

[Chronic hepatitis C virus infection and subsequent HIV viral load among women with HIV initiating antiretroviral therapy.](#) Willis SJ1, Cole SR1, Westreich D1, et al. AIDS. 2018 Mar 13;32(5):653-661. doi: 10.1097/QAD.0000000000001745.

OBJECTIVES: One in four persons living with HIV is coinfecting with hepatitis C virus (HCV). Biological and behavioral mechanisms may increase HIV viral load among coinfecting persons. Therefore, we estimated the longitudinal effect of chronic HCV on HIV suppression after ART initiation among women with HIV (WWH). **DESIGN:** HIV RNA was measured every 6 months among 441 WWH in the Women's Interagency HIV Study who initiated ART from 2000 to 2015. **METHODS:** Log-binomial regression models were used to compare the proportion of study visits with detectable HIV RNA between women with and without chronic HCV. Robust sandwich variance estimators accounted for within-person correlation induced by repeated HIV RNA measurements during follow-up. We controlled for confounding and selection bias (because of loss to follow-up and death) using inverse probability-of-exposure-and-censoring weights. **RESULTS:** One hundred and fourteen women (25%) had chronic HCV before ART initiation. Overall, the proportion of visits with detectable HIV RNA was similar among women with and without chronic HCV [relative risk (RR) 1.19 (95% CI 0.72, 1.95)]. Six months after ART initiation, the proportion of visits with detectable HIV RNA among women with chronic HCV was 1.88 (95% CI 1.41-2.51) times that among women without HCV, at 2 years, the ratio was 1.60 (95% CI 1.17-2.19), and by 6 years there was no difference (1.03; 95% CI 0.60-1.79). **CONCLUSION:** Chronic HCV may negatively impact early HIV viral response to ART. These findings reaffirm the need to test persons with HIV for HCV infection, and increase engagement in HIV care and access to HCV treatment among persons with HIV/HCV coinfection.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[Hepatitis C Virus Screening Trends: Serial Cross-Sectional Analysis of the National Health Interview Survey Population, 2013-2015.](#)

Kasting ML^{1,2}, Giuliano AR^{2,3}, Reich RR⁴, Roetzheim RG^{1,5}, Nelson DR⁶, Shenkman E^{7,8}, Vadaparampil ST^{9,2}. *Cancer Epidemiol Biomarkers Prev.* 2018 Mar 27. doi: 10.1158/1055-9965.EPI-17-0855. [Epub ahead of print]

BACKGROUND: Rates of hepatitis C virus (HCV) infection are markedly higher for baby boomers compared with other birth cohorts, and they are now recommended for universal one-time screening. This study examines HCV screening rates and predictors for four birth cohorts [born <1945, born 1945-1965 (baby boomers), born 1966-1985, and born >1985] of a nationally representative sample over time. **METHODS:** We used data from the 2013-2015 National Health Interview Surveys, an annual weighted survey of the U.S. civilian noninstitutionalized population. We assessed HCV screening prevalence stratified birth cohort with bivariate and multivariable logistic regression analyses. **RESULTS:** There were 15,100 participants born <1945, 28,725 baby boomers, 28,089 born 1966-1985, and 13,296 born >1985 in the final analytic sample. Screening was 11.5%-12.8% for baby boomers. The second youngest birth cohort was similar to baby boomers (13.7%-14.9%), whereas the older birth cohort was screened less. After excluding participants who typically have higher rates of HCV screening than the general population, we developed a multivariable model of the general population. In the final model for baby boomers the odds of HCV screening increased significantly with each subsequent year (OR=1.20; 95% CI=1.05-1.38 and OR=1.31; 95% CI=1.13-1.52). HCV screening was also significantly associated with age, gender, and race/ethnicity in baby boomers. **CONCLUSIONS:** While HCV screening is increasing over time, these increases are minimal and there is substantial room for improvement. Impact: Future research should develop interventions to increase HCV screening with special focus on groups demonstrating significantly lower screening rates, such as Hispanics and females.

[Sub-optimal Testing and Awareness of HCV and HBV Among High Risk Individuals at an Underserved Safety-Net Hospital.](#)

Wong RJ¹, Campbell B², Liu B³, Baden R⁴, Bhuket T³. *J Community Health.* 2018 Feb;43(1):65-69. doi: 10.1007/s10900-017-0388-6.

Sub-optimal screening for chronic hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) among high risk groups delays diagnosis and treatment. We aimed to evaluate overall rates of HCV and HBV screening and patient knowledge of their testing result. Adults age ≥ 18 years undergoing elective outpatient endoscopy at a large, urban safety-net hospital from July 2015 to July 2016 were prospectively evaluated to determine rates of HCV and HBV testing, the results of those completed tests, and patient knowledge of test results among high risk individuals (as determined by U.S. Preventative Services Task Force). Among 1125 patients (52.3% male, 70.4% foreign-born), 66.5% were high risk for chronic HCV; only 30.9% received prior testing. 14.7% had positive chronic HCV infection. Patients born in the 1945-1965 cohort were more likely to have received prior HCV testing compared to those born outside of this cohort (32.7 vs. 16.9%, $p = 0.01$). Among patients who received HCV screening, 29.3% were aware of test results. Overall, 61.6% were high risk for chronic HBV; only 25.1% received prior testing. 4.1% were positive for chronic HBV. Compared to Caucasians, Asians (19.0 vs. 44.4%, $p < 0.001$) and Hispanics (20.0 vs. 44.4%, $p < 0.001$) were less likely to have previous HBV testing. Among patients who received prior HBV screening, 18.4% were aware of test results. Less than one-third of high risk patients received HCV and HBV screening among an ethnically diverse safety-net population. Equally low rates of patient knowledge of testing results were observed.

[Race/ethnicity and insurance status disparities in access to direct acting antivirals for hepatitis C virus treatment.](#)

Wong RJ1, Jain MK2,3, Theraponodos G4, Shiffman ML5, Kshirsagar O6, Clark C3, Thamer M6. Am J Gastroenterol. 2018 Mar 9. doi: 10.1038/s41395-018-0033-8. [Epub ahead of print] **OBJECTIVE:** Despite availability of highly effective direct acting antivirals (DAA), barriers in access to these therapies limit our ability to achieve HCV eradication. We aim to evaluate overall rates and predictors of HCV treatment across four community-based health-care systems focusing on race/ethnicity and insurance-specific disparities. **METHODS:** We retrospectively evaluated all adults with chronic HCV at four health care systems from 1 January 2011 to 28 February 2017, which included a large proportion of ethnic minorities, two safety-net systems, and a broad payer mix across four states. Overall and stratified HCV treatment rates were calculated using Kaplan-Meier methods. Multivariate logistic regression models evaluated for predictors of receiving treatment. **RESULTS:** Among 29,544 chronic HCV patients (60.5% male, 38.4% black, 8.8% Hispanic, 18.7% Medicaid, 25.9% Medicare, 22.5% private/commercial), overall annual treatment rates were stable from 2011 (0.5%) to 2013 (2.0%), but increased from 2014 (4.8%) to 2017 (16.9%) after availability of DAAs. While similar treatment rates were observed by sex, significantly lower odds of treatment were observed in Hispanics (OR 0.48, 95% CI 0.39-0.60, $p < 0.001$) compared to non-Hispanic whites and among those with Medicaid (OR 0.21, 95% CI 0.20-0.24, $p < 0.001$) compared to commercially insured patients. **CONCLUSIONS:** Among our cohort of 29,544 chronic HCV patients, we observed significant improvements in HCV treatment rates after the availability of DAAs in 2014, but overall treatment rates remained $< 20\%$ in 2017. The lowest rates of treatment were seen among Hispanics and those with Medicaid or indigent care insurance, which is concerning given these are particularly vulnerable populations.

[Population level outcomes and cost-effectiveness of expanding the recommendation for age-based hepatitis C testing in the United States.](#)

Barocas JA1, Tasillo A2, Eftekhari Yazdi G2, et al. Clin Infect Dis. 2018 Feb 6. doi: 10.1093/cid/ciy098. [Epub ahead of print] **BACKGROUND:** The U.S. Centers for Disease Control and Prevention and the U.S. Preventive Services Task Force recommend one-time hepatitis C virus (HCV) testing for persons born 1945-1965 and targeted testing for high-risk persons. This strategy targets HCV testing to a prevalent population at high risk for HCV morbidity and mortality, but does not include younger populations with high incidence. To address this gap and improve access to HCV testing, age-based strategies should be considered. **METHODS:** We used a simulation of HCV to estimate the effectiveness and cost-effectiveness of HCV testing strategies: 1) standard of care (SOC) - recommendation for one-time testing for all persons born 1945-1965, 2) recommendation for one-time testing for adults ≥ 40 years (≥ 40 strategy), 3) ≥ 30 years (≥ 30 strategy), and 4) ≥ 18 years (≥ 18 strategy). All strategies assumed targeted testing of high-risk persons. Inputs were derived from national databases, observational cohorts and clinical trials. Outcomes included quality-adjusted life expectancy, costs, and cost-effectiveness. **RESULTS:** Expanded age-based testing strategies increased U.S. population lifetime case identification and cure rates. Greatest increases were observed in the ≥ 18 strategy. Compared to the SOC, this strategy resulted in an estimated 256,000 additional infected persons identified and 280,000 additional cures at the lowest cost per QALY gained (ICER = \$28,000/QALY). **CONCLUSIONS:** In addition to risk-based testing, one-time HCV testing of persons 18 and older appears to be cost-effective, leads to

improved clinical outcomes and identifies more persons with HCV than the current birth cohort recommendations. These findings could be considered for future recommendation revisions.

Hepatitis C virus knowledge improves hepatitis C virus screening practices among primary care physicians. Samuel ST1, Martinez AD1, Chen Y2, Markatou M2, Talal AH1. World J Hepatol. 2018 Feb 27;10(2):319-328. doi: 10.4254/wjh.v10.i2.319.

AIM: To understand the role of knowledge as a promoter of hepatitis C virus (HCV) screening among primary care physicians (PCP). **METHODS:** A 45-item online questionnaire assessing knowledge of HCV natural history, risk factors, and treatment was distributed to 163 PCP. Logistic regression, adjusted for survey responses, assessed associations between PCP knowledge of HCV natural history and treatment and birth cohort (i.e., birth between 1945 and 1965) screening. Response stratification and weighting were used to account for nonresponse and to permit extension of responses to the entire survey population. Associations between various predictors including demographic characteristics, level of training, and HCV treatment experience and HCV knowledge were assessed. **RESULTS:** Ninety-one individuals (55.8%) responded. Abnormal liver enzymes (49.4%), assessment of HCV-related risk factors (30.6%), and birth cohort membership (20%) were the leading HCV screening indications. Most PCP (64.7%) felt that the combination of risk-factor and birth cohort screening utilizing a self-administered survey while awaiting the physician (55.3%) were the most efficient screening practices. Implementation of birth cohort screening was associated with awareness of the recommendations (P-value = 0.01), knowledge of HCV natural history (P-value < 0.01), and prior management of HCV patients (P-value < 0.01). PCP with knowledge of HCV treatment was also knowledgeable about HCV natural history (P-value < 0.01). Similarly, awareness of age-based screening recommendations was associated with HCV treatment knowledge (P-value = 0.03). **CONCLUSION:** Comprehensive knowledge of HCV is critical to motivate HCV screening. PCP-targeted educational interventions are required to expand the HCV workforce and linkage-to-care opportunities as we seek global HCV eradication.

Tattooing in prison: a risk factor for HCV infection among inmates in the Quebec's provincial correctional system. Poulin C1, Courtemanche Y1, Serhir B2, Alary M3. Ann Epidemiol. 2018 Apr;28(4):231-235. doi: 10.1016/j.annepidem.2018.02.002. Epub 2018 Feb 10.

PURPOSE: To determine the prevalence of hepatitis C virus (HCV) and identify related risk factors among inmates in Quebec provincial prisons. **METHODS:** Anonymous cross-sectional data were collected between May 2014 and March 2015 for 1315 men and 250 women who completed a questionnaire and provided oral fluid samples. **RESULTS:** The global prevalence of HCV infection was 11.9% in male participants and 19.2% in female participants (P = .003). Among people who inject drugs (PWID), the prevalence was much higher compared to that in persons who does not: 51.0% versus 2.4% in men (P < .001) and 61.4% versus 2.8% in women (P < .001). In the multivariable analysis, lifetime history of injection drug use was the most important risk factor for HCV infection (adjusted odds ratio [AOR]: 14.2; 95% confidence interval [95% CI]: 9.5-21.4), with needle sharing significantly associated with HCV among PWID (AOR: 1.4; 95% CI: 1.1-1.7). Tattooing in prison was frequent, especially among men (37.2%), and independently associated with HCV infection among non-PWID (AOR: 2.8; 95% CI: 1.4-5.6). **CONCLUSION:** Inmates are at high risk for HCV infection especially because of a high proportion of active or past PWID among them. In addition, tattooing while in prison seems to contribute to HCV infection among non-PWID.

Moral Distress with Obstacles to Hepatitis C Treatment: A Council of Academic Family Medicine Educational Research Alliance (CERA) Study of Family Medicine Program

Directors. Simha A1, Maria Webb C2, Prasad R2, Kolb NR2, Veldkamp PJ2. J Am Board Fam Med. 2018 Mar-Apr;31(2):286-291. doi: 10.3122/jabfm.2018.02.170220.

BACKGROUND AND OBJECTIVE: To determine whether family medicine program directors (PDs) experienced moral distress due to obstacles to Hepatitis C virus (HCV) treatment, and to explore whether they found those obstacles to be unethical. **DESIGN:** An omnibus survey by the Council of Academic Family Medicine's Educational Research Alliance was administered to 452 and completed by 273 US-based PDs. The survey gauged attitudes and opinions regarding ethical dilemmas in patient access to HCV treatment. **RESULTS:** Most of the respondents were male. Sixty-four percent of respondents believed that treatment should be an option for all patients regardless of cost. Forty-one percent believed that it was unethical to deny treatment based on past or current substance use, and 38% believed treatment should be offered to patients who were substance abusers. Moral distress was reported by 61% (score >3) of participants when they were unable to offer treatment to patients due to the patient's failure to meet eligibility criteria. In addition, PDs reporting moderate-to-high levels of moral distress were also likely to report the following opinions: 1) treatment should be offered regardless of cost, 2) it is unethical to deny treatment based on past behavior, 3) substance abusers should be offered treatment, 4) it is unethical for medicine to be prohibitively expensive, and 5) Medicaid policy that limits treatment will worsen racial and ethnic disparities. **CONCLUSIONS:** Currently, important ethical dilemmas exist in the access and delivery of HCV therapy. Although a diversity of opinions is noted, a significant proportion of PDs are concerned about patients' inability to avail equitable care and experience distress. In some cases, this moral distress is in response to, and in conflict with, current guidelines.

A Systematic Comparison of African American and Non-African American Patients on Psychosocial Aspects of Hepatitis C Infection.

Sims OT1,2,3,4, Hong BA5, Ji S6, Pollio

DE7,8,9, North CS10,11.

Author information: J Relig Health. 2018 Feb 6. doi: 10.1007/s10943-018-0565-7. [Epub ahead

of print]

The purpose of this study was to compare African American and non-African American hepatitis C virus (HCV) patients on self-reported symptoms of HCV liver disease and psychosocial characteristics commonly affected by it in a sample of 309 patients enrolled in a randomized controlled trial. African Americans (n = 196) rated a higher reliance on religion/spirituality for coping with HCV compared to non-African Americans. This study's findings are a basis for encouragement of public health efforts and programs to seek partnerships with African American faith and religious communities to identify and treat undiagnosed cases of HCV and promote HCV awareness.

A Descriptive Analysis of a Community Clinic Providing Hepatitis C Treatment to Poor and Uninsured Patients.

Sims OT1,2,3,4, Melton PA5, Ji S6. J Community Health. 2018 Mar

6. doi: 10.1007/s10900-018-0476-2. [Epub ahead of print]

This study describes clinical characteristics of poor and uninsured patients living with hepatitis C virus (HCV) who received care from a multidisciplinary HCV clinic, reports treatment completion and cure rates, and estimates the cost of HCV medications provided at no cost to

uninsured patients. A retrospective chart review was performed and identified 69 uninsured HCV patients who received medical care at Mercy Health Center, a small non-profit community clinic, between January 2008 and March 2015. Three-fourths of the patients were unemployed, a third had multiple HCV exposures, nearly half acquired HCV due to illicit drug use, and more than half had active psychiatric disorders. Of those who received HCV treatment, 81% completed treatment and 85% were achieved virological cure. The multidisciplinary community clinic provided > \$1.4 million of HCV antivirals at no cost to uninsured patients. Findings suggest a multidisciplinary community clinic comprised of a social worker, pharmacist, gastroenterologist, nurse, nurse practitioner, psychologist, and dietitian can help patients achieve HCV treatment completion and cure rates comparable to traditional physician-led clinics, and successfully manage uninsured and underserved HCV patients-who are often regarded as "difficult-to-treat" patients. Public health social workers and other health professionals are encouraged to advocate for treatment and care of poor and uninsured patients living with HCV in health agencies and health systems, otherwise population-wide reductions in HCV morbidity and mortality will not be realized.

[Race affects SVR12 in a large and ethnically diverse hepatitis C-infected patient population following treatment with direct-acting antivirals: Analysis of a single-center Department of Veterans Affairs cohort.](#) Benhammou JN^{1,2}, Dong TS^{1,2}, et al. *Pharmacol Res Perspect.* 2018 Feb 22;6(2):e00379. doi: 10.1002/prp2.379. eCollection 2018 Apr.

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. HCV cure has been linked to improved patient outcomes. In the era of direct-acting antivirals (DAAs), HCV cure has become the goal, as defined by sustained virological response 12 weeks (SVR12) after completion of therapy. Historically, African-Americans have had lower SVR12 rates compared to White people in the interferon era, which had been attributed to the high prevalence of non-CC interleukin 28B (IL28B) type. Less is known about the association between race/ethnicity and SVR12 in DAA-treated era. The aim of the study is to evaluate the predictors of SVR12 in a diverse, single-center Veterans Affairs population. We conducted a retrospective study of patients undergoing HCV therapy with DAAs from 2014 to 2016 at the VA Greater Los Angeles Healthcare System. We performed a multivariable logistic regression analysis to determine predictors of SVR12, adjusting for age, HCV genotype, DAA regimen and duration, human immunodeficiency virus (HIV) status, fibrosis, nonalcoholic fatty liver disease (NAFLD) fibrosis score, homelessness, mental health, and adherence. Our cohort included 1068 patients, out of which 401 (37.5%) were White people and 400 (37.5%) were African-American. Genotype 1 was the most common genotype (83.9%, N = 896). In the adjusted models, race/ethnicity and the presence of fibrosis were statistically significant predictors of non-SVR. African-Americans had 57% lower odds for reaching SVR12 (adj.OR = 0.43, 95% CI = 1.5-4.1) compared to White people. Advanced fibrosis (adj.OR = 0.40, 95% CI = 0.26-0.68) was also a significant predictor of non-SVR. In a single-center VA population on DAAs, African-Americans were less likely than White people to reach SVR12 when adjusting for covariates.

[Cost-effectiveness of hepatitis C screening and treatment linkage intervention in US methadone maintenance treatment programs.](#)

Schackman BR¹, Gutkind S², Morgan JR³, et al. *Drug Alcohol Depend.* 2018 Feb 13. pii: S0376-8716(18)30025-5. doi: 10.1016/j.drugalcdep.2017.11.031. [Epub ahead of print]

BACKGROUND: We evaluated the cost-effectiveness of a hepatitis C (HCV) screening and active linkage to care intervention in US methadone maintenance treatment (MMT) patients using data from a randomized trial conducted in New York City and San Francisco.

METHODS: We used a decision analytic model to compare 1) no intervention; 2) HCV screening and education (control); and 3) HCV screening, education, and care coordination (active linkage intervention). We also explored an alternative strategy wherein HCV/HIV co-infected participants linked elsewhere. Trial data include population characteristics (67% male, mean age 48, 58% HCV infected) and linkage rates. Data from published sources include treatment efficacy and HCV re-infection risk. We projected quality-adjusted life years (QALYs) and lifetime medical costs using an established model of HCV (HEP-CE). Incremental cost-effectiveness ratios (ICERs) are in 2015 US\$/QALY discounted 3% annually. **RESULTS:** The control strategy resulted in a projected 35% linking to care within 6 months and 31% achieving sustained virologic response (SVR). The intervention resulted in 60% linking and 54% achieving SVR with an ICER of \$24,600/QALY compared to no intervention from the healthcare sector perspective and was a more efficient use of resources than the control strategy. The intervention had an ICER of \$76,500/QALY compared to the alternative strategy. From a societal perspective, the intervention had a net monetary benefit of \$511,000-\$975,600.

CONCLUSIONS: HCV care coordination interventions that include screening, education and active linkage to care in MMT settings are likely cost-effective at a conventional \$100,000/QALY threshold for both HCV mono-infected and HIV co-infected patients.

HEPATOCELLULAR (LIVER) CANCER

[Rate of hepatocellular carcinoma surveillance remains low for a large, real-life cohort of patients with hepatitis C cirrhosis.](#) Tran SA1, Le A1, Zhao C2, Hoang J1, Yasukawa LA3, Weber S3, Henry L1, Nguyen MH1. *BMJ Open Gastroenterol.* 2018 Mar 20;5(1):e000192. doi: 10.1136/bmjgast-2017-000192. eCollection 2018.

BACKGROUND: In patients with chronic hepatitis C (CHC) cirrhosis, imaging for hepatocellular carcinoma (HCC) is recommended every 6 months to maximise eligibility for curative treatment. The aim was to determine the adherence rate and outcomes among patients with CHC cirrhosis and whether the adherence rate has improved over time. **METHODS:** Retrospective cohort study of patients with CHC cirrhosis (n=2366) monitored for ≥ 1 year at Stanford University Medical Center between January 2001 and August 2015. **RESULTS:** Overall demographics: mean age 54; 62.3% men; 48.3% Caucasian. 24.4% adherent to imaging every 6 months per European Association for the Study of the Liver 2000 and American Association for the Study of Liver Diseases (AASLD) 2011 criteria and 44% at least every 12 months per AASLD 2005 criteria. No significant change in adherence before and after 2011. Predictors of multivariable analysis of adherence were age >54 (OR 1.74, $p<0.0001$), Asian ethnicity (OR 2.23, $p<0.0001$), liver decompensation (OR 2.40, $p<0.0001$) and having ≥ 2 clinical visits per year (OR 1.33, $p=0.01$). During follow-up, 9.6% were diagnosed with HCC. Adherent patients were more likely to have smaller tumours (2.3 vs 3.3 cm, $p=0.0020$), be within the Milan criteria for liver transplants (73.2% vs 54.8%, $p=0.006$) and receive curative HCC treatment (43.6% vs 24.0%, $p=0.005$). On multivariable analysis, curative treatment (HR 0.32, $p=0.001$) and every 6-month imaging (HR 0.34, $p=0.005$), but not every 6-12 month imaging, were associated with reduced risk of mortality. **CONCLUSIONS:** Adherence to HCC surveillance

continues to be poor. Adherent patients with HCC were more likely to undergo curative treatment and have better survival. Research understanding barriers to surveillance is needed.

The Role of Circulating Free DNA and MicroRNA in Non-Invasive Diagnosis of HBV- and HCV-Related Hepatocellular Carcinoma.

Pezzuto F1, Buonaguro L2, Buonaguro FM3, Tornesello ML4. *Int J Mol Sci.* 2018 Mar 28;19(4). pii: E1007. doi: 10.3390/ijms19041007. Hepatocellular carcinoma (HCC) is the third and the fifth leading cause of cancer related death worldwide in men and in women, respectively. HCC generally has a poor prognosis, with a very low 5-year overall survival, due to delayed diagnosis and treatment. Early tumour detection and timely intervention are the best strategies to reduce morbidity and mortality in HCC patients. Histological evaluation of liver biopsies is the gold standard for cancer diagnosis, although it is an invasive, time-consuming and expensive procedure. Recently, the analysis of circulating free DNA (cfDNA) and RNA molecules released by tumour cells in body fluids, such as blood serum, saliva and urine, has attracted great interest for development of diagnostic assays based on circulating liver cancer molecular biomarkers. Such "liquid biopsies" have shown to be useful for the identification of specific molecular signatures in nucleic acids released by cancer cells, such as gene mutations and altered methylation of DNA as well as variations in the levels of circulating microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Body fluids analysis may represent a valuable strategy to monitor liver disease progression in subjects chronically infected with hepatitis viruses or cancer relapse in HCC treated patients. Several studies showed that qualitative and quantitative assays evaluating molecular profiles of circulating cell-free nucleic acids could be successfully employed for early diagnosis and therapeutic management of HCC patients. This review describes the state of art on the use of liquid biopsy for cancer driver gene mutations, deregulated DNA methylation as well as miRNA levels in HCC diagnosis.

Palliative Care for People With Hepatocellular Carcinoma, and Specific Benefits for Older Adults. Woodrell CD1, Hansen L2, Schiano TD3, Goldstein NE4. *Clin Ther.* 2018 Mar 20. pii: S0149-2918(18)30092-4. doi: 10.1016/j.clinthera.2018.02.017. [Epub ahead of print]

PURPOSE: Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, has a rapidly rising prevalence in the United States and a very poor overall rate of survival. This epidemic is driven by the cohort of aging Baby Boomers with hepatitis C viral infection and the increasing prevalence of cirrhosis as a result of nonalcoholic steatohepatitis. Because curative options are limited, the disease course creates, in patients and their families, distressing uncertainty around prognosis and treatment decisions. Older adults are disproportionately affected by HCC and have more comorbidities, adding to the complexity of the disease. This population would benefit from increased access to palliative care services, which can potentially complement the treatments throughout the disease trajectory. The purpose of this review was to use existing evidence to propose a new model of palliative care integration in patients with HCC. Thus, we focus on the HCC stage and the treatment algorithm, the ways that palliative care can offer support in this population at each stage, as well as elements that can enhance patient and family support throughout the entire disease trajectory, with an emphasis on the care of older adults with HCC. **METHODS:** This is a narrative review in which we identify evidence-based ways that palliative care can help younger and older adults with HCC and their families, at each stage of HCC and throughout the disease trajectory. **FINDINGS:** We propose ways to integrate HCC and palliative care based on the existing evidence in both fields. Palliative care offers support in symptom management, advanced care planning, and decision making in ways that are specific to each stage of HCC. We also discuss the evidence that illustrates the palliative care

needs of patients with HCC that span the entire course of illness, including coping with the stigmatization of liver disease, addressing informational needs at different stages, and discussing quality of life longitudinally. **IMPLICATIONS:** Integrating palliative care into the treatment of patients with HCC has the potential to improve outcomes, although more research is needed to build this evidence base.

[Interaction Between Hepatocellular Carcinoma and Hepatitis C Eradication With Direct-acting Antiviral Therapy.](#) Konjeti VR1, John BV2. *Curr Treat Options Gastroenterol.* 2018 Mar 22. doi: 10.1007/s11938-018-0178-y. [Epub ahead of print]

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.

[Hepatocellular carcinoma risk assessment by the measurement of liver stiffness variations in HCV cirrhotics treated with direct acting antivirals.](#) Ravaioli F1, Conti F1, Brillanti S1, et al.

BACKGROUND: Direct-acting antivirals (DAA) are an effective treatment for hepatitis C virus infection. However, sustained virologic response (SVR) after DAA treatment does not seem to reduce the risk of hepatocellular carcinoma (HCC) development in these patients. Liver stiffness measurement (LSM) may predict the risk of developing HCC in liver cirrhosis patients.

AIMS: The aim of our study was to evaluate the role of LSM variation as predictor of HCC development in patients treated with DAA. **METHODS:** In 139 HCV-related cirrhotic patients, LSM and laboratory tests were carried out at baseline (BL) and at the end of DAA treatment (EOT). Patients were followed for at least 6 months after the EOT. LSM reduction was expressed as Delta LS (Δ LS). Cox regression analysis was used to identify prognostic factors for HCC development after DAA. **RESULTS:** Median LSM values were significantly reduced from BL

to EOT (from 18.6 to 13.8 kPa; $p < 0.001$). The median Δ LS was -26.7% (IQR: -38.4% -13.6%). During a median follow-up of 15 months after DAA treatment, 20 (14.4%) patients developed HCC. Significant LSM reduction was observed both in patients who developed HCC and in those who did not, but this was significantly lower in the patients who developed HCC (-18.0% vs -28.9% $p = 0.005$). At multivariate analysis, Δ LS lower than -30%, Child-Turcotte-Pugh-B and history of HCC were independently associated with HCC development. **CONCLUSION:** Our results indicate that Δ LS is a useful non-invasive marker for predicting HCC development after DAA treatment.

Autophagy, apoptosis, vitamin D, and vitamin D receptor in hepatocellular carcinoma associated with hepatitis C virus. Abdel-Mohsen MA1, El-Braky AA1, Ghazal AAE2, Shamseya MM3. Author information: Medicine (Baltimore). 2018 Mar;97(12):e0172. doi: 10.1097/MD.00000000000010172.

The aims of this study were to investigate the interplay between autophagy and apoptosis and to investigate the association between both of autophagy and apoptosis and vitamin D and its receptor in hepatitis C virus (HCV) viral infection and its implication in the progression into hepatocellular carcinoma (HCC). A cross-sectional study where serum levels of microtubule-associated protein 1A/1B-light chain 3 (LC3); marker of autophagy, caspase-3; marker of apoptosis, vitamin D3 and vitamin D receptor (VDR) were measured in healthy subjects as well as HCV and HCV-HCC patients using enzyme-linked immunosorbent assay technique. Collectively, the liver profile revealed hepatic dysfunctions in HCV patients with or without HCC. A significant reduction in the serum concentration levels LC3 and caspase-3 were observed referring to the down regulation of autophagy and host-mediated apoptosis in HCV patients with or without HCC. Deficiency of vitamin D and decreased levels of its receptor were observed in HCV and HCV-HCC patients. The perturbation in vitamin D/VDR axis, which modulates both of autophagy and apoptosis in HCV infection, may point out to its involvement and implication in the pathogenesis of HCV infection and the development of HCV-related HCC. Therefore, supplementation with vitamin D may not be the only solution to restore the vital biological functions of vitamin D but VDR-targeted therapy may be of great importance in this respect.

Persistent Hepatic Inflammation Plays a Role in Hepatocellular Carcinoma After Sustained Virological Response in Patients with HCV Infection. Nirei K1, Kanda T1, Nakamura H1, Matsuoka S1, Takayama T2, Sugitani M3, Moriyama M1. Int J Med Sci. 2018 Mar 8;15(5):466-474. doi: 10.7150/ijms.23147. eCollection 2018.

OBJECTIVE: Hepatitis C virus (HCV) infection has long been treated with interferon therapy (IFN). Currently, more than 90% of IFN-treated patients show a sustained virological response (SVR) when also treated with ribavirin and/or a protease inhibitor. Histological inflammation and fibrosis improve in IFN-treated patients, which indicates HCV clearance. IFN also reduces the incidence of hepatocellular carcinoma (HCC). However, a small proportion of patients with SVR develop HCC. To investigate the causes of hepatic carcinogenesis after SVR, we compared the liver histological findings before IFN to those after the development of HCC. **PATIENTS AND METHODS:** In total, 602 patients infected with type C chronic hepatitis or with liver cirrhosis who received IFN therapy during the period from 1992 through 2015 were included in this study. We assessed 14 of the 287 patients who achieved an SVR. **RESULTS:** HCC was diagnosed by computed tomography, angiography or liver biopsy. The longest time from the

SVR until HCC detection was 16.5 years, and the mean was 7.2±4.6 years. Nine of the 14 patients underwent surgery and one radiofrequency ablation. The histological findings of 10 patients were available for comparison. The comparison of the histological findings before treatment with those after the HCC diagnosis revealed an amelioration of liver fibrosis and other inflammatory changes. All ten patients showed improvements in fibrosis and steatosis. However, we observed that mild inflammatory change persisted from 1.8 years to 16.5 years after the confirmation of SVR in all cases. **CONCLUSION:** We suspect that persistent histological inflammation is one of the factors contributing to hepatocarcinogenesis (i.e., HCC development) even after successful treatment.

[Post-treatment alpha fetoprotein and platelets predict hepatocellular carcinoma development in dual-infected hepatitis B and C patients after eradication of hepatitis C.](#)

Yeh ML^{1,2,3}, Huang CI², Huang CF^{2,3}, et al. *Oncotarget*. 2018 Jan 13;9(15):12240-12249. doi: 10.18632/oncotarget.24219. eCollection 2018 Feb 23.

We investigated the long-term risk of hepatocellular carcinoma (HCC) in dual-infected hepatitis B and C patients after eradication of hepatitis C virus (HCV). A total of 164 (62% male, median age, 50.5 years) hepatitis B and C dual-infected patients who achieved HCV sustained virological response were recruited. Half the patients were HCV genotype 1 with a median viral load of 5.5 log₁₀ IU/mL, and 22.6% had an HBV DNA level ≥ 2000 IU/mL before therapy. HCC developed in 14 patients (8.5%), with an annual incidence of 1.38% per person-year. The 3-year, 5-year, 10-year, and 15-year cumulative probabilities were 2.5%, 5.1%, 12.6%, and 22.7%, respectively. Six months after treatment, a Cox regression hazard analysis revealed platelet level (HR: 0.98, 95% CI: 0.957-0.999, P = 0.038) and AFP level (HR: 1.20, 95% CI: 1.031-1.400, P = 0.019) to be independent factors in HCC. A higher 10-year cumulative risk of HCC was detected in patients with 6-month post-treatment AFP levels > 5.0 ng/mL and platelet levels < 130 x1000/μL (54.9%), compared to patients with neither (8.6%). Although the risk of HCC is low, surveillance of HCC is encouraged in dual-infected patients after eradication of HCV. Post-treatment AFP and platelet levels predict HCC development.

["Newly diagnosed Hepatocellular Carcinoma in patients with advanced hepatitis C treated with DAAs: a prospective population study"](#). Romano A1, Angeli P1, Piovesan S2, et al. *J Hepatol*. 2018 Mar 15. pii: S0168-8278(18)30172-7. doi: 10.1016/j.jhep.2018.03.009. [Epub ahead of print]

BACKGROUND & AIMS: Direct-acting antiviral agents (DAAs) are safe and effective in patients with hepatitis C. Conflicting data were reported on the risk of Hepatocellular carcinoma (HCC) during/after therapy with DAAs. Aim of this study was to evaluate incidence of newly diagnosed hepatocellular carcinoma and associated risk factors in patients with advanced hepatitis C treated with DAAs. **METHODS:** The study is based on the NAVIGATORE platform, a prospectively recording database of all patients with hepatitis C receiving DAAs in Veneto region (Italy). **INCLUSION CRITERIA:** fibrosis stage ≥ F3. **EXCLUSION CRITERIA:** Child-Pugh C, liver transplantation before DAAs, history or presence of HCC, follow-up <4 weeks after starting DAAs **RESULTS:** 3917 of 4234 consecutive patients were included, with a mean follow-up of 536.2±197.6 days. Overall, HCC was diagnosed in 55 patients. During the first year, HCC incidence was 0.46% (95% CI: 0.12-1.17) in F3, 1.49% (1.03-2.08) in Child-Pugh-A and 3.61% (1.86-6.31) in Child-Pugh-B cirrhotics. In the second year HCC incidences were: 0%, 0.2%, and 0.69%, respectively. By multivariate analysis, HCC

was significantly associated with an APRI \geq 2.5 (HR: 2.03, 95% CI: 1.14-3.61; p=0.016) and HBV (HR: 3.99, 1.24- 12.91; p=0.021). Failure to achieve SVR was strongly associated with development of HCC (HR: 9.09, 5.2-16.1; p=0.0001). 29% of the patients with HCC had an aggressive tumor, often seen in the early phase of treatment. **CONCLUSIONS:** These data, obtained in a large, prospective, population-based study, indicate that in patients with advanced hepatitis C receiving DAAs, the risk of "de novo" hepatocarcinoma during the first year is not higher, and might be lower, than that of untreated patients, and further declines thereafter. Early hepatocarcinoma appearance may reflect pre-existing, microscopic, undetectable tumors.

LAY SUMMARY: Hepatocellular carcinoma is one of the complications of Hepatitis C related cirrhosis. Therapy of patients with advanced hepatitis C with the new interferon-free direct-acting antiviral agents has been associated with improvement in liver function and survival, while more conflicting data have been reported regarding the risk of hepatocellular carcinoma. We report the results of a prospective population study on the incidence of newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with direct-acting antiviral agents, clearly indicating that the residual HCC risk is reduced and decline progressively with time after a sustained virological response. Development of a liver tumor during/after therapy was associated with known risk cofactors and with virological failure.

[Epidemiology of Hepatitis B Virus \(HBV\) and Hepatitis C Virus \(HCV\) Related Hepatocellular Carcinoma.](#) PetruzzIELLO A1. Open Virol J. 2018 Feb 28;12:26-32. doi: 10.2174/1874357901812010026. eCollection 2018.

INTRODUCTION: Hepatocellular carcinoma (HCC) is one of the most prevalent primary malignant tumors and accounts for about 90% of all primary liver cancers. Its distribution varies greatly according to geographic location and it is more common in middle and low-income countries than in developed ones especially in Eastern Asia and Sub Saharan Africa (70% of all new HCCs worldwide), with incidence rates of over 20 per 100,000 individuals.

EXPLANATION: The most important risk factors for HCC are Hepatitis B Virus (HBV) infection, Hepatitis C Virus (HCV) infection, excessive consumption of alcohol and exposition to aflatoxin B1. Its geographic variability and heterogeneity have been widely associated with the different distribution of HBV and HCV infections worldwide. Chronic HBV infection is one of the leading risk factors for HCC globally accounting for at least 50% cases of primary liver tumors worldwide. Generally, while HBV is the main causative agent in the high incidence HCC areas, HCV is the major etiological factor in low incidence HCC areas, like Western Europe and North America. **CONCLUSION:** HBV-induced HCC is a complex, stepwise process that includes integration of HBV DNA into host DNA at multiple or single sites. On the contrary, the cancerogenesis mechanism of HCV is not completely known and it still remains controversial as to whether HCV itself plays a direct role in the development of tumorigenic progression.

[Identification of race-associated metabolite biomarkers for hepatocellular carcinoma in patients with liver cirrhosis and hepatitis C virus infection.](#) Di Poto C1, He S1, Varghese RS1, et al. PLoS One. 2018 Mar 14;13(3):e0192748. doi: 10.1371/journal.pone.0192748. eCollection 2018.

Disparities in hepatocellular carcinoma (HCC) incidence and survival have been observed between ethnic groups including African-Americans (AA) and European-Americans (EA). The evaluation of the changes in the levels of metabolites in samples stratified by race could provide a snapshot of ethnically diverse disease related pathways and identify reliable biomarkers. In this

study, we considered AA and EA to investigate metabolites that may be associated with HCC in a race-specific manner. The levels of 46 metabolites in plasma samples, collected from patients recruited at MedStar Georgetown University Hospital, were analyzed by Agilent GC-qMS in selected ion monitoring (SIM) mode. A least absolute shrinkage and selection operator (LASSO) regression model was applied to select metabolites with significant changes in HCC vs. cirrhosis in three groups: (1) AA and EA combined; (2) AA separately; and (3) EA separately. In addition, metabolites that distinguish HCC cases from cirrhosis in these three groups were selected by excluding those without HCV infection. The performances of the metabolites selected by LASSO in each group were evaluated through a leave-one-out cross-validation. We identified race-specific metabolites that differentiated HCC cases from cirrhotic controls, yielding better area under the receiver operating characteristics (ROC) curve (AUC) compared to alpha-fetoprotein (AFP), the serological marker widely used for the diagnosis of HCC. This study sheds light on metabolites that could potentially be used as biomarkers for HCC by monitoring their levels in high-risk population of cirrhotic patients in a race-specific manner.

[Direct-acting antiviral treatment for patients with hepatocellular carcinoma.](#) Kushner T1, Dieterich D, Saberi B. *Curr Opin Gastroenterol.* 2018 Mar 6. doi: 10.1097/MOG.0000000000000431. [Epub ahead of print]

Abstract

PURPOSE OF REVIEW: Hepatocellular carcinoma (HCC) affects a significant portion of patients with hepatitis C. The use of direct-acting antiviral (DAA) agents has transformed the disease outcomes in this patient group. **RECENT FINDINGS:** Hepatitis C virus (HCV) response to DAAs can be affected by the presence of HCC, whereas DAA therapy may affect the risk of HCC recurrence in patients with a history of HCC. **SUMMARY:** Emerging data are demonstrating lower sustained virologic response (SVR) rates in patients with HCC compared with patients without HCC. Conflicting studies have also suggested that rates of HCC recurrence in patients with a history of HCC can potentially be increased or decreased on DAA therapy. This review will provide a brief overview of these data and inform practitioners on important considerations to make when prescribing DAA therapy for patients with HCV and HCC.

[Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study.](#) Singer AW1, Reddy KR2, Telep LE1, Osinusi AO1, Brainard DM1, Buti M3, Chokkalingam AP1,4. *Aliment Pharmacol Ther.* 2018 Mar 7. doi: 10.1111/apt.14593. [Epub ahead of print]

BACKGROUND: Eradication of hepatitis C virus (HCV) infection via interferon-based treatment lowers hepatocellular carcinoma risk; some research suggests this effect extends to interferon-free treatment. **AIMS:** The objective of this retrospective cohort study was to examine the association of direct-acting antiviral (DAA) exposure with risk of incident liver cancer in real-world data. **METHODS:** From United States administrative claims data through March 31, 2017, we identified 30 183 adult HCV patients exposed to DAAs. For comparison, we identified contemporary adult HCV patients without evidence of HCV treatment (N = 137 502), and historical HCV patients treated with interferon prior to the introduction of DAAs (N = 12 948). Included patients had at least 12 months of prior enrolment and no evidence of prior liver cancer at baseline. Hazard ratios (HRs) estimating risk of incident liver cancer associated with DAA treatment were calculated using Cox proportional hazards methods. **RESULTS:** Relative to untreated HCV patients, DAA-treated patients were older, more likely to be male, and more

likely to have cirrhosis at baseline. After adjustment, DAA treatment was associated with a significantly reduced risk of liver cancer relative to no treatment (adjusted HR = 0.84, 95% CI: 0.73-0.96), and relative to interferon-based treatment in the pre-DAA era (HR = 0.69, 95% CI: 0.59-0.81). **CONCLUSIONS:** In this large, population-based study, DAA-based treatment was associated with a reduced risk of incident liver cancer relative to both no HCV treatment and to interferon-based treatment in the pre-DAA era. As additional follow-up time of DAA-treated patients accrues, we anticipate that the long-term benefits of DAA treatment will become more apparent.