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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES
HIV/HCV COINFECTION
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LIVER CANCER

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[A randomized, controlled study of peginterferon lambda-1a/ribavirin ± daclatasvir for hepatitis C virus genotype 2 or 3.](#) Foster GR1, Chayama K2, Chuang WL3, et al. Springerplus. 2016 Aug 19;5(1):1365. doi: 10.1186/s40064-016-2920-z. eCollection 2016.

BACKGROUND AND PURPOSE: Peginterferon Lambda was being developed as an alternative to alfa interferon for the treatment of chronic hepatitis C virus (HCV) infection. We compared peginterferon Lambda-1a plus ribavirin (Lambda/RBV) and Lambda/RBV plus daclatasvir (DCV; pangenotypic NS5A inhibitor) with peginterferon alfa-2a plus RBV (alfa/RBV) in treatment-naïve patients with HCV genotype 2 or 3 infection. **METHODS:** In this multicenter, double-blind, phase 3 randomized controlled trial, patients were assigned 2:2:1 to receive 24 weeks of Lambda/RBV, 12 weeks of Lambda/RBV + DCV, or 24 weeks of alfa/RBV. The primary outcome measure was sustained virologic response at post-treatment Week 12 (SVR12). **RESULTS:** Overall, 874 patients were treated: Lambda/RBV, n = 353; Lambda/RBV + DCV, n = 349; alfa/RBV, n = 172. Patients were 65 % white and 33 % Asian, 57 % male, with a mean age of 47 years; 52 % were infected with genotype 2 (6 % cirrhotic) and 48 % with genotype 3 (9 % cirrhotic). In the Lambda/RBV + DCV group, 83 % (95 % confidence interval [CI] 78.5, 86.5) achieved SVR12 (90 % genotype 2, 75 % genotype 3) whereas SVR12 was achieved by 68 % (95 % CI 63.1, 72.9) with Lambda/RBV (72 % genotype 2, 64 % genotype 3) and 73 % (95 % CI 66.6, 79.9) with peginterferon alfa/RBV (74 % genotype 2, 73 % genotype 3). Lambda/RBV + DCV was associated with lower incidences of flu-like symptoms, hematological abnormalities, and discontinuations due to adverse events compared with alfa/RBV. **CONCLUSION:** The 12-week regimen of Lambda/RBV + DCV was superior to peginterferon alfa/RBV in the combined population of treatment-naïve patients with genotype 2 or 3 infection, with an improved tolerability and safety profile compared with alfa/RBV.

[Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: a phase III randomized controlled trial.](#) Sperl J1, Horvath G2, Halota W3, et al. J Hepatol. 2016 Aug 16. pii: S0168-8278(16)30429-9. doi: 10.1016/j.jhep.2016.07.050. [Epub ahead of print]

BACKGROUND & AIMS: Direct-acting antiviral agents have improved treatment outcomes for patients with hepatitis C virus (HCV) infection; however, head-to-head comparisons are limited. The C-EDGE Head-2-Head Study compared the safety and efficacy of elbasvir/grazoprevir (EBR/GZR) with sofosbuvir plus pegylated interferon/ribavirin (SOF/PR) in

patients with HCV infection. **METHODS:** This was a randomized, open-label, phase III trial. Two hundred fifty-seven patients with HCV genotype (GT)1 or 4 infection and baseline viral load >10,000 IU/mL were randomized to receive 12 weeks of EBR /GZR 50 mg/100 mg once daily (n = 129) or sofosbuvir (400 mg once daily) plus PR (n = 128). Primary efficacy objective was sustained virologic response 12 weeks after the end of therapy (SVR12, HCV RNA <15 IU/mL). The primary safety objective was the proportion of patients experiencing a Tier 1 safety event. **RESULTS:** The majority of patients were noncirrhotic (83.1%), treatment-naïve (74.9%) and had HCV GT1b infection (82.0%). SVR12 rates were 99.2% (128/129) and 90.5% (114/126) in the EBR/GZR and SOF/PR groups, respectively. The estimated adjusted difference in SVR12 was 8.8% (95% confidence interval [CI], 3.6-15.3%). Because the lower bound of the 1-sided 1-sample exact test was greater than -10% and greater than zero, both noninferiority and superiority of EBR/GZR vs. SOF/PR were established. The frequency of Tier 1 safety events was lower among patients receiving EBR/GZR than SOF/PR (0.8% vs. 27.8%, between group difference, 27.0% [95% CI, -35.5% to -19.6%; p < 0.001]). **CONCLUSIONS:** EBR/GZR has a superior efficacy and safety profile in patients with HCV GT1 and 4 infection compared with SOF/PR.

[Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial.](#) Dore GJ, Altice F, Litwin AH, et al. Ann Intern Med. 2016 Aug 9. doi: 10.7326/M16-0816. [Epub ahead of print]

BACKGROUND: Hepatitis C virus (HCV) infection is common in persons who inject drugs (PWID). **OBJECTIVE:** To evaluate elbasvir-grazoprevir in treating HCV infection in PWID. **DESIGN:** Randomized, placebo-controlled, double-blind trial. (ClinicalTrials.gov: NCT02105688). **SETTING:** Australia, Canada, France, Germany, Israel, the Netherlands, New Zealand, Norway, Spain, Taiwan, the United Kingdom, and the United States. **PATIENTS:** 301 treatment-naïve patients with chronic HCV genotype 1, 4, or 6 infection who were at least 80% adherent to visits for opioid-agonist therapy (OAT). **INTERVENTION:** The immediate-treatment group (ITG) received elbasvir-grazoprevir for 12 weeks; the deferred-treatment group (DTG) received placebo for 12 weeks, no treatment for 4 weeks, then open-label elbasvir-grazoprevir for 12 weeks. **MEASUREMENTS:** The primary outcome was sustained virologic response at 12 weeks (SVR12), evaluated separately in the ITG and DTG. Other outcomes included SVR24, viral recurrence or reinfection, and adverse events. **RESULTS:** The SVR12 was 91.5% (95% CI, 86.8 to 95.0) in the ITG and 89.5% (95% CI, 81.5 to 94.8) in the active phase of the DTG. Drug use at baseline and during treatment did not affect SVR12 or adherence to HCV therapy. Among 18 patients with posttreatment viral recurrence through 24-week follow-up, 6 had probable reinfection. If the probable reinfections were assumed to be responses, SVR12 was 94.0% (CI, 89.8 to 96.9) in the ITG. One patient in the ITG (1 of 201) and 1 in the placebo-phase DTG (1 of 100) discontinued treatment because of an adverse event. **LIMITATION:** These findings may not be generalizable to PWID who are not receiving OAT, nor do they apply to persons with genotype 3 infection, a common strain in PWID. **CONCLUSION:** Patients with HCV infection who were receiving OAT and treated with elbasvir-grazoprevir had high rates of SVR12, regardless of ongoing drug use. These results support the removal of drug use as a barrier to interferon-free HCV treatment for patients receiving OAT.

[Drug-Drug Interactions Between the Anti-Hepatitis C Virus 3D Regimen of Ombitasvir, Paritaprevir/Ritonavir, and Dasabuvir and Eight Commonly Used Medications in Healthy Volunteers.](#) Polepally AR1, King JR2, Ding B3, Shuster DL2, Dumas EO4, Khatri A2, Chiu YL3, Podsadecki TJ4, Menon RM2. Clin Pharmacokinet. 2016 Aug;55(8):1003-14. doi: 10.1007/s40262-016-0373-8.

BACKGROUND AND AIMS: The three direct-acting antiviral regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir (3D regimen) is approved for treatment of hepatitis C virus (HCV) genotype 1 infection. Drug-drug interaction (DDI) studies of the 3D regimen and commonly used medications were conducted in healthy volunteers to provide information on coadministering these medications with or without dose adjustments.

METHODS: Three phase I studies evaluated DDIs between the 3D regimen (ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily + dasabuvir 250 mg twice daily) and hydrocodone bitartrate/acetaminophen (5/300 mg), metformin hydrochloride (500 mg), diazepam (2 mg), cyclobenzaprine hydrochloride (5 mg), carisoprodol (250 mg), or sulfamethoxazole/trimethoprim (SMZ/TMP) (800/160 mg twice daily), all administered orally. DDI magnitude was determined using geometric mean ratios and 90 % confidence intervals for the maximum plasma concentration (C max) and area under the plasma concentration-time curve (AUC).

RESULTS: Changes in exposures (C max and AUC geometric mean ratios) of acetaminophen, metformin, sulfamethoxazole, trimethoprim, and diazepam were ≤ 25 % upon coadministration with the 3D regimen. The C max and AUC of nordiazepam, an active metabolite of diazepam, increased by 10 % and decreased by 44 %, respectively. Exposures of cyclobenzaprine and carisoprodol decreased by ≤ 40 and ≤ 46 %, respectively, whereas exposures of hydrocodone increased up to 90 %. Ombitasvir, paritaprevir, ritonavir, and dasabuvir exposures changed by ≤ 25 %, except for a 37 % decrease in paritaprevir C max with metformin and a 33 % increase in dasabuvir AUC with SMZ/TMP. **CONCLUSIONS:** Acetaminophen, metformin, sulfamethoxazole, and trimethoprim can be coadministered with the 3D regimen without dose adjustment. Higher doses may be needed for diazepam, cyclobenzaprine, and carisoprodol based on clinical monitoring. A 50 % lower dose and/or clinical monitoring should be considered for hydrocodone. No dose adjustment is necessary for the 3D regimen.

[Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia.](#) Gagnani L1, Visentini M2, Fognani E1, et al. Hepatology. 2016 Aug 2. doi: 10.1002/hep.28753. [Epub ahead of print]

Hepatitis C virus (HCV)-associated mixed cryoglobulinemia (MC) vasculitis commonly regresses upon virus eradication, but conventional therapy with pegylated interferon and ribavirin yields approximately 40% sustained virologic responses (SVR). We prospectively evaluated the efficacy and safety of sofosbuvir-based direct-acting antiviral therapy, individually tailored according to the latest guidelines, in a cohort of 44 consecutive patients with HCV-associated MC. In two patients MC had evolved into an indolent lymphoma with monoclonal B-cell lymphocytosis. All patients had negative HCV viremia at week 12 (SVR12) and at week 24 (SVR24) posttreatment, at which time all had a clinical response of vasculitis. The mean (\pm standard deviation) Birmingham Vasculitis Activity Score decreased from 5.41 (± 3.53) at baseline to 2.35 (± 2.25) ($P < 0.001$) at week 4 on treatment to 1.39 (± 1.48) ($P < 0.001$) at SVR12 and to 1.27 (± 1.68) ($P < 0.001$) at SVR24. The mean cryocrit value fell from 7.2 (± 15.4)% at baseline to 2.9 (± 7.4)% ($P < 0.01$) at SVR12 and to 1.8 (± 5.1)% ($P < 0.001$) at SVR24. Intriguingly, in the 2 patients with MC and lymphoma there was a partial clinical response of

vasculitis and ~50% decrease of cryocrit, although none experienced a significant decrease of monoclonal B-cell lymphocytosis. Adverse events occurred in 59% of patients and were generally mild, with the exception of 1 patient with ribavirin-related anemia requiring blood transfusion. **CONCLUSION:** Interferon-free, guideline-tailored therapy with direct-acting antivirals is highly effective and safe for HCV-associated MC patients; the overall 100% rate of clinical response of vasculitis, on an intention-to-treat basis, opens the perspective for curing the large majority of these so far difficult-to-treat patients. (Hepatology 2016).

Effectiveness of Ledipasvir-Sofosbuvir Combination in Patients With Hepatitis C Virus Infection and Factors Associated of Sustained Virologic Response.

Terrault NA1, Zeuzem S2, Di Bisceglie AM3, et al. Gastroenterology. 2016 Aug 23. pii: S0016-5085(16)34927-7. doi: 10.1053/j.gastro.2016.08.004. [Epub ahead of print]

BACKGROUND & AIMS: The combination of ledipasvir and sofosbuvir has been approved for treatment of genotype 1 hepatitis C virus (HCV) infection, including an 8-week regimen for treatment-naïve patients without cirrhosis and a baseline level of HCV RNA <6 million IU/mL. We analyzed data from a multicenter, prospective, observational study to determine real-world sustained virologic responses 12 weeks after treatment (SVR12) with regimens containing ledipasvir and sofosbuvir and identify factors associated with treatment failure. **METHODS:** We collected data from 2099 participants in the HCV-TARGET study with complete virologic data (per protocol population). We analyzed data from 1788 patients receiving ledipasvir-sofosbuvir (282 for 8 weeks, 910 for 12 weeks, 510 for 24 weeks, and 86 for a different duration) and 311 receiving ledipasvir-sofosbuvir plus ribavirin (212 for 12 weeks and 81 for 24 weeks, 18 for other duration) to estimate SVR12 (with 95% CI), and logistic regression methods to identify factors that predicted an SVR12. **RESULTS:** The overall study population was 25% Black, 66% with HCV genotype 1A infection, 41% with cirrhosis, 50% treatment experienced, and 30% receiving proton pump inhibitors (PPIs) at start of treatment. In the per protocol population, SVR12s were achieved by 96% of patients receiving ledipasvir-sofosbuvir for 8 weeks (95% CI, 93%-98%), 97% receiving the drugs for 12 weeks (95% CI, 96%-98%), and 95% receiving the drugs for 24 weeks (95% CI, 93%-97%). Among patients also receiving ribavirin, SVR12s were achieved by 97% of the patients receiving the drugs for 12 weeks (95% CI, 94%-99%) and 95% receiving the drugs for 24 weeks (95% CI, 88%-99%). Of the 586 patients who qualified for 8 weeks treatment, only 255 (44%) received the drugs for 8 weeks. The rate of SVR12 among those who qualified for and received 8 weeks therapy was similar in those who qualified for 8 weeks but received 12 weeks therapy (96%; 95% CI, 92%-99% vs 98%; 95% CI, 95%-99%). Factors that predicted SVR12 were higher albumin (≥ 3.5 g/dL), lower total bilirubin (≤ 1.2 g/dL), absence of cirrhosis, and absence of PPI use. **CONCLUSIONS:** Regimens containing ledipasvir and sofosbuvir are highly effective for a broad spectrum of patients with HCV genotype 1 infection treated in different clinical practice settings. Expanded use of 8-week treatment regimens for eligible patients is supported by these real-world results. Modification of PPI use may increase rates of SVR.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Role of Conserved E2 Residue W420 in Receptor Binding and Hepatitis C Virus Infection.

Cowton VM1, Angus AG1, Cole SJ1, et al. J Virol. 2016 Jul 27;90(16):7456-68. doi: 10.1128/JVI.00685-16. Print 2016 Aug 15.

Hepatitis C virus (HCV) enters cells via interactions with several host factors, a key one being that between the viral E2 envelope glycoprotein and the CD81 receptor. We previously identified E2 tryptophan residue 420 (W420) as an essential CD81-binding residue. However, the importance of W420 in the context of the native virion is unknown, as those previous studies predate the infectious HCV cell culture (cell culture-derived HCV [HCVcc]) system. Here, we introduced four separate mutations (F, Y, A, or R) at position 420 within the infectious HCVcc JFH-1 genome and characterized their effects on the viral life cycle. While all mutations reduced E2-CD81 binding, only two (W420A and W420R) reduced HCVcc infectivity. Further analyses of mutants with hydrophobic residues (F or Y) found that interactions with the receptors SR-BI and CD81 were modulated, which in turn determined the viral uptake route. Both mutant viruses were significantly less dependent on SR-BI, and its lipid transfer activity, for virus entry. Furthermore, these viruses were resistant to the drug erlotinib, which targets epidermal growth factor receptor (EGFR) (a host cofactor for HCV entry) and also blocks SR-BI-dependent high-density lipoprotein (HDL)-mediated enhancement of virus entry. Together, our data indicate a model where an alteration at position 420 causes a subtle change in the E2 conformation that prevents interaction with SR-BI and increases accessibility to the CD81-binding site, in turn favoring a particular internalization route. These results further show that a hydrophobic residue with a strong preference for tryptophan at position 420 is important, both functionally and structurally, to provide an additional hydrophobic anchor to stabilize the E2-CD81 interaction. **IMPORTANCE:** Hepatitis C virus (HCV) is a leading cause of liver disease, causing up to 500,000 deaths annually. The first step in the viral life cycle is the entry process. This study investigates the role of a highly conserved residue, tryptophan residue 420, of the viral glycoprotein E2 in this process. We analyzed the effect of changing this residue in the virus and confirmed that this region is important for binding to the CD81 receptor. Furthermore, alteration of this residue modulated interactions with the SR-BI receptor, and changes to these key interactions were found to affect the virus internalization route involving the host cofactor EGFR. Our results also show that the nature of the amino acid at this position is important functionally and structurally to provide an anchor point to stabilize the E2-CD81 interaction.

[Viral Eradication reduces all-Cause Mortality, Including non-Liver-Related Disease, in Patients With Progressive Hepatitis C Virus-Related Fibrosis.](#) Tada T1, Kumada T1, Toyoda H1, et al. *J Gastroenterol Hepatol.* 2016 Aug 30. doi: 10.1111/jgh.13589. [Epub ahead of print]

BACKGROUND & AIM: Eradication of hepatitis C virus (HCV) with interferon (IFN)-based therapy has been reported to reduce all-cause mortality in patients with chronic HCV infection. However, the impact of HCV eradication on non-liver-related mortality and causes of death has not been sufficiently investigated in patients with progressive HCV-related fibrosis.

METHODS: We enrolled 784 chronic HCV patients with progressive liver fibrosis (aspartate aminotransferase to platelet ratio index >1). Cause of death, incidence of hepatocellular carcinoma (HCC), and all-cause mortality including non-liver-related mortality were analyzed.

RESULTS: Of these 784 patients, 170 achieved sustained virological response (SVR) (eradication of HCV) with IFN-based therapy (IFN-SVR), and 614 did not receive IFN-based therapy (non-IFN patients, chronic HCV infection). The median follow-up duration was 10.3 years. Two hundred seventy-three patients died during follow-up (liver-related death, n = 171; non-liver-related death, n = 102). The mortality rate from non-liver-related disease was 63.6% (7/11) in IFN-SVR patients and 36.3% (95/262) in non-IFN patients, respectively. In multivariate analysis, the eradication of HCV associated with not only HCC incidence (hazard

ratio (HR), 0.162; 95% confidence interval (CI), 0.092-0.284) and all-cause mortality (HR, 0.094; 95% CI, 0.047-0.187), but non-liver-related mortality (HR, 0.286; 95% CI, 0.127-0.644) as well. **CONCLUSIONS:** Eradication of HCV reduced both liver-related and non-liver-related mortality in patients with progressive HCV-related fibrosis. This article is protected by copyright. All rights reserved.

[Association between vitamin D deficiency and pre-existing resistance-associated hepatitis C virus NS5A variants.](#) Okubo T1, Atsukawa M1, Tsubota A2, et al. *Hepatology Res.* 2016 Aug 2. doi: 10.1111/hepr.12784. [Epub ahead of print]

AIM: Although interferon-free therapy with direct-acting antivirals has developed as a standard of care for chronic hepatitis C, the existence of resistance-associated variants (RAVs) has a negative impact on treatment results. Recently, several studies indicated a relationship between chronic hepatitis C and serum vitamin D levels. However, the relationship between RAVs at the hepatitis C virus non-structure 5A (NS5A) region and serum vitamin D level has not yet been examined. **METHODS:** Among patients with genotype 1 chronic hepatitis C who were enrolled in a multicenter cooperative study, our subjects comprised 247 patients in whom it was possible to measure RAVs at the NS5A region. These RAVs were measured using a direct sequencing method. **RESULTS:** The median age of patients was 70 years (range, 24-87 years), and the number of female patients was 135 (54.7%). The median serum 25(OH) D3 level was 22 ng/mL (range, 6-64 ng/mL). L31 and Y93 RAVs at the NS5A region were detected in 3.7% (9/247) and 13.4% (33/247) of patients, respectively. Multivariate analysis identified vitamin D deficiency (serum 25(OH) D3 \leq 20 ng/mL) ($P = 5.91 \times 10^{-5}$, odds ratio = 5.015) and elderly age (>70 years) ($P = 1.85 \times 10^{-3}$, odds ratio = 3.364) as contributing independent factors associated with the presence of the L31 and/or Y93 RAVs. The Y93H RAV was detected in 25.9% (29/112) of patients with a vitamin D deficiency, and in 8.9% (12/135) of those with a serum 25(OH) D3 level >20 ng/mL ($P = 4.90 \times 10^{-3}$). **CONCLUSION:** We showed that RAVs at the NS5A region are associated with vitamin D deficiency and elderly age, which may have a negative influence on innate/adaptive immune responses to hepatitis C virus infection.

[Resistance Analyses of HCV NS3/4A Protease and NS5B Polymerase from Clinical Studies of Deleobuvir and Faldaprevir.](#) Berger KL1,2, Sarrazin C3, Nelson DR4, et al. *PLoS One.* 2016 Aug 5;11(8):e0160668. doi: 10.1371/journal.pone.0160668. eCollection 2016.

BACKGROUND & AIM: The resistance profile of anti-hepatitis C virus (HCV) agents used in combination is important to guide optimal treatment regimens. We evaluated baseline and treatment-emergent NS3/4A and NS5B amino-acid variants among HCV genotype (GT)-1a and -1b-infected patients treated with faldaprevir (HCV protease inhibitor), deleobuvir (HCV polymerase non-nucleoside inhibitor), and ribavirin in multiple clinical studies. **METHODS:** HCV NS3/4A and NS5B population sequencing (Sanger method) was performed on all baseline plasma samples ($n = 1425$ NS3; $n = 1556$ NS5B) and on post-baseline plasma samples from patients with virologic failure ($n = 113$ GT-1a; $n = 221$ GT-1b). Persistence and time to loss of resistance-associated variants (RAVs) was estimated using Kaplan-Meier analysis. **RESULTS:** Faldaprevir RAVs (NS3 R155 and D168) and deleobuvir RAVs (NS5B 495 and 496) were rare ($<1\%$) at baseline. Virologic response to faldaprevir/deleobuvir/ribavirin was not compromised by common baseline NS3 polymorphisms (e.g. Q80K in 17.5% of GT-1a) or by NS5B A421V, present in 20% of GT-1a. In GT-1b, alanine at NS5B codon 499 (present in 15% of baseline sequences) was associated with reduced response. Treatment-emergent RAVs consolidated

previous findings: NS3 R155 and D168 were key faldaprevir RAVs; NS5B A421 and P495 were key deleobuvir RAVs. Among on-treatment virologic breakthroughs, RAVs emerged in both NS3 and NS5B (>90%). Virologic relapse was associated with RAVs in both NS3 and NS5B (53% GT-1b; 52% GT-1b); some virologic relapses had NS3 RAVs only (47% GT-1a; 17% GT-1b). Median time to loss of GT-1b NS5B P495 RAVs post-treatment (5 months) was less than that of GT-1b NS3 D168 (8.5 months) and GT-1a R155 RAVs (11.5 months). **CONCLUSION:** Faldaprevir and deleobuvir RAVs are more prevalent among virologic failures than at baseline. Treatment response was not compromised by common NS3 polymorphisms; however, alanine at NS5B amino acid 499 at baseline (wild-type in GT-1a, polymorphism in GT-1b) may reduce response to this deleobuvir-based regimen.

[Interaction between Nonstructural Proteins NS4B and NS5A Is Essential for Proper NS5A Localization and Hepatitis C Virus RNA Replication.](#) Biswas A1, Treadaway J1, Tellinghuisen TL2. J Virol. 2016 Jul 27;90(16):7205-18. doi: 10.1128/JVI.00037-16. Print 2016 Aug 15.

The hepatitis C virus NS5A protein is tethered to cellular membranes via an amphipathic amino-terminal helix that is inserted in-plane into the outer endoplasmic reticulum (ER)-derived membrane leaflet. The charged face of the helix faces the cytoplasm and may contribute to interactions involved in replicase assembly and function. Using an aggressive charge flip mutagenesis strategy, we identified a number of essential residues for replication on the charged face of the NS5A anchor and identified a double charge face mutant that is lethal for RNA replication but generates suppressor mutations in the carboxy-terminal helix of the NS4B protein. This suppressor restores RNA replication of the NS5A helix double flip mutant (D1979K/D1982K) and, interestingly, seems to function by restoring the proper localization of NS5A to the viral replicase. These data add to our understanding of the complex organization and assembly of the viral replicase via NS4B-NS5A interactions. **IMPORTANCE:** Information about the functional role of the cytosolic face of the NS5A anchoring helix remains obscure. In this study, we show that while the hydrophobic face of the NS5A anchor helix mediates membrane association, the polar cytosolic face of the helix plays a key role during hepatitis C virus (HCV) replication by mediating the interaction of NS5A with other HCV nonstructural proteins via NS4B. Such an interaction determines the subcellular localization of NS5A by engaging NS5A in the HCV replication process during the formation of a functional HCV replication complex. Thus, collectively, it can be stated that the findings in the present study provide further information about the interactions between the HCV nonstructural proteins during HCV RNA replication and provide a platform to gain more insights about the molecular architecture of HCV replication complexes.

[Nonstructural 3 Protein of Hepatitis C Virus Modulates the Tribbles Homolog 3/Akt Signaling Pathway for Persistent Viral Infection.](#) Tran SC1, Pham TM1, Nguyen LN1, Park EM2, Lim YS1, Hwang SB3. J Virol. 2016 Jul 27;90(16):7231-47. doi: 10.1128/JVI.00326-16. Print 2016 Aug 15.

Hepatitis C virus (HCV) infection often causes chronic hepatitis, liver cirrhosis, and ultimately hepatocellular carcinoma. However, the mechanisms underlying HCV-induced liver pathogenesis are still not fully understood. By transcriptome sequencing (RNA-Seq) analysis, we recently identified host genes that were significantly differentially expressed in cell culture-grown HCV (HCVcc)-infected cells. Of these, tribbles homolog 3 (TRIB3) was selected for

further characterization. TRIB3 was initially identified as a binding partner of protein kinase B (also known as Akt). TRIB3 blocks the phosphorylation of Akt and induces apoptosis under endoplasmic reticulum (ER) stress conditions. HCV has been shown to enhance Akt phosphorylation for its own propagation. In the present study, we demonstrated that both mRNA and protein levels of TRIB3 were increased in the context of HCV replication. We further showed that promoter activity of TRIB3 was increased by HCV-induced ER stress. Silencing of TRIB3 resulted in increased RNA and protein levels of HCV, whereas overexpression of TRIB3 decreased HCV replication. By employing an HCV pseudoparticle entry assay, we further showed that TRIB3 was a negative host factor involved in HCV entry. Both in vitro binding and immunoprecipitation assays demonstrated that HCV NS3 specifically interacted with TRIB3. Consequently, the association of TRIB3 and Akt was disrupted by HCV NS3, and thus, TRIB3-Akt signaling was impaired in HCV-infected cells. Moreover, HCV modulated TRIB3 to promote extracellular signal-regulated kinase (ERK) phosphorylation, activator protein 1 (AP-1) activity, and cell migration. Collectively, these data indicate that HCV exploits the TRIB3-Akt signaling pathway to promote persistent viral infection and may contribute to HCV-mediated pathogenesis. **IMPORTANCE:** TRIB3 is a pseudokinase protein that acts as an adaptor in signaling pathways for important cellular processes. So far, the functional involvement of TRIB3 in virus-infected cells has not yet been demonstrated. We showed that both mRNA and protein expression levels of TRIB3 were increased in the context of HCV RNA replication. Gene silencing of TRIB3 increased HCV RNA and protein levels, and thus, overexpression of TRIB3 decreased HCV replication. TRIB3 is known to promote apoptosis by negatively regulating the Akt signaling pathway under ER stress conditions. Most importantly, we demonstrated that the TRIB3-Akt signaling pathway was disrupted by NS3 in HCV-infected cells. These data provide evidence that HCV modulates the TRIB3-Akt signaling pathway to establish persistent viral infection.

Biochemical Characterization of the Active Anti-Hepatitis C Virus Metabolites of 2,6-Diaminopurine Ribonucleoside Prodrug Compared to Sofosbuvir and BMS-986094.

Ehteshami M1, Tao S1, Ozturk T1, et al. *Antimicrob Agents Chemother.* 2016 Jul 22;60(8):4659-69. doi: 10.1128/AAC.00318-16. Print 2016 Aug.

Ribonucleoside analog inhibitors (rNAI) target the hepatitis C virus (HCV) RNA-dependent RNA polymerase nonstructural protein 5B (NS5B) and cause RNA chain termination. Here, we expand our studies on β -d-2'-C-methyl-2,6-diaminopurine-ribonucleotide (DAPN) phosphoramidate prodrug 1 (PD1) as a novel investigational inhibitor of HCV. DAPN-PD1 is metabolized intracellularly into two distinct bioactive nucleoside triphosphate (TP) analogs. The first metabolite, 2'-C-methyl-GTP, is a well-characterized inhibitor of NS5B polymerase, whereas the second metabolite, 2'-C-methyl-DAPN-TP, behaves as an adenosine base analog. In vitro assays suggest that both metabolites are inhibitors of NS5B-mediated RNA polymerization. Additional factors, such as rNAI-TP incorporation efficiencies, intracellular rNAI-TP levels, and competition with natural ribonucleotides, were examined in order to further characterize the potential role of each nucleotide metabolite in vivo. Finally, we found that although both 2'-C-methyl-GTP and 2'-C-methyl-DAPN-TP were weak substrates for human mitochondrial RNA (mtRNA) polymerase (POLRMT) in vitro, DAPN-PD1 did not cause off-target inhibition of mtRNA transcription in Huh-7 cells. In contrast, administration of BMS-986094, which also generates 2'-C-methyl-GTP and previously has been associated with toxicity in humans, caused detectable inhibition of mtRNA transcription. Metabolism of BMS-986094 in Huh-7 cells leads

to 87-fold higher levels of intracellular 2'-C-methyl-GTP than DAPN-PD1. Collectively, our data characterize DAPN-PD1 as a novel and potent antiviral agent that combines the delivery of two active metabolites.

HIV/HCV COINFECTION

[Prevalence and predictors of low muscle mass in HIV/viral hepatitis coinfection.](#) Gowda C1, Brown TT, Compher C, Forde KA, Kostman J, Shaw PA, Tien PC, Re VL 3rd. AIDS. 2016 Aug 3. [Epub ahead of print]

OBJECTIVE: Low muscle mass is associated with reduced survival in HIV, possibly mediated by systemic inflammation. Viral hepatitis coinfection can induce additional inflammation and hepatic dysfunction that may exacerbate low muscle mass. We determined the prevalence of and risk factors for low muscle mass in HIV/viral hepatitis coinfection. **DESIGN AND METHODS:** A cross-sectional study of participants in the Multicenter AIDS Cohort Study and Women's Interagency HIV Study with anthropometry performed after January 1, 2000. Viral hepatitis defined by positive hepatitis B virus surface antigen and/or hepatitis C virus RNA. Low muscle mass defined as <10 percentile of age- and sex-matched reference values for mid-upper arm circumference. Using multivariable logistic regression, we determined adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of: 1) the association of HIV/viral hepatitis coinfection with low muscle mass; and 2) factors associated with low muscle mass in coinfecting persons. Analyses adjusted for age, race, body mass index, alcohol use and injection drug use (also, nadir CD4 and HIV RNA where appropriate). **RESULTS:** Among 3,518 participants (164 HIV/viral hepatitis; 223 viral hepatitis alone; 1,070 HIV alone; 2,061 uninfected), HIV/viral hepatitis-coinfecting persons had a 3.50-fold (95% CI, 1.51-8.09), 1.93-fold (1.17-3.20), and 2.65-fold (1.62-4.35) higher odds of low muscle mass than viral hepatitis-monoinfecting, HIV-monoinfecting, and uninfected persons, respectively. Lack of HIV RNA suppression (OR: 2.26 [1.10-4.63]) was the only factor associated with low muscle mass in coinfecting persons. **CONCLUSIONS:** HIV/viral hepatitis-coinfecting persons have a higher likelihood of low muscle mass than those with viral hepatitis monoinfection, HIV monoinfection, or neither infection. HIV viremia is an important risk factor for low muscle mass among coinfecting persons.

[Estimated glomerular filtration rate but not solute carrier polymorphisms influences anemia in HIV-hepatitis C virus coinfecting patients treated with boceprevir or telaprevir-based therapy.](#)

Kheloufi F1, Bellissant E, Cotte L, et al. AIDS. 2016 Aug 24;30(13):2085-90. doi: 10.1097/QAD.0000000000001143.

OBJECTIVES: Ribavirin (RBV) induced anemia may be influenced by host genetic factors affecting RBV transport solute carrier (SLC) or metabolism inosine triphosphatase (ITPA), as already reported. We investigated the influence of single nucleotide polymorphisms (SNPs) on SLC genes on anemia, RBV trough concentration (C_{trough}) and response in HIV-hepatitis C virus coinfecting patients receiving triple therapy with boceprevir or telaprevir. **METHODS:** Patients from the ANRS HC26/HC27 studies were genotyped for SLC28A3 SNPs (rs10868138 and rs56350726) and SLC29A1 SNPs (rs760370). Hemoglobin (Hb) decline was collected at baseline day 0 (D0), week 4 (W4) and week 8 (W8), and RBV C_{trough} was measured at W4 and W8 by HPLC. A multivariate analysis including SLC SNPs, estimated glomerular filtration rate

(eGFR), ITPA deficiency and RBV Ctrough was performed to determine predictive factors of anemia and response. **RESULTS:** SLC genotyping was performed in 130 patients. Neither SLC28A3 nor SLC29A1 SNPs were associated with Hb decline both at W4 and W8. No association was found between SLC polymorphisms and RBV Ctrough. Independent predictive factors of Hb decline at W4 were D0 Hb, ITPA deficiency and W4 RBV Ctrough in the multivariate analysis ($P < 0.05$). Only D0 Hb, W4 RBV Ctrough and eGFRD0-W8 were predictive of anemia at W8 ($P < 0.05$). Response was not influenced by SLC SNPs. **CONCLUSION:** eGFR, but not SLC polymorphisms, influences anemia in HIV-hepatitis C virus coinfecting patients receiving boceprevir-based or telaprevir-based therapy. RBV is still a cornerstone of hepatitis C treatment, thus renal function and RBV Ctrough should be monitored in patients receiving RBV regimen combined with first-generation direct-acting antiviral agent.

[Assessment of factors associated with the quality of life of patients living with HIV/HCV co-infection.](#) Pereira M1, Fialho R2,3. J Behav Med. 2016 Oct;39(5):767-81. doi: 10.1007/s10865-016-9778-y. Epub 2016 Aug 9.

This study compared the quality of life (QoL) of HIV-infected patients with and without hepatitis C and examined the sociodemographic, HIV-related and psychological symptoms associated with the QoL domains in patients with HIV/HCV co-infection. The sample consisted of 248 HIV/HCV co-infected patients (18-74 years, 81.5 % male) and 482 patients only with HIV (24-78 years, 62.7 % male). Participants completed the WHOQOL-HIV-Bref questionnaire and the Brief Symptom Inventory. The HIV/HCV co-infected patients reported significantly lower QoL in all domains, as well as significantly lower scores in 10 of the 17 specific facets. Overall, among the co-infected patients, male gender, employment, combination antiretroviral therapy use and fewer depressive and anxiety symptoms were significantly associated with higher QoL. Symptoms of psychological distress accounted for significant variability in the QoL scores of co-infected patients. These data reinforce the need for tailored interventions to improve the overall well-being of HIV/HCV co-infected patients.

[Direct-acting antivirals in hepatitis C virus \(HCV\)-infected and HCV/HIV-coinfecting patients: real-life safety and efficacy.](#) Milazzo L1, Lai A1, Calvi E1, et al. HIV Med. 2016 Aug 1. doi: 10.1111/hiv.12429. [Epub ahead of print]

OBJECTIVES: Clinical trials of all-oral direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) infection reported high response rates in HCV/HIV coinfection, similar to those obtained in HCV monoinfection. We evaluated the safety and efficacy of these regimens in a clinical practice setting. **METHODS:** In this prospective observational study, all the HCV-monoinfected and HCV/HIV-coinfecting patients undergoing HCV treatment with all-oral DAA regimens in a routine clinical setting from December 2014 to December 2015 were included in the analysis. Sustained virological response 12 weeks after the end of therapy (SVR12) and reported adverse events (AEs) were evaluated. Resistance-associated variants (RAVs) were analysed in a subgroup of patients at baseline and at the time of viral rebound in those with virological failure. **RESULTS:** One-hundred and nine patients (51 HCV-infected and 58 HCV/HIV-coinfecting) were enrolled in the study. Sixty per cent had cirrhosis and 52% were pegylated interferon and ribavirin (pegIFN/RBV)-experienced. Thirty-six per cent received ombitasvir + paritaprevir/ritonavir + dasabuvir, 25% sofosbuvir + daclatasvir, 16% sofosbuvir + simeprevir, 17% sofosbuvir + ribavirin and 6% sofosbuvir + ledipasvir; ribavirin was used in 57% of subjects. The SVR12 rate was 91% and 96% in HIV-infected and uninfected patients,

respectively ($P = 0.44$). The 4-week HCV viral decline was similar in the two groups. RAVs were found at baseline in 23 of 49 patients and did not affect SVR12. No predictors of SVR12 were identified in our cohort. **CONCLUSIONS:** Treatment with all-oral DAA combinations of patients infected with HCV and with HCV/HIV under real-life conditions led to high and similar rates of SVR12. Moreover, the historical factors associated with a sustained virological response to pegIFN/RBV were not predictive of the response to all-oral DAAs.

[Association between chronic hepatitis C and hepatitis C/HIV co-infection and the development of colorectal adenomas.](#) Hurtado-Cordovi J1, Davis-Yadley AH2, Lipka S3, Vardaros M4, Shen H5. *J Gastrointest Oncol.* 2016 Aug;7(4):609-14. doi: 10.21037/jgo.2016.03.11.

BACKGROUND: Limited knowledge exists about the effects chronic hepatitis C virus (HCV) infection has in the development of colorectal adenomas (CRA). Data regarding the association between chronic HIV infection and the development of CRA is scarce as well. We aim to determine if there is an association between the development of CRA and chronic infection with HCV and HCV/HIV co-infection. **METHODS:** From July 1, 2009 to March 31, 2011 a total of 2,051 patients that underwent colonoscopy were included in our study. The population was divided into 2 study groups: those patients who tested positive for HCV, and HCV/HIC; the control groups consisted of patients whose results were negative. Fisher's exact χ^2 test for categorical variables and t-test for continuous variables was used to analyze data between groups. Logistic regression was performed to obtain odds ratios (OR). **RESULTS:** CRA detection was higher in the HCV than in the control group (26.3% vs. 20.2%; $P=1.02$); Likewise, the incidence of CRA (25.5% vs. 20.8%; $P=0.63$) was higher in the co-infection group. However, in both of the study groups this difference was non-statistical. **CONCLUSIONS:** A higher detection rate of CRA was seen in the HCV population; however, it failed to reach statistical significance. Whether co-infection with HIV/HCV increases the incidence of CRA and/or has a synergistic effect remains to be determined. The small sample population and the retrospective single institution nature of our study, as well as other confounders may have contributed to our negative results. However, our findings question whether HCV and HIV/HCV co-infected patients will benefit from screening colonoscopy at an earlier age. This issue merits further investigation with a large multi-center prospective study.

[Antiretroviral therapy does not affect response to chronic hepatitis C therapy in HIV-coinfected patients.](#) De Leon LB1, Tovo CV, Kliemann DA, De Mattos AA, Feltrin AA, Pacheco LS, De Almeida PR. *J Infect Dev Ctries.* 2016 Aug 2;10(7):762-9. doi: 10.3855/jidc.7542.

INTRODUCTION: Many patients coinfecting with the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are using highly active antiretroviral therapy (HAART) and HCV therapy with peginterferon (PEG-IFN) and ribavirin (RBV) because the use of direct-acting antivirals is not a reality in some countries. To know the impact of such medications in the sustained virological response (SVR) during HCV treatment is of great importance.

METHODOLOGY: This was a retrospective cohort study of 215 coinfecting HIV/HCV patients. The patients were treated with PEG-IFN and RBV between 2007 and 2013 and analyzed by intention to treat. Treatment-experienced patients to HCV and carriers of hepatitis B were excluded. Demographic data (gender, age), mode of infection, HCV genotype, HCV viral load, hepatic fibrosis, HIV status, and type of PEG were evaluated. One hundred eighty-eight

(87.4%) patients were using HAART. **RESULTS:** SVR was achieved in 55 (29.3%) patients using HAART and in 9 (33.3%) patients not using HAART ($p = 0.86$). There was no difference in SVR between different HAART medications and regimens using two reverse transcriptase inhibitor nucleosides (NRTIs) or the use of protease inhibitors and non-NRTIs (27.1% versus 31.5%; $p = 0.61$). The predictive factors for obtaining SVR were low HCV viral load, non-1 genotype, and the use of peginterferon- α 2a. **CONCLUSIONS:** The use of HAART does not influence the SVR of HCV under PEG-IFN and RBV therapy in HIV/HCV coinfecting patients.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[Health Disparities in Hepatitis C Screening and Linkage to Care at an Integrated Health System in Southeast Michigan.](#) Bourgi K1, Brar I2, Baker-Genaw K1. PLoS One. 2016 Aug 15;11(8):e0161241. doi: 10.1371/journal.pone.0161241. eCollection 2016.

With recommended screening for hepatitis C among the 1945-1965 birth cohort and advent of novel highly effective therapies, little is known about health disparities in the Hepatitis C care cascade. Our objective was to evaluate hepatitis C screening rates and linkage to care, among patients who test positive, at our large integrated health system. We used electronic medical records to retrospectively identify patients, in the birth cohort, who were seen in 21 Internal Medicine clinics from July 2014 to June 2015. Patients previously screened for hepatitis C and those with established disease were excluded. We studied patients' sociodemographic and medical conditions along with provider-specific factors associated with likelihood of screening. Patients who tested positive for HCV antibody were reviewed to assess appropriate linkage to care and treatment. Of 40,561 patients who met inclusion criteria, 21.3% (8657) were screened, 1.3% (109) tested positive, and 30% (30/100) completed treatment. Multivariate logistic regression showed that African American race, male gender, electronic health engagement, residency teaching clinic visit, and having more than one clinic visit were associated with higher odds of screening. Patients had a significant decrease in the likelihood of screening with sequential interval increase in their Charlson comorbidity index. When evaluating hepatitis C treatment in patients who screened positive, electronic health engagement was associated with higher odds of treatment whereas Medicaid insurance was associated with significantly lower odds. This study shows that hepatitis C screening rates and linkage to care continue to be suboptimal with a significant impact of multiple sociodemographic and insurance factors. Electronic health engagement emerges as a tool in linking patients to the hepatitis C care cascade.

[Frequency of and Factors Associated with Receipt of Liver-Related Specialty Care Among Patients with Hepatitis C in the Chronic Hepatitis Cohort Study.](#) Foster MA1, Xing J2, Moorman AC2, et al. Dig Dis Sci. 2016 Aug 10. [Epub ahead of print]

BACKGROUND: Linking persons with hepatitis C virus (HCV) to care and treatment is critical to reduction in disease burden; typically, this entailed referral to a specialist. However, data regarding the frequency and factors associated with referral among patients in healthcare organizations (HCOs) are lacking. **METHODS:** Among persons in four US HCOs with newly diagnosed HCV during 2006-2011, we determined the frequency of liver-related specialist care after diagnosis. We also identified sociodemographic and clinical characteristics associated with such care by multivariate analysis, adjusted for all variables. **RESULTS:** Among 3592 patients with newly diagnosed HCV, 57 % (range among sites 45-90 %) received specialist care; of these, 57 % received care within 90 days of diagnosis. Patient characteristics associated with receipt of specialist care included: affiliation with one of the study sites [adjusted odds ratio (aOR) 4.8 vs. the referent site]; having Medicare plus private insurance (aOR 1.6 vs. Medicaid); and having elevated alanine aminotransferase (ALT) (aOR 1.6 vs. normal ALT) or lower platelet values (aOR 1.4 vs. normal platelet level). Specialist care within 90 days of diagnosis was associated with private insurance (aOR 1.5 vs. Medicaid), elevated ALT levels (aOR 1.3-2.3 vs. normal), and having ≥ 2 comorbid conditions (aOR 1.4 vs. no comorbid conditions). Compared to patients not referred, those referred were more likely to be treated (aOR 3.5). **CONCLUSIONS:** Receipt of specialist care among persons with newly diagnosed HCV varied among HCOs. Clinical evidence of liver disease and having private insurance were associated with prompt receipt of specialist care and HCV treatment.

[Cigarette smoking behaviors and beliefs in persons living with hepatitis C.](#) Shuter J1, Litwin AH2, Sulkowski MS3, et al. *Nicotine Tob Res.* 2016 Aug 22. pii: ntw212. [Epub ahead of print]

BACKGROUND AND RATIONALE: Tobacco use is common among persons living with hepatitis C (PLHC), yet little is known about their smoking behaviors and beliefs. Modern hepatitis C treatment offers a unique opportunity to intensively engage this population about other health risks, including smoking. **MAIN RESULTS:** 77 tobacco users (40 hepatitis C virus [HCV] seropositive and 37 HCV seronegative) enrolled in an interview study in a New York City clinic. The mean age was 51.6, 57.1% were male, 40.3% Latino, and 49.4% Black. 67.5% were single and 18.2% were employed. HCV+ smokers differed from HCV- smokers in having a higher prevalence of illicit substance use, depression, and hypertension. PLHC smokers were highly motivated to quit, with 52.5% stating an intention to quit within 30 days. Most of the PLHC smokers had used cessation-directed pharmacotherapy, but almost none had tried a quitline or a quit smoking website. PLHC smokers scored higher on the intrapersonal locus of control subscale. Almost a quarter (22.5%) believed that smoking "helped fight the hepatitis C virus." **CONCLUSIONS:** PLHC smokers have a high burden of psychiatric and substance use comorbidity. They exhibit characteristics that distinguish them from uninfected smokers, and many harbor false beliefs about imagined benefits of smoking. They are highly motivated to quit but underutilize cessation aids. Without aggressive intervention, smoking-related morbidity will likely mute the health benefits and longevity gains associated with hepatitis C treatment. Research such as this may prove useful in guiding the development of future tobacco treatment strategies. **IMPLICATIONS:** This is the first paper to examine, in detail, sociobehavioral correlates of tobacco use in persons infected with hepatitis C (PLHC). PLHC are recognized by the Department of Health and Human Services as a high priority health disparities population. We are not aware of any tobacco treatment services designed specifically for PLHC. The first step in designing an intervention is defining the characteristics of the target group. Our findings

will begin to address this need, and may prove useful in optimizing tobacco treatment strategies for smokers living with hepatitis C.

The Burden of Hepatitis C Infection-Related Liver Fibrosis in the United States. Klevens RM1, Canary L1, Huang X2, Denniston MM1, Yeo AE2, Pesano RL2, Ward JW1, Holmberg S1. Clin Infect Dis. 2016 Aug 9. pii: ciw468. [Epub ahead of print]

BACKGROUND: Knowledge of the estimated proportion of hepatitis C virus (HCV)-infected persons with advanced fibrosis or cirrhosis is critical to estimating healthcare needs.

METHODS: We analyzed HCV-related testing conducted by Quest Diagnostics from January 2010 through December 2013. Tests included hepatitis C antibody, HCV RNA, HCV genotype (nucleic acid tests [NAT]), liver function tests, and platelet counts; patient age was also determined. Aspartate aminotransferase (AST)-to-platelet ratio (APRI) was calculated as $= 100 \times (\text{aspartate aminotransferase [AST]} / \text{upper limit of AST}) / \text{platelet}$. Fibrosis-4 (FIB-4) was calculated as $(\text{age} \times \text{AST}) / (\text{platelet} \times \sqrt{\text{alanine aminotransferase [ALT]}})$. Persons were "currently infected" if they had ≥ 1 positive HCV NAT; "in care" if a positive RNA test was followed < 6 months by ≥ 1 additional NAT(s), or ALT, AST, and platelets < 90 days, or any test ordered by an infectious diseases or gastroenterology specialist; and "evaluated for treatment" if they had a genotype test. **RESULTS:** Approximately 10 million HCV test results were analyzed, representing 5.6 million unique patients. Of the 2.6 million patients with data to estimate liver disease, 5% were currently infected. Among those currently infected, APRI and FIB-4 scores indicated that 23% overall-and 27% among the cohort born during 1945-1965-had advanced fibrosis or cirrhosis at first diagnosis. A total of 54% of infected were in care and 51% of infected with advanced fibrosis or cirrhosis were evaluated for treatment. **CONCLUSIONS:** Testing from a large US commercial laboratory indicates that about 1 in 4 HCV-infected persons have levels of liver disease put them at highest risk for complications and could benefit from immediate antiviral therapy.

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Mixed-Methods Study of Uptake of the Extension for Community Health Outcomes (ECHO) Telemedicine Model for Rural Veterans With HIV.

Moeckli J1,2, Stewart KR1,2, Ono S3, Alexander B1,2, Goss T1, Maier M3,4,5, Tien PC6,7, Howren MB1, Ohl ME1,2,8. J Rural Health. 2016 Aug 24. doi: 10.1111/jrh.12200. [Epub ahead of print]

PURPOSE: Extension for Community Health Outcomes (ECHO) is a provider-level telemedicine model successfully applied to hepatitis C care, but little is known about its application to Human Immunodeficiency Virus (HIV) care. We performed a mixed-methods evaluation of 3 HIV ECHO programs in the Veterans Health Administration, focusing on uptake by primary care clinics and veterans. **METHODS:** Administrative data were used to assess program uptake, including adoption (ie, proportion of primary care clinics participating) and reach (ie, proportion of eligible veterans participating). Veterans were considered eligible if they had an HIV diagnosis and lived nearer to a primary care clinic than to the HIV specialty clinic. We interviewed 31 HIV specialists, primary care providers (PCPs), and administrators engaged in HIV ECHO, and we analyzed interview transcripts to identify factors that influenced program adoption and reach. **FINDINGS:** Nine (43%) of 21 primary care clinics adopted HIV ECHO (range 33%-67% across sites). Program reach was limited, with 47 (6.1%) of 776 eligible

veterans participating. Reach was similar among rural and urban veterans (5.3% vs 6.3%). In interviews, limited adoption and reach were attributed partly to: (1) a sense of "HIV exceptionalism" that complicated shifting ownership of care from HIV specialists to PCPs, and (2) low HIV prevalence and long treatment cycles that prevented rapid learning loops for PCPs. **CONCLUSIONS:** There was limited uptake of HIV ECHO telemedicine programs in settings where veterans historically traveled to distant specialty clinics. Other telemedicine models should be considered for HIV care.

Relationship between vitamin A deficiency and the thyroid axis in clinically stable patients with liver cirrhosis related to hepatitis C virus. El-Eshrawy MM1, Arafa MM2, Elzeheery RR3, Elhelaly RM3, Elrakhawy MM4, El-Baiomy AA3.

Vitamin A deficiency (VAD) and altered thyroid function are commonly encountered in patients with liver cirrhosis. The link between vitamin A metabolism and thyroid function has been previously identified. The aim of this study was to explore the association between VAD and the thyroid axis in clinically stable patients with cirrhosis related to hepatitis C virus (HCV). One hundred and twelve patients with clinically stable HCV-related cirrhosis and 56 healthy controls matched for age, sex, and socioeconomic status were recruited for this study. Vitamin A status, liver function, thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), reverse triiodothyronine (rT3), anti-thyroid peroxidase antibodies (anti-TPO), and thyroid volume were evaluated. The prevalence of VAD among patients with HCV-related cirrhosis was 62.5% compared with 5.4% among controls ($P < 0.001$). Patients with HCV-related cirrhosis had significantly higher FT4, FT3, TSH, and thyroid volume than did healthy controls. Of the 112 patients initially recruited, 18 were excluded (patients with subclinical hypothyroidism and/or anti-TPO positive), so a total of 94 patients with HCV-related cirrhosis were divided into 2 groups according to vitamin A status: VAD and normal vitamin A. Patients with VAD had significantly lower vitamin A intake and serum albumin and higher serum bilirubin, FT4, FT3, and TSH than patients with normal vitamin A status. Multiple logistic regression analysis revealed that VAD was associated with Child-Pugh score ($\beta = 0.11$, $P = 0.05$) and TSH ($\beta = -1.63$, $P = 0.02$) independently of confounding variables. We conclude that VAD may be linked to central hyperthyroidism in patients with clinically stable HCV-related liver cirrhosis.

Prevention of progression to cirrhosis in hepatitis C with fibrosis: effectiveness and cost effectiveness of sequential therapy with new direct-acting anti-virals. Faria R1, Woods B1, Griffin S1, Palmer S1, Sculpher M1, Ryder SD2. *Aliment Pharmacol Ther.* 2016 Aug 25. doi: 10.1111/apt.13775. [Epub ahead of print]

BACKGROUND: The new direct-acting anti-virals (DAAs) for hepatitis C virus (HCV) infection offer higher cure rates, but at a much higher cost than the standard interferon-based treatments. **AIM:** To identify the cost-effective treatment for patients with HCV infection with F3 liver fibrosis who are at high risk of progression to cirrhosis. **METHODS:** A decision-analytic Markov model compared the health benefits and costs of all currently licensed treatments as single treatments and in sequential therapy of up to three lines. Costs were expressed in pound sterling from the perspective of the UK National Health Service. Health benefits were expressed in quality-adjusted life years. **RESULTS:** Treatment before progression to cirrhosis always offers the most health benefits for the least costs. Sequential therapy with multiple treatment lines cures over 89% of patients across all HCV genotypes while ensuring a cost-effective use of resources. Cost-effective regimes for HCV genotype 1 patients include first-

line oral therapy with sofosbuvir-ledipasvir while peginterferon continues to have a role in other genotypes. **CONCLUSIONS:** The cost-effective treatment for HCV can be established using decision analytic modelling comparing single and sequential therapies. Sequential therapy with DAAs is effective and cost-effective in HCV patients with F3 fibrosis. This information is of significant benefit to health care providers with budget limitations and provides a sound scientific basis for drug treatment choices.

Patient satisfaction with the clinical pharmacist and prescribers during hepatitis C virus management. Martin MT^{1,2}, Faber DM³. J Clin Pharm Ther. 2016 Aug 31. doi:

10.1111/jcpt.12436. [Epub ahead of print]

WHAT IS KNOWN AND OBJECTIVES: Clinical pharmacists play an important role in the management of patients undergoing hepatitis C virus (HCV) treatment. No satisfaction surveys have been published on clinical pharmacist interventions in HCV management. The objective was to evaluate patient satisfaction with clinical pharmacist and prescriber services in the HCV patient population at an urban academic hepatology clinic. **METHODS:** An anonymous patient satisfaction survey was offered to patients who were initiating or receiving HCV treatment under the care of a clinical pharmacist. Survey items assessed demographics and satisfaction with HCV care. Satisfaction was assessed with 17 or 20 Likert-scale questions (1 = poor, 2 = fair, 3 = okay, 4 = good, 5 = great) and two or three open-ended questions. Survey results were analysed via comparative and descriptive statistics. A qualitative content analysis was used for the open-ended survey questions. **RESULTS AND DISCUSSION:** Sixty-four patients completed 77 (24 pharmacist and 53 prescriber) patient satisfaction surveys. The mean age was 53 (± 9.72) years. Patients reported high levels of satisfaction with the pharmacist and prescribers. All 24 (100%) patients ranked overall satisfaction with services provided by pharmacists as 'great', and 36 (69%) of 52 patients ranked overall satisfaction with services provided by prescribers as 'great'. Patients supported the inclusion of a clinical pharmacist on health care teams for other disease states. **WHAT IS NEW AND CONCLUSION:** Patients reported high levels of satisfaction with the clinical pharmacist involved in HCV treatment management at an urban academic medical centre. Clinical pharmacist services were highly valued and recommended by the patients surveyed. The survey was able to identify areas in need of improvement in the clinic. Clinical pharmacists play an important role in the treatment and management of HCV. This survey may serve as a model for assessment of satisfaction in other pharmacist-run clinic settings.

Sharing of Snorting Straws and Hepatitis C Virus Infection in Pregnant Women. Fernandez N1, Towers CV, Wolfe L, Hennessy MD, Weitz B, Porter S. Obstet Gynecol. 2016 Aug;128(2):234-7. doi: 10.1097/AOG.0000000000001507.

OBJECTIVE: To evaluate possible modes of hepatitis C virus (HCV) acquisition in pregnant women found to be HCV-infected in the prenatal period and to assess transmission risk factors. **METHODS:** This was a prospective cohort study conducted from March 2014 through June 2015 involving the distribution of an anonymous survey to HCV-infected pregnant women that assessed for numerous modes of potential HCV transmission involving, intravenous drug use, blood transfusion, organ transplant, sexual contact, tattoos, and snorting drugs with a straw. Participants were drawn from our institutional obstetric high-risk clinic. Statistical analysis involved simple percentages and χ comparisons where appropriate; $P < .05$ was considered

significant. To test biologic plausibility, snorting utensils confiscated by law enforcement authorities from patients not in this study were tested for the presence of human blood.

RESULTS: A total of 189 HCV-infected pregnant patients completed the survey, and no approached patients declined. Of these, 136 (72%, 95% confidence interval [CI] 65-78%) admitted to intravenous drug use, of whom 89 (65%, 95% CI 57-73%) reported sharing needles. Of the 178 (94%, 95% CI 90-97%) who admitted snorting drugs, 164 (92%, 95% CI 87-96%) reported sharing straws. The difference between the proportion reporting sharing of snorting utensils compared with the proportion sharing intravenous drug use utensils was significant ($P < .001$). Twenty-nine patients (15%, 95% CI 11-21%) reported snorting drugs and sharing straws but denied any other risk factor except sexual contact. Of the 54 straws confiscated by law enforcement authorities, 13 (24%, 95% CI 13-38%) tested positive for the presence of human blood. **CONCLUSION:** Sharing snorting utensils (straws) in noninjection drug use may be an additional risk factor for HCV and other virus transmission.

[Management of Neurologic Manifestations in Patients with Liver Disease.](#) Ferro JM1,2, Viana P3, Santos P4. *Curr Treat Options Neurol.* 2016 Aug;18(8):37. doi: 10.1007/s11940-016-0419-0.

OPINION STATEMENT: Liver disease, both in its acute and chronic forms, can be associated with a wide spectrum of neurologic manifestations, both central and peripheral, ranging in severity from subclinical changes to neurocritical conditions. Neurologists are frequently consulted to participate in their management. In this review, we present an overview of management strategies for patients with hepatic disease whose clinical course is complicated by neurologic manifestations. Type A hepatic encephalopathy (HE), which occurs in acute liver failure, is a neurologic emergency, and multiple measures should be taken to prevent and treat cerebral edema. In Type C HE, which occurs in chronic liver disease, management should be aimed at correcting precipitant factors and hyperammonemia. There is an increasing spectrum of drug treatments available to minimize ammonia toxicity. Acquired hepatocerebral degeneration is a rare complication of the chronic form of HE, with typical clinical and brain MRI findings, whose most effective treatment is liver transplantation. Epilepsy is frequent and of multifactorial cause in patients with hepatic disease, and careful considerations should be made regarding choice of the appropriate anti-epileptic drugs. Several mechanisms increase the risk of stroke in hepatic disease, but many of the drugs used to treat and prevent stroke are contraindicated in severe hepatic failure. Hepatitis C infection increases the risk of ischemic stroke. Hemorrhagic stroke is more frequent in patients with liver disease of alcoholic etiology. Viral hepatitis is associated with a wide range of immune-mediated complications, mostly in the peripheral nervous system, which respond to different types of immunomodulatory treatment. Several drugs used to treat hepatic disease, such as the classical and the new direct-acting antivirals, may have neurologic complications which in some cases preclude its continued use.

[Assessing the Effect of Potential Reductions in Non-Hepatic Mortality on the Estimated Cost-Effectiveness of Hepatitis C Treatment in Early Stages of Liver Disease.](#) Leidner AJ1, Chesson HW2, Spradling PR3, Holmberg SD3. *Appl Health Econ Health Policy.* 2016 Aug 1. [Epub ahead of print]

BACKGROUND: Most cost-effectiveness analyses of hepatitis C (HCV) therapy focus on the benefits of reducing liver-related morbidity and mortality. **OBJECTIVES:** Our objective was to assess how cost-effectiveness estimates of HCV therapy can vary depending on assumptions

regarding the potential impact of HCV therapy on non-hepatic mortality. **METHODS:** We adapted a state-transition model to include potential effects of HCV therapy on non-hepatic mortality. We assumed successful treatment could reduce non-hepatic mortality by as little as 0 % to as much as 100 %. Incremental cost-effectiveness ratios were computed comparing immediate treatment versus delayed treatment and comparing immediate treatment versus non-treatment. **RESULTS:** Comparing immediate treatment versus delayed treatment, when we included a 44 % reduction in non-hepatic mortality following successful HCV treatment, the incremental cost per quality-adjusted life year (QALY) gained by HCV treatment fell by 76 % (from US\$314,100 to US\$76,900) for patients with no fibrosis and by 43 % (from US\$62,500 to US\$35,800) for patients with moderate fibrosis. Comparing immediate treatment versus non-treatment, assuming a 44 % reduction in non-hepatic mortality following successful HCV treatment, the incremental cost per QALY gained by HCV treatment fell by 64 % (from US\$186,700 to US\$67,300) for patients with no fibrosis and by 27 % (from US\$35,000 to US\$25,500) for patients with moderate fibrosis. **CONCLUSION:** Including reductions in non-hepatic mortality from HCV treatment can have substantial effects on the estimated cost-effectiveness of treatment.

Development of a specialty medication prior-authorization service at an urban academic medical center. Martin MT1, Telebak E2, Taylor PA2, Volozhina O2. Am J Health Syst Pharm. 2016 Aug 1;73(15):1174-9. doi: 10.2146/ajhp160059.

PURPOSE: The project in which a clinical pharmacist enlisted the help of pharmacy students to create a team responsible for prior-authorization (PA) paperwork associated with hepatitis C virus (HCV) infection treatment is described. **SUMMARY:** Many insurance companies require completion of a time-consuming PA process for approval of high-cost specialty medications, such as those used in the treatment of HCV infection. A clinical pharmacist at an urban academic medical center recruited pharmacy students to assist with and streamline the HCV medication PA process. After training, the students developed a protocol to increase the efficiency of completing PA requests, appealing denials, obtaining PA extensions, and documenting progress in the electronic medical record to ensure continuity of care. The PA team collaborated with clinicians to document proof of medical need and worked with insurers, pharmacies, and patients to achieve timely approval and receipt of medications. From June 2014 to March 2015, three students spent 240 hours developing the PA protocol and completing 88 PA requests, with an overall medication approval rate of 87.7%; 18 patients were also referred to medication assistance programs. The PA team's work allowed the clinical pharmacist to spend more time on clinical activities and scholarship, while the students increased their knowledge of HCV disease and HCV-targeted therapies and improved their skills in written and verbal communication with patients, providers, and insurance companies. **CONCLUSION:** Pharmacy students successfully implemented a PA team to manage prescription approval for HCV medications with assistance from a clinical pharmacist.

Association of Hepatitis C Virus With Alcohol Use Among U.S. Adults: NHANES 2003-2010. Taylor AL1, Denniston MM2, Klevens RM2, McKnight-Eily LR3, Jiles RB2. Am J Prev Med. 2016 Aug;51(2):206-15. doi: 10.1016/j.amepre.2016.02.033. Epub 2016 May 10.

INTRODUCTION: Excessive alcohol use exacerbates morbidity and mortality among hepatitis C virus (HCV)-infected people. The purpose of this study was to describe self-reported patterns of alcohol use and examine the association with HCV infection and other sociodemographic and

health-related factors. **METHODS:** Data from 20,042 participants in the 2003–2010 National Health and Nutrition Examination Survey were analyzed in 2014. Estimates were derived for self-reported demographic characteristics, HCV-RNA (indicative of current HCV infection) status, and alcohol use at four levels: lifetime abstainers, former drinkers, non-excessive current drinkers, and excessive current drinkers. **RESULTS:** Former drinkers and excessive current drinkers had a higher prevalence of HCV infection (2.2% and 1.5%, respectively) than never or non-excessive current drinkers (0.4% and 0.9%, respectively). HCV-infected adults were estimated to ever drink five or more drinks/day almost every day at some time during their lifetime about 3.3 times more often (43.8% vs 13.7%, $p < 0.001$) than those who were never infected with HCV. Controlling for age, sex, race/ethnicity, education, and having a usual source of health care, HCV infection was significantly associated with excessive current drinking (adjusted prevalence ratio, 1.3; 95% CI=1.1, 1.6) and former drinking (adjusted prevalence ratio, 1.3; 95% CI=1.1, 1.6). **CONCLUSIONS:** Chronic HCV infection is associated with both former and excessive current drinking. Public health HCV strategies should implement interventions with emphasis on alcohol abuse, which negatively impacts disease progression for HCV-infected individuals.

Fibrosis Progression in Patients with Chronic Hepatitis C Virus Infection. Zeremski M1, Dimova RB2, Pillardy J3, de Jong YP1, Jacobson IM4, Talal AH5. *J Infect Dis.* 2016 Aug 2. pii: jiw332. [Epub ahead of print]

BACKGROUND: Fibrosis progression varies markedly in hepatitis C virus (HCV)-infected individuals. We investigated factors that influence fibrosis progression in chronic HCV infection. **METHODS:** HCV-infected patients with at least two liver biopsies were included in this study. Associations between fibrosis progression and epidemiologic, virologic and disease-associated factors were analyzed using logistic regression and multistate Markov modeling. **RESULTS:** We analyzed 936 biopsies obtained from 378 individuals. Mean age at first biopsy was 48.3 ± 9.3 years, 59.3% of patients were male, 59.9% Caucasian, and 86.7% HCV genotype 1-infected. Fibrosis progression and cirrhosis occurred in 57.4% and 5.8%, respectively. Fibrosis progression between the first and last biopsies was associated with lower fibrosis on the first biopsy ($p < 0.001$) and with the occurrence of at least one ALT flare (> 200 U/L, $p = 0.007$). We found the highest fibrosis progression rate between stages 0 and 1 and the lowest between stages 2 and 3. Increased necroinflammation and higher ALT were associated with faster progression. HCV genotype 3-infected patients were more likely to progress to cirrhosis ($p < 0.001$). **CONCLUSIONS:** Fibrosis progression in HCV is not linear but varies according to stage with the highest progression in patients with the lowest fibrosis. Patients who experience ALT flares are also more likely to progress.

Practices of partnership: Negotiated safety among couples who inject drugs. Rance J1, Rhodes T2, Fraser S3, Bryant J4, Treloar C5. *Health (London).* 2016 Aug 3. pii: 1363459316660859. [Epub ahead of print]

Despite the majority of needle-syringe sharing occurring between sexual partners, the intimate partnerships of people who inject drugs have been largely overlooked as key sites of both hepatitis C virus prevention and transmission, and risk management more generally. Drawing on interviews with 34 couples living in inner-city Australia, this article focuses on participants' accounts of 'sharing'. While health promotion discourses and conventional epidemiology have tended to interpret the practice of sharing (like the absence of condom use) in terms of

'noncompliance', we are interested in participants' socially and relationally situated 'rationalities'. Focussing on participants' lived experiences of partnership, we endeavour to make sense of risk and safety as the participants themselves do. How did these couples engage with biomedical knowledge around hepatitis C virus and incorporate it into their everyday lives and practices? Revisiting and refashioning the concept of 'negotiated safety' from its origins in gay men's HIV prevention practice, we explore participants' risk and safety practices in relation to multiple and alternative framings, including those which resist or challenge mainstream epidemiological or health promotion positions. Participant accounts revealed the extent to which negotiating safety was a complex and at times contradictory process, involving the balancing or prioritising of multifarious, often competing, risks. We argue that our positioning of participants' partnerships as the primary unit of analysis represents a novel and instructive way of thinking about not only hepatitis C virus transmission and prevention, but the complexities and contradictions of risk production and its negotiation more broadly.

Implementation of Birth-Cohort Testing for Hepatitis C Virus: Lessons Learned From Three Primary Care Sites. Kruger DL1, Rein DB2, Kil N3, Jordan C4, Brown KA5, Yartel A6, Smith BD6. *Health Promot Pract.* 2016 Aug 5. pii: 1524839916661495. [Epub ahead of print] Hepatitis C virus infection affects approximately 2.2 to 3.2 million Americans. In 2012, the Centers for Disease Control and Prevention recommended a one-time antibody test of all persons belonging to the 1945-1965 birth cohort. Efforts to implement this recommendation in clinical settings are in their infancy; this case study report therefore seeks to share the experiences of three sites that implemented interventions to increase birth-cohort testing through participation in the Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C. At each site, project managers completed standardized questionnaires about their implementation experiences, and a qualitative analysis was conducted of the responses. The testing interventions used in-person recruitment, mail recruitment, and an electronic health record prompt. Sites reported that early efforts to obtain stakeholder buy-in were critical to effectively implement and sustain interventions and that the intervention required additional staffing resources beyond those being used for risk-based testing. In each case, administrative barriers were more extensive than anticipated. For the electronic health record-based intervention, technological support was critical in achieving study goals. Despite these barriers, interventions in all sites were successful in increasing rates of testing and case identification, although future studies will need to evaluate the relative costs and benefits of each intervention.

Early Treatment in HCV: Is it a Cost-Utility Option from the Italian Perspective?

Marcellusi A1,2, Viti R3, Damele F4, Cammà C5, Taliani G6, Mennini FS3,7. *Clin Drug Investig.* 2016 Aug;36(8):661-72. doi: 10.1007/s40261-016-0414-y.

BACKGROUND AND OBJECTIVE: In Italy, the Italian Pharmaceutical Agency (AIFA) criteria used F3-F4 fibrosis stages as the threshold to prioritise the treatment with interferon (IFN)-free regimens, while in genotype 1 chronic hepatitis C (G1 CHC) patients with fibrosis of liver stage 2, an approach with pegylated interferon (PEG-IFN)-based triple therapy with simeprevir was suggested. The key clinical question is whether, in an era of financial constraints, the application of a universal IFN-free strategy in naïve G1 CHC patients is feasible within a short time horizon. The aim of this study is to perform an economic analysis to estimate the cost-utility of the early innovative therapy in Italy for managing hepatitis C virus (HCV)-infected patients. **METHODS:** The incremental cost-utility analysis was carried out to quantify the

benefits of the early treatment approach in HCV subjects. A Markov simulation model including direct and indirect costs and health outcomes was developed from an Italian National Healthcare Service and societal perspective. A total of 5000 Monte Carlo simulations were performed on two distinct scenarios: standard of care (SoC) which includes 14,000 genotype 1 patients in Italy treated with innovative interferon-free regimens in the fibrosis of liver stages 3 and 4 (F3-F4) versus early-treatment scenario (ETS) where 2000 patients were additionally treated with simeprevir plus PEG-IFN and ribavirin in the fibrosis stage 2 (F2) (based on Italian Medicines Agency AIFA reimbursement criteria). A systematic literature review was carried out to identify epidemiological and economic data, which were subsequently used to inform the model. Furthermore, a one-way probabilistic sensitivity was performed to measure the relationship between the main parameters of the model and the cost-utility results. **RESULTS:** The model shows that, in terms of incremental cost-effectiveness ratio (ICER) per quality adjusted life year (QALY) gained, ETS appeared to be the most cost-utility option compared with both perspective societal (ICER = EUR11,396) and NHS (ICER = EUR14,733) over a time period of 10 years. The cost-utility of ETS is more sustainable as it extends the time period analysis [ICER = EUR 6778 per QALY to 20 years and EUR4474 per QALY to 30 years]. From the societal perspective, the ETS represents the dominant option at a time horizon of 30 years. If we consider the sub-group population of treated patients [16,000 patients of which 2000 not treated in the SoC, the ETS scenario was dominant after only 5 years and the cost-utility at 2 years of simulation. The one-way sensitivity analysis on the main variables confirmed the robustness of the model for the early-treatment approach. **CONCLUSION:** Our model represents a tool for policy makers and health-care professionals, and provided information on the cost-utility of the early-treatment approach in HCV-infected patients in Italy. Starting innovative treatment regimens earlier keeps HCV-infected patients in better health and reduces the incidence of HCV-related events; generating a gain both in terms of health of the patients and correct resource allocation.

HEPATOCELLULAR (LIVER) CANCER

[Aspartate aminotransferase to platelet ratio index and sustained virologic response are associated with progression from hepatitis C associated liver cirrhosis to hepatocellular carcinoma after treatment with pegylated interferon plus ribavirin.](#) Ng KJ1, Tseng CW2, Chang TT3, et al. Clin Interv Aging. 2016 Aug 1;11:1035-41. doi: 10.2147/CIA.S108589. eCollection 2016.

BACKGROUND: The aim of this study was to evaluate the clinically significant predictors of hepatocellular carcinoma (HCC) development among hepatitis C virus (HCV) cirrhotic patients receiving combination therapy. **PATIENTS AND METHODS:** One hundred and five compensated cirrhosis patients who received pegylated interferon plus ribavirin between January 2005 and December 2011 were enrolled. All the patients were examined with abdominal sonography and liver biochemistry at baseline, end of treatment, and every 3-6 months posttreatment. The occurrence of HCC was evaluated every 3-6 months posttreatment. **RESULTS:** A total of 105 patients were enrolled (mean age 58.3±10.4 years). The average follow-up time for each patient was 4.38 years (standard deviation 1.73 years; range 1.13-9.27 years). Fifteen (14.3%) patients developed HCC during follow-up period. Thirteen of them had high baseline aspartate aminotransferase to platelet ratio index (APRI) (ie, an APRI >2.0). Multivariate analysis showed that those without sustained virologic response (SVR) (hazard ratio

[HR] 5.795; 95% confidence interval [CI] 1.370-24.5; P=0.017) and high APRI (HR 5.548; 95% CI 1.191-25.86; P=0.029) had a significantly higher risk of HCC occurrence. The cumulative incidence of HCC was significantly higher (P=0.009) in patients without SVR (3-year cumulative incidence 21.4%; 95% CI 7.4%-35.5%; 5-year cumulative incidence 31.1%; 95% CI 11.2%-51.1%) compared to those with SVR (3- and 5-year cumulative incidence 6.2%; 95% CI 0%-1.3%). Further, the cumulative incidence of HCC was significantly higher (P=0.006) in patients with high APRI (3-year cumulative incidence 21.8%; 95% CI 8.2%-35.3%; 5-year cumulative incidence 30.5%, 95% CI 11.8%-49.3%) compared to those with low APRI (3- and 5-year cumulative incidence 4.2%, 95% CI 0%-1.0%). **CONCLUSION:** In HCV-infected cirrhotic patients who received combination therapy, APRI and SVR are the two major predictors of HCC development.

[Multifucosylated Alpha-1-acid Glycoprotein as a Novel Marker for Hepatocellular Carcinoma.](#)

Tanabe K1, Kitagawa K2, Kojima N2, Iijima S3. J Proteome Res. 2016 Sep 2;15(9):2935-44. doi: 10.1021/acs.jproteome.5b01145. Epub 2016 Aug 9.

High-sensitivity and -specificity diagnostic techniques to detect early-stage hepatocellular carcinoma (HCC) are in high demand. Screening with serum HCC markers, such as alpha-fetoprotein, is not practical because they possess poor sensitivity and specificity. As such, we focused on glycan alterations of glycoproteins found in patient sera in an attempt to discover novel HCC markers that are more specific and sensitive than current HCC markers. Sera from 42 HCC patients and 80 controls, composed of 27 chronic hepatitis B patients, 26 chronic hepatitis C patients, and 27 healthy volunteers, were analyzed in this study. Glycopeptides obtained from serum proteins by trypsin digestion were enriched by ultrafiltration and Aleuria aurantia lectin-based affinity chromatography, followed by analysis using liquid chromatography time-of-flight mass spectrometry. The data were analyzed by our newly developed software, which calculates peak intensities and positions (m/z and elution time), aligns all sample peaks, and integrates all data into a single table. HCC markers were extracted from more than 30 000 detected glycopeptide peaks by t test, mean-fold change, and ROC analyses. As a result, we revealed that alpha-1-acid glycoprotein with multifucosylated tetraantennary N-glycans was significantly elevated in HCC patients, whereas the single fucosylated derivative was not.

[Lower expressed miR-198 and its potential targets in hepatocellular carcinoma: a clinicopathological and in silico study.](#)

Huang WT1, Wang HL1, Yang H2, et al. Onco Targets Ther. 2016 Aug 22;9:5163-80. doi: 10.2147/OTT.S108828. eCollection 2016.

PURPOSE: To investigate the clinicopathological value and potential roles of microRNA-198 (miR-198) in hepatocellular carcinoma (HCC). **METHODS:** Ninety-five formalin-fixed paraffin-embedded HCC and the para-cancerous liver tissues were gathered. Real-time reverse transcription quantitative polymerase chain reaction was applied to determine the miR-198 expression. The association between the miR-198 expression and clinicopathological features was examined. Meanwhile, potential target messenger RNAs of miR-198 in HCC were obtained from 14 miRNA prediction databases and natural language processing method, in which we pooled the genes related to the tumorigenesis and progression of HCC and classified them by their frequency. The selected target genes were finally analyzed in the Gene Ontology analysis and Kyoto Encyclopedia of Genes and Genomes pathway. **RESULTS:** miR-198 expression was significantly lower in HCC than that in adjacent noncancerous liver tissues (1.30 ± 0.72 vs 2.01 ± 0.58 , $P < 0.001$). Low miR-198 expression was also correlated to hepatitis C virus infection

($r=-0.48$, $P<0.001$), tumor capsular infiltration ($r=-0.43$, $P<0.001$), metastasis ($r=-0.26$, $P<0.010$), number of tumor nodes ($r=-0.25$, $P=0.013$), vaso-invasion ($r=-0.24$, $P=0.017$), and clinical tumor node metastasis stage ($r=-0.23$, $P=0.024$). Altogether, 1,048 genes were achieved by the concurrent prediction from at least four databases and natural language processing indicated 1,800 genes for HCC. Further, 127 overlapping targets were further proceeded with for pathway analysis. The most enriched Gene Ontology terms in the potential target messenger RNAs of miR-198 were cell motion, cell migration, cell motility, and regulation of cell proliferation in biological process; organelle lumen, membrane-enclosed lumen, and nuclear lumen in cellular component; and enzyme binding, protein domain-specific binding, and protein kinase activity in molecular function. Kyoto Encyclopedia of Genes and Genomes analysis showed that these target genes were obviously involved in focal adhesion and pathways in cancer.

CONCLUSION: Lower expression of miR-198 was related to several clinicopathological parameters in HCC patients. miR-198 might play a regulatory role through its target genes in the development of HCC.

[Global profiling of alternative RNA splicing events provides insights into molecular differences between various types of hepatocellular carcinoma.](#) Tremblay MP1, Armero VE1, Allaire A1, et al. BMC Genomics. 2016 Aug 26;17:683. doi: 10.1186/s12864-016-3029-z.

BACKGROUND: Dysregulations in alternative splicing (AS) patterns have been associated with many human diseases including cancer. In the present study, alterations to the global RNA splicing landscape of cellular genes were investigated in a large-scale screen from 377 liver tissue samples using high-throughput RNA sequencing data. **RESULTS:** Our study identifies modifications in the AS patterns of transcripts encoded by more than 2500 genes such as tumor suppressor genes, transcription factors, and kinases. These findings provide insights into the molecular differences between various types of hepatocellular carcinoma (HCC). Our analysis allowed the identification of 761 unique transcripts for which AS is misregulated in HBV-associated HCC, while 68 are unique to HCV-associated HCC, 54 to HBV&HCV-associated HCC, and 299 to virus-free HCC. Moreover, we demonstrate that the expression pattern of the RNA splicing factor hnRNPC in HCC tissues significantly correlates with patient survival. We also show that the expression of the HBx protein from HBV leads to modifications in the AS profiles of cellular genes. Finally, using RNA interference and a reverse transcription-PCR screening platform, we examined the implications of cellular proteins involved in the splicing of transcripts involved in apoptosis and demonstrate the potential contribution of these proteins in AS control. **CONCLUSIONS:** This study provides the first comprehensive portrait of global changes in the RNA splicing signatures that occur in hepatocellular carcinoma. Moreover, these data allowed us to identify unique signatures of genes for which AS is misregulated in the different types of HCC.

[Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection.](#) Kobayashi M1, Suzuki F1, Fujiyama S1, et al. J Med Virol. 2016 Aug 17. doi: 10.1002/jmv.24663. [Epub ahead of print] The aim of this study was to assess the rate of development of hepatocellular carcinoma (HCC) in patients who achieved sustained virologic response (SVR) by direct antiviral agents (DAA). We retrospectively evaluated patients who achieved SVR by oral DAA interferon-free regimens ($n = 77$) (daclatasvir/asunaprevir [$n = 67$], ombitasvir/paritaprevir/ritonavir [$n = 9$], and telaprevir [$n = 1$]) and by pegylated-interferon plus ribavirin (Peg-IFN/RBV, $n = 528$). In all patients, the

background was chronic hepatitis or cirrhosis caused by HCV genotype 1b. During a median follow-up period of 4.0 years, two (2.6%) of DAA-treated patients developed HCC. The 3- and 5-year cumulative HCC development rates were 1.30% and 3.03%, respectively, in the DAA group, and 1.02% and 2.19% in the Peg-IFN/RBV group (P not significant). In patients with Fib-4 score of >3.25, the 3-year HCC development rates were 4.35% and 3.95%, whereas those of the 5 year were 9.66% and 8.37%, in the DAA and Peg-IFN/RBV group, respectively. In patients with Fib-4 score of ≤3.25, none of the DAA group developed HCC, whereas 0.48% at 3-year and 1.05% at 5-year of patients of the Peg-IFN/RBV group did. Propensity score analysis using the inverse probability of treatment weights (IPTW) also showed no significant difference in HCC development rate between the two groups. Serum AFP gradually and similarly decreased after initiation of antiviral therapy in both groups. Our data indicate that the HCC risk rate after SVR is similar regardless of whether the latter was achieved by DAA or IFN-based regimens.

Natural History of Untreated Hepatocellular Carcinoma in a US Cohort and the Role of Cancer Surveillance. Khalaf N, Ying J, Mittal S, Temple S, Kanwal F, Davila J, El-Serag HB. Clin Gastroenterol Hepatol. 2016 Aug 10. pii: S1542-3565(16)30517-1. doi: 10.1016/j.cgh.2016.07.033. [Epub ahead of print]

BACKGROUND & AIMS: Determining the natural history and predictors of survival in patients with untreated hepatocellular carcinoma (HCC) in the United States is useful to test existing tumor classifications, identify subgroups of patients likely to benefit from treatment, and estimate lead time related to HCC surveillance. **METHODS:** We identified a national cohort of 518 veterans diagnosed with HCC from 2004 through 2011, with follow up ending in 2014, who received no palliative or curative treatment. We examined the association between post-diagnosis survival and patient factors, tumor characteristics, and pre-diagnosis surveillance. **RESULTS:** The mean age at HCC diagnosis was 65.7 years and most patients had hepatitis C (60.6%). Almost all patients (99%) died within the observation period; the median overall survival time was 3.6 months and survival times were 13.4, 9.5, 3.4 and 1.6 months for patients of Barcelona Clinic Liver Cancer (BCLC) stages 0/A, B, C and D, respectively. In addition, model for end-stage liver disease and levels of alpha-fetoprotein were predictive of survival. Nearly 28% received pre-diagnosis HCC surveillance, which was associated with detection of disease at an earlier stage (BCLC 0/A/B, 26.4% vs 14.4%; P=.0006) and slightly longer survival than patients with no surveillance overall (5.2 vs 3.4 months, P=.021); there was no difference in survival times of patients with 0/A stage who did vs did not receive surveillance (10.3 vs 10.5 months). **CONCLUSIONS:** Patients with HCCs, including those detected through surveillance, survived for short time periods in the absence of treatment, irrespective of their initial stage at diagnosis. Model for end-stage liver disease scores and levels of alpha-fetoprotein were prognostic factors, independent of BCLC stage. The lead time related to detection by surveillance was modest (<2 months) and therefore unlikely to explain the survival benefit associated with surveillance in previous studies.