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Hepatitis C Newsletter  
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**CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

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**[Short-Duration AL-335, Odalasvir, With or Without Simeprevir, in Patients With HCV GT1 or 3 Infection Without Cirrhosis.](#)**

Gane EJ1, Stedman CA2, Schwabe C1, et al. Hepatology. 2018 Dec;68(6):2145-2157. doi: 10.1002/hep.30126. Epub 2018 Nov 19. This open-label, phase IIa study assessed the safety, pharmacokinetics, and efficacy of direct-acting antiviral agent (DAA) regimens in patients with chronic hepatitis C virus (HCV) infection. Multiple 6-12-week oral regimens of 400-800 mg once daily (QD) AL-335 + 50 mg QD/every other day odalasvir ± 75-150 mg QD simeprevir were evaluated in treatment-naïve, HCV genotype (GT)1/3-infected patients without cirrhosis. Safety/pharmacokinetic parameters, HCV-RNA, and sequencing data were assessed. Treatment regimens for later study cohorts were adjusted based on emerging data. In total, 112 patients were enrolled. Three serious treatment-emergent adverse events occurred, one of which (a Mobitz type 1 second-degree atrioventricular block [Wenckebach]) was possibly related to high odalasvir exposure and resulted in premature discontinuation of study drugs. No other clinically significant safety findings were identified. GT1-infected patients receiving 3-DAA for 6-8 weeks achieved 100% sustained virologic response 12 weeks and 24 weeks after the end of treatment (sustained virologic response [SVR12/24]). GT1-infected patients receiving 2-DAA or GT3-infected patients receiving 3-DAA had SVR12/24 less than 90%, whether treated for 8 weeks or 12 weeks. Virologic failure was associated with the emergence of generally persistent NS5A and/or transient NS5B resistance-associated substitutions in most patients. Pharmacokinetic characteristics of the three drugs were also elucidated. Conclusions: In treatment-naïve subjects without cirrhosis, AL-335 + odalasvir + simeprevir for 6-8 weeks was generally safe and highly efficacious against HCV GT1. However, inadequate efficacy was observed for the 2-DAA regimen in GT1-infected subjects and the 3-DAA regimen in GT3-infected subjects.

**[Sustained virological response does not improve long-term glycemic control in patients with type 2 diabetes and chronic hepatitis C.](#)**

Li J1, Gordon SC2, Rupp LB3, et al. Liver Int. 2018 Dec 20. doi: 10.1111/liv.14031. [Epub ahead of print]

**BACKGROUND:** Sustained virological response (SVR) to treatment for chronic hepatitis C (HCV) may improve short-term glucose control among patients with type 2 diabetes (T2D), but the long-term impact remains largely unknown. We used data from the Chronic Hepatitis Cohort Study to investigate the impact of SVR on long-term trends in HbA1c in patients with T2D.

**METHODS:** "Index date" was defined as the date of treatment initiation (treated patients) or HCV diagnosis (untreated patients). To address treatment selection bias, we used a propensity score approach. We used a piecewise, linear-spline, mixed-effects model to evaluate changes in HbA1c over a five-year period. **RESULTS:** Our sample included 384 HCV patients with T2D (192 untreated, 192 treated, with SVR or treatment failure [TF]). After adjusting for BMI, HbA1c was stable among untreated and TF patients. In SVR patients, HbA1c trajectories evolved in three phases: 1) index through 6 months post-index, average HbA1c decreased significantly from 7.7-5.4% per 90 days ( $p < 0.001$ ); 2) 6-30 months post-index, HbA1c rebounded at a rate of 1.5% every 90 days ( $p = 0.003$ ); and 3) from 30 months onward, HbA1c stabilized at an average level of 7.9 ( $p$ -value = 0.34). Results from an analysis restricted to patients receiving direct-acting antivirals were consistent with the main findings. **CONCLUSION:** Successful HCV treatment among patients with T2D significantly reduces HbA1c shortly after treatment, but these decreases are not sustained long-term. Less than three years after SVR, HbA1c rebounds to levels similar to untreated/TF patients, and higher than recommended for type 2 diabetic maintenance. This article is protected by copyright. All rights reserved.

**[Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection \(ENDURANCE-5,6\): an open-label, multicentre, phase 3b trial.](#)**

Asselah T1, Lee SS2, Yao BB3, et al. Lancet Gastroenterol Hepatol. 2019 Jan;4(1):45-51. doi: 10.1016/S2468-1253(18)30341-8. Epub 2018 Nov 2.

**BACKGROUND:** The pangenotypic direct-acting antiviral regimen of glecaprevir coformulated with pibrentasvir is approved to treat chronic hepatitis C virus (HCV) genotype 1-6 infection in adults. In registrational studies, 84 (99%) of 85 patients with HCV genotype 5 or 6 infection achieved a sustained virological response (SVR) with glecaprevir/pibrentasvir, with no virological failures. To increase the body of data for these less prevalent genotypes, ENDURANCE-5,6 evaluated the efficacy and safety of glecaprevir/pibrentasvir exclusively in patients infected with HCV genotype 5 or 6. **METHODS:** ENDURANCE-5,6 was a phase 3b, single-arm, open-label, multicentre trial done in 24 hospitals or clinics in Europe, Oceania, North America, South Africa, and southeast Asia. Adults with chronic HCV genotype 5 or 6 infection who were previously untreated or treatment-experienced were eligible to be enrolled. Glecaprevir/pibrentasvir (300 mg/120 mg) was given orally once daily for 8 weeks (for patients without cirrhosis) or 12 weeks (for patients with compensated cirrhosis). The primary efficacy endpoint was SVR12 (ie, HCV RNA  $< 15$  IU/mL at 12 weeks post-treatment), assessed within each HCV genotype, and analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02966795. **FINDINGS:** Between Feb 9, 2017, and Aug 28, 2018, 84 patients were enrolled: 23 with genotype 5 infection and 61 with genotype 6 infection. Overall, 82 (97.6%, 95% CI 94.4-100.0) of the 84 patients achieved SVR12. 22 (95.7%, 95% CI 87.3-100.0) of 23 patients with genotype 5 infection achieved SVR12, as did 60 (98.4%, CI 95.2-100.0) of 61 with genotype 6 infection. One patient with an HCV genotype 6f infection and cirrhosis had on-treatment virological failure at treatment week 12, and one patient with HCV genotype 5a without cirrhosis who had achieved SVR at post-treatment week 4 relapsed at post-treatment week 12. Five (6%) patients had serious adverse events, none of which were deemed related to glecaprevir/pibrentasvir or led to discontinuation. Fatigue (11 [13%] patients) and

headache (11 [13%]) were the only adverse events that occurred in 10% or more of patients. No post-baseline grade 3 or higher increases in aminotransferase concentrations were reported.

**INTERPRETATION:** Glecaprevir/pibrentasvir achieved high SVR12 rates, comparable with data reported in registrational studies, and was well tolerated in patients with HCV genotype 5 or 6 infection with compensated liver disease.

**Outcomes of Treatment and Predictors of Response to Sofosbuvir plus Simeprevir in Hepatitis C Virus with Genotype-4 Infection.**

Ahmed OA1, Elsebaey MA2, Fouad MHA1, et al. Infect Disord Drug Targets. 2018 Dec 17. doi: 10.2174/1871526519666181218104600. [Epub ahead of print]

**BACKGROUND & AIMS:** Treatment plan of chronic HCV infection has dramatically improved after the introduction of different groups of direct-acting antiviral (DAA) drugs. These drugs have been found to be safe and effective. Sofosbuvir (SOF) plus simeprevir (SMV) regimen has been shown to be tolerable and effective in treatment of patients with HCV genotype 1. The aim of the study was to evaluate the safety and the efficacy of combined sofosbuvir plus simeprevir treatment in genotype 4 chronic HCV patients. **METHODS:** This open-label multicenter prospective study was carried out on 381 Egyptian patients with chronic hepatitis C virus- infection. Treatment experienced and treatment-naive patients were included. Subjects administrated a regimen of sofosbuvir (400 mg/ day) plus semiprevir (150 mg /day) for twelve weeks. Sustained virological response (SVR) was confirmed by undetectable HCV RNA by quantitative PCR 3 months after the end of treatment. **RESULTS:** 97.6% (372 /381) of patients had SVR. None of the studied clinical and demographic characteristics were associated with the SVR status. However, patients who failed to achieve SVR showed low albumin level and high total leucocyte. The most common side effects of the studied regimen were headache, fatigue, itching, photosensitivity, and cough. **CONCLUSIONS:** Twelve weeks regimen of sofosbuvir plus simeprevir was considered to be safe and tolerable in treatment of HCV genotype 4; also it was associated with high SVR (97.6%).

**Insulin resistance does not impair response of chronic hepatitis C virus to direct-acting antivirals, and improves with the treatment.**

Elhelbawy M1, Abdel-Razek W, Alsebaey A, Hashim M, Elshenawy H, Waked I. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):16-23. doi: 10.1097/MEG.0000000000001215.

**BACKGROUND:** Insulin resistance (IR) is a common complication in chronic hepatitis C virus (HCV) patients. The impact of IR on outcome of therapy with direct antivirals has not been studied. **AIM:** The aim was to assess the impact of direct-acting antiviral (DAA) therapy on IR status in chronic HCV patients. **PATIENTS AND METHODS:** A total of 511 patients [mean age: 50.7±10.4 years, 29.7% pegylated interferon and ribavirin (RBV) experienced] were enrolled. Patients with uncontrolled diabetes, decompensated liver disease, or previous nonresponse to DAAs were excluded. Homeostatic model assessment (HOMA) was calculated before and 12 weeks after treatment, and IR was defined as HOMA greater than 1.9. Patients were treated according to the treating physician's choice, and received 12 weeks of either ombitasvir/ritonavir/paritaprevir/RBV (n=28); sofosbuvir (SOF)/simeprevir (n=36); SOF/ravidasvir (n=101); SOF/pegylated interferon/RBV (n=192); or 24 weeks of SOF/RBV (n=154). **RESULTS:** Most patients received IR pretreatment (80.6%); 51.3% had fibrosis stage F4 and 24.7% had diabetes. A sustained virological response (SVR) at 12 weeks after treatment (SVR12) was achieved in 465 (91%) patients. SVR12 was achieved in 90.5% of patients with IR

and in 92.9% of patients without IR (P=0.560), and pretreatment HOMA was not different in responders and nonresponders (P=0.098). The number of patients with IR decreased significantly in patients who achieved an SVR much more than in nonresponders (P<0.0001) and HOMA improved significantly more in patients with SVR than in nonresponders (P=0.001). All treatment protocols were associated with a comparable improvement in HOMA (P=0.101). Predictors of SVR12 included age, platelets, and liver stiffness, but not pretreatment IR. **CONCLUSION:** IR does not impair the response of patients with HCV treated with DAAs, and improves significantly in patients who achieve an SVR.

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## **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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**[Characterization of a Threonine-Rich Cluster in Hepatitis C Virus Nonstructural Protein 5A and Its Contribution to Hyperphosphorylation.](#)** Schenk C1, Meyrath M1, Warnken U2, Schnölzer M2, Mier W3, Harak C1, Lohmann V4. *J Virol.* 2018 Nov 27;92(24). pii: e00737-18. doi: 10.1128/JVI.00737-18. Print 2018 Dec 15.

Hepatitis C virus (HCV) nonstructural protein 5A (NS5A) is a phosphoprotein with key functions in regulating viral RNA replication and assembly. Two phosphoisoforms are discriminated by their different apparent molecular weights: a basally phosphorylated (p56) and a hyperphosphorylated (p58) variant. The precise mechanisms governing p58 synthesis and specific functions of the isoforms are poorly understood. Our study aimed at a deeper understanding of determinants involved in p58 synthesis. We analyzed two variants of p56 and p58 of isolate JFH-1 separately by mass spectrometry using an expression model and thereby identified a threonine-rich phosphopeptide exclusively found in the hyperphosphorylated variant. Individual exchange of possible phosphoacceptor sites to phosphoablatant or -mimetic residues had little impact on HCV replication or assembly in cell culture. A phosphospecific antibody recognizing pT242 revealed that this position was indeed phosphorylated only in p58 and depended on casein kinase I $\alpha$ . Importantly, phosphoablative mutations at positions T244 and S247 abrogated pT242 detection without substantial effects on global p58 levels, whereas mutations in the preceding serine-rich cluster dramatically reduced total p58 levels but had minor impact on pT242 levels, suggesting the existence of distinct subspecies of hyperphosphorylated NS5A. Mass spectrometry analyses of different genotypes showed variable phosphorylation patterns across NS5A and suggested that the threonine-rich region is also phosphorylated at T242 in gt4a and at S249 in gt1a, gt1b, and gt4a. Our data therefore indicate that p58 is not a single homogeneously phosphorylated protein species but rather a population of various phosphoisoforms, with high variability between genotypes. **IMPORTANCE** Hepatitis C virus infections affect 71 million people worldwide and cause severe chronic liver disease. Recently, efficient antiviral therapies have been established, with inhibitors of nonstructural protein NS5A as a cornerstone. NS5A is a central regulator of HCV replication and assembly but is still enigmatic in its molecular functions. It exists in two phosphoisoforms, p56 and p58. We identified a phosphopeptide exclusively found in p58 and analyzed the determinants involved in phosphorylation of this region. We found evidence for very different phosphorylation patterns resulting in p58. These results challenge the concept of p58 being a homogenous species of NS5A molecules phosphorylated at the same positions and argues for at least two independently phosphorylated variants showing the same electrophoretic mobility, likely serving different functions.

### [Development of an Infectious Cell Culture System for Hepatitis C Virus Genotype 6a Clinical Isolate Using a Novel Strategy and Its Sensitivity to Direct-Acting Antivirals.](#)

Chen M1,2, Zheng F1,2, et al. Front Microbiol. 2018 Dec 4;9:2950. doi: 10.3389/fmicb.2018.02950. eCollection 2018.

Hepatitis C virus (HCV) is classified into seven major genotypes, and genotype 6 is commonly prevalent in Asia, thus reverse genetic system representing genotype 6 isolates in prevalence is required. Here, we developed an infectious clone for a Chinese HCV 6a isolate (CH6a) using a novel strategy. We determined CH6a consensus sequence from patient serum and assembled a CH6a full-length (CH6aFL) cDNA using overlapped PCR product-derived clones that shared the highest homology with the consensus. CH6aFL was non-infectious in hepatoma Huh7.5 cells. Next, we constructed recombinants containing Core-NS5A or 5'UTR-NS5A from CH6a and the remaining sequences from JFH1 (genotype 2a), and both were engineered with 7 mutations identified previously. However, they replicated inefficiently without virus spread in Huh7.5 cells. Addition of adaptive mutations from CH6a Core-NS2 recombinant, with JFH1 5'UTR and NS3-3'UTR, enhanced the viability of Core-NS5A recombinant and acquired replication-enhancing mutations. Combination of 22 mutations in CH6a recombinant with JFH1 5'UTR and 3'UTR (CH6aORF) enabled virus replication and recovered additional four mutations. Adding these four mutations, we generated two efficient recombinants containing 26 mutations (26m), CH6aORF\_26m and CH6aFL\_26m (designated "CH6acc"), releasing HCV of 104.3-104.5 focus-forming units (FFU)/ml in Huh7.5.1-VISI-mCherry and Huh7.5 cells. Seven newly identified mutations were important for HCV replication, assembly, and release. The CH6aORF\_26m virus was inhibited in a dose- and genotype-dependent manner by direct-acting-antivirals targeting NS3/4A, NS5A, and NS5B. The CH6acc enriches the toolbox of HCV culture systems, and the strategy and mutations applied here will facilitate the culture development of other HCV isolates and related viruses.

### [Association of genetic polymorphisms of chemokines and their receptors with clearance or persistence of hepatitis C virus infection.](#)

El-Bendary M1, Neamatallah M2, Elalfy H1, et al. Br J Biomed Sci. 2019 Jan;76(1):11-16. doi: 10.1080/09674845.2018.1518299. Epub 2018 Oct 29.

**BACKGROUND:** Polymorphisms of certain genes may have an effect on either persistence of infection or spontaneous clearance of hepatitis C virus (HCV). We hypothesized that one or more variants of chemokines (CCL2 and CCL5) and chemokine receptors (CC chemokine receptor type 2 [CCR2]) genes are associated with the susceptibility to HCV infection.

**METHODS:** We recruited 1460 patients with chronic HCV (CHC), 108 subjects with spontaneous virus clearance (SVC) and 1446 individuals as a healthy control group. All were genotyped for single nucleotide polymorphisms: rs13900 C/T of CCL2, rs3817655 T/A of CCL5 and rs743660 G/A and rs1799864 G/A of CCR2 using allelic discrimination real-time PCR technique. **RESULTS:** The carriage of the A allele of CCR2 rs743660 was significantly higher in CHC compared to SVC (odds ratio [OR] 4.03) and to controls (1.42) and in controls compared to SVC (2.85) (all  $P < 0.01$ ). Similarly, the A allele of CCR2 rs1799864 was significantly higher in the CHC group when compared with both SVC (1.97) and controls (2.13) (both  $P < 0.01$ ), but the OR between controls and SVC was not significant (1.08,  $P = 0.723$ ). Carriage of C allele of CCL2 rs13900 and the T allele of CCL5 rs3817655 were significantly higher in SVC group when compared with both CHC (OR = 0.19 and OR = 0.24, respectively) and control groups (OR = 0.65 and OR = 0.45, respectively [all  $P < 0.01$ ]). **CONCLUSIONS:** Susceptibility to

HCV infection is associated with A alleles of both (rs743660 and rs1799864 G/A) of CCR2 while spontaneous clearance of HCV is associated with the C allele of rs13900 of CCL2 and T allele of rs3817655 of CCL5.

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## HIV/HCV COINFECTION

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[The acceptability and effectiveness of a questionnaire for the identification of risk factors for HIV and hepatitis B and C: An observational study in general practice.](#) Aïm-Eusébi A1, Prothon E2, Majerholc C1, Barger D3, Yazdanpanah Y4, Aubert JP1,5. Eur J Gen Pract. 2018 Dec;24(1):60-67. doi: 10.1080/13814788.2017.1400529. Epub 2017 Nov 27.

**BACKGROUND:** Many people in Europe remain undiagnosed for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV). **OBJECTIVES:** To evaluate acceptability and effectiveness of a questionnaire designed to facilitate identification of risk factors for these viruses. **METHODS:** We performed an observational study, in a prospectively enrolled cohort of patients in Paris (France) seen in 2014. Eighteen GPs administered a questionnaire to the first 50 patients, collecting information about risk factors. GPs were randomized into two groups: A (self-administered questionnaire) and B (GP-administered questionnaire). We used the overall response rate to assess the acceptability of the questionnaire. We used the rate of newly identified risk factors and compared the number of tests performed one year before and immediately after the intervention to assess the effectiveness of the questionnaire. **RESULTS:** 842 patients were randomized: 349 (41.5%) in group A and 493 (58.5%) in group B. Acceptability was 88.5% (95%CI: 86.3-90.6); 93.1% (95%CI: 90.5-95.8) in group A and 85.2% (95%CI: 82.1-88.3) in group B (P = 0.0004). Prevalence of risk factors was 51.8% (95%CI: 48.2-54.4) and 58.3% were newly identified (95%CI: 52.9-63.7). The number of HIV tests performed during the four weeks after intervention increased by 27% compared to the same period one year before (P = 0.22). It increased by 113% (P = 0.005) and 135% (P = 0.005) for HBV and HCV, respectively. **CONCLUSION:** The questionnaire proved acceptable and effective in identifying risk factors for HIV, HBV and HCV in general practice.

[Real-world impact of direct acting antiviral therapy on health-related quality of life in HIV/Hepatitis C co-infected individuals.](#) Saeed S1,2, Moodie EEM1, Strumpf E1,3, et al. J Viral Hepat. 2018 Dec;25(12):1507-1514. doi: 10.1111/jvh.12985. Epub 2018 Sep 27.

Clinical trial results of direct acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) have shown improvements in health-related quality of life (HR-QoL). However, the extent to which these results are broadly generalizable to real-world settings is unknown. We investigated the real-world impact of oral DAA therapy on HR-QoL among individuals coinfecting with HIV/HCV. We used data from the Canadian HIV/HCV Co-Infection Cohort Study that prospectively follows 1795 participants from 18 centres. Since 2007, clinical, lifestyle, and HR-QoL data have been collected biannually through self-administered questionnaires and chart review. HR-QoL was measured using the EQ-5D instrument. Participants initiating oral DAAs, having at least one visit before treatment initiation and at least one visit after DAA treatment response was ascertained, were included. Successful treatment response was defined as a sustained viral response (SVR). Segmented multivariate linear mixed models were used to evaluate the impact of SVR on HR-QoL, controlling for pretreatment trends. 227 participants met our eligibility criteria, 93% of whom achieved SVR. Before treatment, the EQ-5D utility index decreased 0.6 percentage-point/y (95% CI, -0.9, -0.3) and

health state was constant over time. The immediate effect of SVR resulted in an increase of 2.3-units (-0.1, 4.7) in patients' health state and 2.0 percentage-point increase (-0.2, 4.0) in utility index. Health state continued to increase post-SVR by 1.4 units/y (-0.9, 3.7), while utility trends post-SVR plateaued over the observation period. Overall using real-world data, we found modest improvements in HR-QoL following SVR, compared to previously published clinical trials.

**[HIV-HBV and HIV-HCV Coinfection and Liver Cancer Development.](#)** Hu J1, Liu K2, Luo J2. *Cancer Treat Res.* 2019;177:231-250. doi: 10.1007/978-3-030-03502-0\_9.

Liver diseases that are caused by the hepatitis B virus (HBV) and hepatitis C virus (HCV), including cirrhosis and hepatocellular carcinoma (HCC), have become increasingly important in patients infected with the human immunodeficiency virus (HIV) as their life expectancy is getting longer with successful anti-HIV therapy. Due to their shared transmission routes, dual infection by HIV and HBV or HIV and HCV, and triple infection by all three viruses are fairly common and affect millions of people worldwide. Whereas the immunodeficiency caused by HIV enhances the likelihood of HBV and HCV persistence, hepatotoxicity associated with anti-HIV therapy can worsen the liver diseases associated with HBV or HCV persistence. Evidence suggests HIV infection increases the risk of HBV- or HCV-associated HCC risk although the precise mechanisms of enhanced hepatocarcinogenesis remain to be fully elucidated. Recent success in curing HCV infection, and the availability of therapeutic options effective in long-term suppression of both HIV and HBV replication, bring hope, fortunately, to those who are coinfecting but also highlight the need for judicious selection of antiviral therapies.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**[Functional MRI and delay discounting in patients infected with hepatitis C.](#)**

McCready H1,2,3, Kohno M1,2,3, et al. *J Neurovirol.* 2018 Dec;24(6):738-751. doi: 10.1007/s13365-018-0670-0. Epub 2018 Oct 8.

Hepatitis C virus-infected (HCV+) adults evidence increased rates of psychiatric and cognitive difficulties. This is the first study to use functional magnetic resonance imaging (fMRI) to examine brain activation in untreated HCV+ adults. To determine whether, relative to non-infected controls (CTLs), HCV+ adults exhibit differences in brain activation during a delay discounting task (DDT), a measure of one's tendency to choose smaller immediate rewards over larger delayed rewards-one aspect of impulsivity. Twenty adults with HCV and 26 CTLs completed an fMRI protocol during the DDT. Mixed effects regression analyses of hard versus easy trials of the DDT showed that, compared with CTLs, the HCV+ group exhibited less activation in the left lateral occipital gyrus, precuneus, and superior frontal gyrus. There were also significant interactive effects for hard-easy contrasts in the bilateral medial frontal gyrus, left insula, left precuneus, left inferior parietal lobule, and right temporal occipital gyrus; the CTL group evidenced a positive relationship between impulsivity and activation, while the HCV+ group exhibited a negative relationship. Within the HCV+ group, those with high viral load chose immediate rewards more often than those with low viral load, regardless of choice difficulty; those with low viral load chose immediate rewards more often on hard choices relative to easy choices. Results show that HCV+ patients exhibit greater impulsive behavior when

presented with difficult choices, and impulsivity is negatively related to activation in regions important for cognitive control. Thus, interventions that decrease impulsive choice may be warranted with some HCV+ patients.

### [Impact of treatment with direct-acting antivirals on anxiety and depression in chronic hepatitis C.](#)

Gallach M1, Vergara M1,2, da Costa JP1, et al. PLoS One. 2018 Dec 19;13(12):e0208112. doi: 10.1371/journal.pone.0208112. eCollection 2018.

**BACKGROUND AND AIM:** Treatment of hepatitis C with direct-acting antiviral agents (DAA) has few side effects. Although pivotal studies suggested that DAA were safe in patients with psychiatric diseases who could not be treated with previous antiviral therapies, their effects on anxiety and depression have not yet been analysed in clinical practice. The aim of our study was to analyse anxiety and depression in the setting of DAA treatment in a clinical practice series. **METHODS:** All patients starting DAA treatment between November 1, 2014 and October 31, 2015 were eligible. Patients completed the Hospital Anxiety and Depression scale at different times during treatment. The results were plotted on line graphs and evaluated using a linear regression model with repeated measures. **RESULTS:** One hundred and forty-five patients were included (11% with major psychiatric disorders; 32% on psychiatric treatment). Sustained virologic response (SVR) was achieved in 97.3% of cases. Anxiety and depression measures did not differ between time points. No differences between patients on psychiatric treatment or with advanced fibrosis or cirrhosis were found at any time point analysed. **CONCLUSION:** DAA treatment had no impact on anxiety or depression during or after chronic hepatitis C infection treatment, even in high-risk patients with major psychiatric disorders.

### [Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11.](#)

Murray KF1, Balistreri WF2, Bansal S3, et al. Hepatology. 2018 Dec;68(6):2158-2166. doi: 10.1002/hep.30123. Epub 2018 Nov 17.

Currently, there are no interferon-free treatments available for hepatitis C virus (HCV)-infected patients younger than 12 years. We evaluated the safety and effectiveness of the all-oral regimen ledipasvir-sofosbuvir ± ribavirin in HCV-infected children aged 6 to <12 years. In an open-label study, patients aged 6 to <12 years received ledipasvir 45 mg-sofosbuvir 200 mg as two fixed-dose combination tablets 22.5/100 mg once daily, with or without ribavirin, for 12 or 24 weeks, depending on HCV genotype and cirrhosis status. The primary efficacy endpoint was sustained virologic response 12 weeks after therapy (SVR12). Twelve patients underwent intensive pharmacokinetic sampling to confirm the appropriateness of the ledipasvir and sofosbuvir dosages. Ninety-two patients were enrolled (88 genotype 1, 2 genotype 3, and 2 genotype 4), with a median age of 9 years (range, 6-11). Most were perinatally infected (97%) and treatment-naïve (78%). Two were confirmed to have cirrhosis, while the degree of fibrosis was unknown in 55 patients. The overall SVR12 rate was 99% (91/92; 95% confidence interval, 94%-100%). The single patient not reaching SVR relapsed 4 weeks after completing 12 weeks of treatment. The most common adverse events were headache and pyrexia. One patient had three serious adverse events, which were considered to be not related to study treatment: tooth abscess, abdominal pain, and gastroenteritis. The area under the concentration-time curve and maximum concentration values for sofosbuvir, its primary metabolite GS-331007, and ledipasvir were within predefined pharmacokinetic equivalence boundaries (50%-200%) compared to values in



adults in phase 2/3 of the ledipasvir and sofosbuvir studies. Conclusion: Ledipasvir-sofosbuvir was well tolerated and highly effective in children 6 to <12 years old with chronic HCV.

**[Assessing Disparities in the Rates of HCV Diagnoses Within American Indian or Alaska Native Populations Served by the U.S. Indian Health Service, 2005-2015.](#)**

Reilley B1, Leston J2, Doshani M3, Haberling DL4, Person M4, Weiser T5, Collier M3, Iralu J6, Mera J7, Haverkate R8. J Community Health. 2018 Dec;43(6):1115-1118. doi: 10.1007/s10900-018-0528-7.

Hepatitis C virus (HCV) disproportionately affects American Indians/Alaska Natives (AI/AN). The Indian Health Service (IHS), via federal and tribal health facilities provides medical services to an estimated 2.2 million AI/AN people in the United States. HCV diagnoses, defined by International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) codes, were analyzed from 2005 to 2015. Results showed 29,803 patients with an HCV diagnosis; 53.4% were among persons born 1945-1965 and overall HCV burden was higher among males than females. These data will help inform local, regional, and national efforts to address, plan for and carry out a national strategy to provide treatment for HCV infected patients and programs to prevent new HCV infections.

**[Efficacy and safety of sofosbuvir and daclatasvir with or without ribavirin in elderly patients with chronic hepatitis C virus infection.](#)**

Elbaz T1, Abdo M1, Omar H1, et al. J Med Virol. 2019 Feb;91(2):272-277. doi: 10.1002/jmv.25287. Epub 2018 Nov 8.

Hepatitis C virus (HCV) infection is considered as a major public health problem that, worldwide, chronically affects 170 million people. Elderly patients are more likely than younger patients to have increased duration of infection, increased rate of disease progression, and subsequently increased incidence of advanced liver disease. Natural history models predicted that the prevalence of HCV infection and its chronic sequelae as well as extrahepatic manifestations will eventually increase through the next decade and will mostly affect those who are greater than 60 years of age. Moreover, polytherapy and polypharmacy are frequent in elderly patients due to associated comorbidities. As advanced age is associated with increasing risk of development of cirrhosis and hepatocellular carcinoma, elderly patients are in special need of safe and effective antiviral therapies. Achievement of sustained viral responses (SVR) is associated with reduced liver-related complications and overall mortality in such patients with the advanced liver disease. With the recent introduction of interferon-free direct-acting antivirals, successful treatment for chronic HCV infection had dramatically improved, with overall cure rates that exceed 90% SVR. In our study, we aimed to study the efficacy and safety of combined sofosbuvir and daclatasvir, with or without ribavirin, in management of chronically infected HCV elderly patients who are more than 60 years old.

**[Skeletal muscle mass depletion in patients with hepatitis C virus infection.](#)**

Fukui A1,2, Kawabe N2, Hashimoto S2, Kamei H1, Yoshioka K2. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):59-66. doi: 10.1097/MEG.0000000000001255.

**OBJECTIVE:** The aim was to assess the relationship between muscle mass depletion and chronic hepatitis C virus (HCV) infection. **PATIENTS AND METHODS:** We retrospectively evaluated abdominal computed tomography data for 611 patients. The participants included 302 patients with HCV infection and 309 patients with gallstones (as a control). The skeletal muscle mass at the level of the third lumbar vertebra (L3) was measured from the computed tomography

images and normalized for height to calculate the L3 skeletal muscle index (L3-SMI, cm/m). Statistical analysis was carried out separately for each sex, given that L3-SMI differs significantly between men and women. **RESULTS:** L3-SMI showed no significant difference between chronic hepatitis patients and gallstone patients in either sex. L3-SMI was significantly lower in male cirrhotic patients than in those with chronic hepatitis ( $P < 0.001$ ). The Child-Pugh score was correlated negatively with L3-SMI in male patients with HCV-related cirrhosis ( $\rho = 0.200$ ,  $P = 0.031$ ). In addition, the BMI in both sexes was associated with L3-SMI in the gallstone and chronic hepatitis group, in the chronic hepatitis and liver cirrhosis group, and in the liver cirrhosis group. **CONCLUSION:** Skeletal muscle mass is not affected by chronic HCV infection in patients without cirrhosis and decreases in accordance with liver disease progression in male patients with chronic HCV infection.

**Nonalcoholic Fatty Liver is Contributing to the Increase in Cases of Liver Disease in US Emergency Departments.** Bush H1, Golabi P1, Otgonsuren M1, Rafiq N1,2, Venkatesan C2, Younossi ZM1,2. Clin Gastroenterol. 2019 Jan;53(1):58-64. doi: 10.1097/MCG.0000000000001026.

**GOALS/BACKGROUND:** We aimed to assess temporal changes in the different types of liver disease (LD) cases and outcomes from emergency departments (EDs) across the United States. **STUDY:** We used data from the National Inpatient Survey database from 2005 to 2011. The International Classification of Diseases, Ninth Revision (ICD-9) clinical modification codes identified hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and other LDs including autoimmune hepatitis. We excluded cases without LD, nonhepatocellular carcinoma-related cancers, human immunodeficiency virus infection, or those with missing information. Logistic regression was used to estimate odds ratios with 95% confidence intervals. Controls were matched to cases without LD. **RESULTS:** During the study period, 20,641,839 cases were seen in EDs. Of these, 1,080,008 cases were related to LD and were matched to controls without LD ( $N = 19,557,585$ ). The number of cases with LD increased from 123,873 (2005) to 188,501 (2011) ( $P < 0.0001$ ). Among cases with LD, diagnosis of HCV, HBV, and ALD remained stable during the study years (41.60% vs. 38.20%, 3.70% vs. 2.80%, and 41.4% vs. 38.5%, respectively), whereas NAFLD doubled [6.00% of all LD (2005) to 11.90% of all LD (2011) ( $P < 0.0001$ )]. Diagnosis of LD in the ED independently predicted increased patient mortality [odds ratio, 1.20 (1.17 to 1.22)]. **CONCLUSIONS:** The number of LD cases presenting to EDs is increasing, and a diagnosis of LD is associated with a higher patient mortality for those admitted through the ED. There is a dramatic increase of NAFLD diagnoses in the ED.

**Race, Age, and Geography Impact Hepatitis C Genotype Distribution in the United States.** Gordon SC1, Trudeau S2, Li J2, Zhou Y2, et al. J Clin Gastroenterol. 2019 Jan;53(1):40-50. doi: 10.1097/MCG.0000000000000872.

**GOALS:** To determine the impact of geography and patient characteristics on hepatitis C virus (HCV) genotype and subtype distribution in a large sample of patients under routine clinical care **BACKGROUND:** HCV genotype impacts disease course and response to treatment. Although several studies have reported genotype distribution within specific US populations, there are no comprehensive descriptions in large, geographically diverse cohorts. **STUDY:** Using data from the Chronic Hepatitis Cohort Study, we present the distribution of HCV genotypes (GT) and subtypes (ST) among a racially diverse cohort of over 8000 HCV-infected patients from four

large US health systems. **RESULTS:** Genotype distribution varied significantly by geographic and demographic factors. In age-adjusted analyses, African American patients had significantly higher prevalence of GT1 (85%) than other racial categories, largely driven by a markedly higher proportion of GT1 subtype b (~34%) than in Asian/other (24%) and white (21%) patients. GT3 represented an increasing proportion of infections as birth decade progressed, from 4% in patients born before 1946 to 18% of those born after 1976. Within the cohort of "living/uncured" patients, highly elevated alanine aminotransferase (>2 times the upper limit of normal) was significantly more common in GT3 patients, whereas Fibrosis-4 Index scores indicative of cirrhosis were most common in the combined group of GT4&6 patients. **CONCLUSION:** Distribution of HCV genotypes and subtypes in the United States is more variable than suggested by previous national-level estimates and single-center studies. "Real-world" prevalence data may improve targeting of prevention, screening, and treatment efforts for hepatitis C.

**Significant Increase in Risk of Fibrosis or Cirrhosis at Time of HCV Diagnosis for Hispanics With Diabetes and Obesity Compared with Other Ethnic Groups.** Turner BJ1, Wang CP2, Melhado TV3, Bobadilla R3, Jain MK4, Singal AG4. Clin Gastroenterol Hepatol. 2018 Dec 6. pii: S1542-3565(18)31336-3. doi: 10.1016/j.cgh.2018.11.059. [Epub ahead of print]

**BACKGROUND & AIMS:** Advanced liver disease, which includes fibrosis and cirrhosis, has been reported to be more prevalent in Hispanics patients at the time of diagnosis of chronic hepatitis C virus (HCV) infection than non-Hispanic black or non-Hispanic white patients. We performed a propensity score-matched analysis to determine whether metabolic risk factors contribute to this disparity. **METHODS:** We collected data from persons with 748 HCV infection (22% Hispanic, 53% non-Hispanic black, and 26% non-Hispanic white; 23% with advanced liver disease), born from 1945 through 1965, diagnosed at 6 healthcare systems in Texas. Advanced liver disease was defined as a FIB-4 index score above 3.25. We examined the association between advanced liver disease and race-ethnicity, metabolic risk (based on diabetes mellitus and body mass index [BMI]) and heavy alcohol use in propensity score-matched analyses. **RESULTS:** In propensity-score matched models, the adjusted odds ratios (AORs) of advanced liver disease for Hispanics who were obese (BMI  $\geq$ 30) with a diagnosis of diabetes were, respectively, 7.89 (95% CI, 3.66 -17.01) vs. non-Hispanic black patients and 12.49 (95% CI, 3.24 - 48.18) vs. non-Hispanic white patients (both  $P < .001$ ). The adjusted odds ratios BMI <25, with or without diabetes, were more than 2-fold greater for Hispanics than non-Hispanic black or non-Hispanic white patients (both  $P < .002$ ). **CONCLUSIONS:** HCV-infected Hispanics with obesity and diabetes have a far higher risk for advanced liver disease than other racial or ethnic groups. These findings highlight the need for HCV treatment and management of probable concurrent fatty liver disease. Even after we accounted for metabolic risk factors, Hispanics were still at higher risk for advanced liver disease, indicating the potential involvement of other factors such as genetic variants.

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## HEPATOCELLULAR (LIVER) CANCER

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**Validation of the Hepatocellular Carcinoma Early detection Screening (HES) algorithm in a Cohort of Veterans with Cirrhosis.** Tayob N1, Christie I2, Richardson P2, et al. Clin Gastroenterol Hepatol. 2018 Dec 14. pii: S1542-3565(18)31378-8. doi: 10.1016/j.cgh.2018.12.005. [Epub ahead of print]

**BACKGROUND & AIMS:** Early detection of hepatocellular carcinoma (HCC) through surveillance reduces mortality associated with this cancer. Guidelines recommend HCC surveillance every 6 months for patients with cirrhosis, via ultrasonography, with or without measurement of serum level of alpha fetoprotein (AFP). **METHODS:** We previously developed and internally validated an HCC early detection screening (HES) algorithm that included patient's current level of AFP, rate of AFP change, age, level of alanine aminotransferase, and platelet count in a department of Veterans affairs (VA) cohort with active hepatitis C virus-related cirrhosis. HES score was associated with 3.84% absolute improvement in sensitivity of detection of HCC compared with AFP alone, at 90% specificity, within 6 months prior to diagnosis of this cancer. We externally validated the HES algorithm in a cohort of 38,431 patients with cirrhosis of any etiology evaluated at a VA medical center from 2010 through 2015. **RESULTS:** A total of 4804 cases of HCC developed during a median follow-up time of 3.12 years. At 90% specificity, the HES algorithm identified patients with HCC with 52.56% sensitivity, compared to 48.13% sensitivity for the AFP assay alone, within 6 months prior to diagnosis; this was an absolute improvement of 4.43% ( $P < .0005$ ). In HCC screening, a positive result leads to follow-up evaluation by computed tomography or magnetic resonance imaging. We estimated that the number of HCC cases detected per 1000 imaging analyses were 198.57 for the HES algorithm vs 185.52 for the AFP assay alone, or detection of 13 additional cases of HCC ( $P < .0005$ ). **CONCLUSION:** We validated the HES algorithm in detection of HCC in patients with cirrhosis of any etiology evaluated at VA medical centers. The algorithm offers a modest but useful advantage over AFP alone in HCC surveillance.

#### [Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy.](#)

Nishibatake Kinoshita M1, Minami T1, et al. J Hepatol. 2019 Jan;70(1):78-86. doi: 10.1016/j.jhep.2018.09.029. Epub 2018 Oct 16.

**BACKGROUND & AIMS:** It remains controversial whether direct-acting antivirals (DAAs) accelerate the recurrence of hepatitis C-related hepatocellular carcinoma (HCC) after curative therapy. This study aimed to evaluate HCC recurrence after DAA treatment of chronic hepatitis C. **METHODS:** We enrolled patients with a history of successful radiofrequency ablation treatment for hepatitis C-related HCC who received antiviral therapy with DAAs (DAA group: 147 patients) or with interferon (IFN)-based therapy (IFN group: 156 patients). We assessed HCC recurrence rates from the initiation of antiviral therapy using the Kaplan-Meier method and evaluated risk factors for HCC recurrence by multivariate Cox proportional hazard regression analysis. The recurrence pattern was categorized as follows: intrahepatic recurrence with a single tumor  $< 2$  cm (stage 0), a single tumor or up to 3 tumors  $\leq 3$  cm (stage A), multinodular (stage B), and extrahepatic metastasis or macrovascular invasion (stage C). **RESULTS:** The recurrence rates at 1 and 2 years were 39% and 61% in the IFN group and 39% and 60% in the DAA group, respectively ( $p = 0.43$ ). Multivariate analysis identified higher lens culinaris agglutinin-reactive fraction of alpha-fetoprotein level, a history of multiple HCC treatments, and a shorter interval between HCC treatment and initiation of antiviral therapy as independent risk factors for HCC recurrence. HCC recurrence in stage 0, A, B, and C was found in 56 (41%), 60 (44%), 19 (14%), and 1 (0.7%) patients in the IFN group and 35 (44%), 32 (40%), 11 (14%), and 2 (2.5%) patients in the DAA group, respectively ( $p = 0.70$ ). **CONCLUSIONS:** HCC recurrence rates and patterns after initiation of antiviral therapy did not differ between patients who received IFN-based therapy and DAA therapy. **LAY SUMMARY:** We detected no significant difference in early

hepatocellular carcinoma (HCC) recurrence rates and patterns between patients who received interferon-based and direct-acting antiviral therapy after HCC treatment. High lens culinaris agglutinin-reactive fraction of alpha-fetoprotein level, short recurrence-free period, and a history of multiple HCC treatments were independent risk factors for early HCC recurrence after the initiation of antiviral therapy.

**Low performance of ultrasound surveillance for the diagnosis of hepatocellular carcinoma in HIV-infected patients.** Merchante N1, Figueruela B2, Rodríguez-Fernández M1, et al. AIDS. 2019 Feb 1;33(2):269-278. doi: 10.1097/QAD.0000000000002065.

**OBJECTIVE:** To assess the performance of ultrasound surveillance for the diagnosis of hepatocellular carcinoma (HCC) in HIV-infected patients. **METHODS:** The GEHEP-002 cohort recruits HCC cases diagnosed in HIV-infected patients from 32 centers across Spain. The proportion of 'ultrasound lack of detection', defined as HCC diagnosed within the first 3 months after a normal surveillance ultrasound, and the proportion of 'surveillance failure', defined as cases in which surveillance failed to detect HCC at early stage, were assessed. To assess the impact of HIV, a control population of 104 HCC cases diagnosed in hepatitis C virus-monoinfected patients during the study period was used. **RESULTS:** A total of 186 (54%) out of 346 HCC cases in HIV-infected patients were diagnosed within an ultrasound surveillance program. Ultrasound lack of detection occurred in 16 (8.6%) of them. Ultrasound surveillance failure occurred in 107 (57%) out of 186 cases diagnosed by screening, whereas this occurred in 18 (29%) out of 62 diagnosed in the control group ( $P < 0.0001$ ). HCC cases after ultrasound surveillance failure showed a lower frequency of undetectable HIV viral load at diagnosis. The probability of 1-year and 2-year survival after HCC diagnosis among those diagnosed by screening was 56 and 45% in HIV-infected patients, whereas it was 79 and 64% in HIV-negative patients ( $P = 0.038$ ). **CONCLUSION:** The performance of ultrasound surveillance of HCC in HIV-infected patients is very poor and worse than that shown outside HIV infection. A HCC surveillance policy based on ultrasound examinations every 6 months might be insufficient in HIV-infected patients with cirrhosis.

**Tumor behavior of hepatocellular carcinoma after hepatitis C treatment by direct-acting antivirals: comparative analysis with non-direct-acting antivirals-treated patients.**

Abdelaziz AO1, Nabil MM1, Abdelmaksoud AH2, et al. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):75-79. doi: 10.1097/MEG.0000000000001264.

**INTRODUCTION:** Scarce reports have commented on hepatocellular carcinoma (HCC) behavior after direct-acting antivirals (DAAs). **AIM:** To analyze differences in tumor behavior between patients with hepatitis C virus (HCV)-induced HCC and were either treated or not using DAAs. **PATIENTS AND METHODS:** This case-control study includes patients with HCV-related HCC who received generic DAAs (group I) and all non-DAA treated patients with HCC who presented to our clinic during the same period (group II). Patient and tumor characteristics, treatment types and outcome were compared between the two groups. **RESULTS:** Group I included 89 patients and group II included 207 patients. No significant difference was detected between groups regarding HCC number or size. Group I showed a more infiltrative HCC pattern, whereas group II had more circumscribed and delineated lesions. The incidence of portal vein thrombosis and significant lymphadenopathy was significantly higher in group I ( $P = 0.03$  and  $0.03$ , respectively). Serum levels of  $\alpha$ -fetoprotein were significantly higher in group I ( $P = 0.02$ ). These factors significantly affected the response to HCC management ( $P = 0.03$ ). Incidence of

complete responses were 47.2 and 49.8% for groups I and II, respectively, whereas incomplete responses were 12.4 and 25.1%, respectively. Supportive treatment was applied to 40.4% in group I and 25.1% in group II. **CONCLUSION:** HCC behavior was more aggressive in DAA-treated patients regarding portal vein thrombosis, malignant lymphadenopathy, and HCC imaging characteristics, which affected the chance of ablation and the treatment response.

**No difference between direct-acting antivirals for hepatitis C in hepatocellular carcinoma risk.** Mun EJ1, Green P2, Berry K2, Ioannou GN3,2. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):47-52. doi: 10.1097/MEG.0000000000001242.

**BACKGROUND AND AIMS:** It is unclear whether there are differences between direct-acting antivirals (DAAs) for hepatitis C virus in risk of hepatocellular carcinoma (HCC) after antiviral therapy. We aimed to compare different DAA regimens with respect to risk of de novo HCC following antiviral therapy. **PATIENTS AND METHODS:** We identified 33 137 patients who initiated hepatitis C virus antiviral treatment in the Veterans Affairs healthcare system between 6 December 2013 and 31 December 2015 with one of four DAA-only regimens ( $\pm$  ribavirin): paritaprevir/ritonavir/ombitasvir/dasabuvir (n=6289), sofosbuvir (n=4356), sofosbuvir+simeprevir (n=3210), and ledipasvir/sofosbuvir (n=19 282). We retrospectively followed patients until 15 June 2017 to identify incident (de novo) cases of HCC. We used propensity score-adjusted Cox proportional hazards regression to compare different DAA regimens with respect to HCC risk. **RESULTS:** During a mean follow-up of 1.52 years, 741 new cases of HCC were diagnosed after antiviral treatment (annual incidence=1.47%). Patients treated with sofosbuvir+simeprevir had the highest annual HCC incidence (2.47%), followed by sofosbuvir (1.91%), ledipasvir/sofosbuvir (1.26%), and paritaprevir/ritonavir/ ombitasvir/ dasabuvir (0.95%). However, there were great differences between DAA-treated patients in the prevalence of cirrhosis, markers of advanced fibrosis, thrombocytopenia, and other HCC risk factors. After adjustment for baseline characteristics associated with HCC, there were no significant differences in HCC risk between the four DAA regimens. **CONCLUSION:** There are no significant differences between DAA regimens in HCC risk after antiviral treatment. This suggests that DAAs do not have direct carcinogenic effects as it would be unlikely that different DAAs would have identical carcinogenic effects.

**Impact of immigration in presentation and outcomes of hepatocellular carcinoma in the USA.** Ashhab AA1, Rodin H2, Powell J1, Debes JD1,3. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):24-28. doi: 10.1097/MEG.0000000000001212.

**BACKGROUND AND AIMS:** Hepatocellular carcinoma's (HCC) epidemiology and prognosis differs among regions across the globe, largely because of environmental factors and underlying liver disease. Little is known about the changes led by immigration and the effect on HCC outcome. We aimed to understand the effect of immigration on HCC. **PATIENTS AND METHODS:** A retrospective cohort study of patients diagnosed with HCC was carried out in a tertiary center in the USA between 2005 and 2016. We characterized individuals as US born or having immigrated there after being born elsewhere. Variables related to clinical presentation, surveillance, therapy, and survival were evaluated. **RESULTS:** A total of 232 HCC cases were included, 169 US born (73%) and 63 immigrants (27%). Both groups were diagnosed with HCC at similar ages (60 vs. 62 years,  $P=0.13$ ). Hepatitis C was the most common underlying liver disease in the US-born population compared with the immigrant population (83 vs. 52%,  $P<0.001$ ), whereas hepatitis B was more common in the latter (4 vs. 29%,  $P<0.001$ ).

Interestingly, hepatitis B virus-related HCC was diagnosed at similar ages in US-born and immigrant individuals (59 and 57 years). At the time of diagnosis, both populations had similar tumor sizes, rates of metastasis, and diagnosis during surveillance. One-year survival was similar in both groups (65 vs. 63%). **CONCLUSION:** Immigrants that develop HCC have different underlying liver disease than those born in the USA, but similar HCC characteristics and outcomes, even when including hepatitis B virus-related HCCs. Our study, albeit small, suggests that changes in the environment by immigration leads to clinical adaptation of HCC.

[Hepatitis B virus infection and the risk of cancer in the elderly US population.](#) Mahale P1, Engels EA1, Koshiol J1. *Int J Cancer*. 2019 Feb 1;144(3):431-439. doi: 10.1002/ijc.31643. Epub 2018 Nov 28.

Hepatitis B virus (HBV) infection causes hepatocellular carcinoma (HCC). Associations with other cancers are not established. We systematically assessed associations between HBV infection and cancers in the US elderly population. We conducted a case-control study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database in US adults aged  $\geq 66$  years. Cases (N = 1,825,316) were people with first cancers diagnosed in SEER registries (1993-2013). Controls (N = 200,000) were randomly selected, cancer-free individuals who were frequency-matched to cases on age, sex, race and calendar year. Associations with HBV infection (ascertained by Medicare claims) were assessed by logistic regression. HBV prevalence was higher in cases than controls (0.6% vs. 0.5%). HBV was positively associated with cancers of the stomach (adjusted odds ratio [aOR] = 1.19; 95% confidence intervals [CI] = 1.03-1.37), anus (1.66; 1.17-2.33), liver (10.6; 9.66-11.6), intrahepatic bile ducts (1.67; 1.18-2.37), nasopharynx (2.08; 1.33-3.25), as well as myelodysplastic syndrome (1.26; 1.07-1.49) and diffuse large B-cell lymphoma (DLBCL) (1.24; 1.06-1.46). Inverse associations were observed with female breast (aOR = 0.86; 95% CI = 0.76-0.98) and prostate (0.81; 0.73-0.91) cancers and chronic lymphocytic leukemia (0.77; 0.62-0.96). Associations were maintained in sensitivity analyses conducted in people without claims for cirrhosis or hepatitis C or human immunodeficiency virus infections. HBV infection is associated with increased risk of cancers other than HCC, such as bile duct cancers and DLBCL. The biological mechanisms by which HBV may lead to these cancers need to be explored.

[Low Rates of Retention Into Hepatocellular Carcinoma \(HCC\) Surveillance Program After Initial HCC Screening.](#) Robinson A1, Tavakoli H1, Cheung R2, Liu B1, Bhuket T1, Wong RJ1. *J Clin Gastroenterol*. 2019 Jan;53(1):65-70. doi: 10.1097/MCG.0000000000001024.

**GOALS:** To evaluate rates and predictors of retention into hepatocellular carcinoma (HCC) surveillance beyond initial screening among underserved cirrhosis patients. **BACKGROUND:** Although initial HCC screening among cirrhosis patients remains low, few studies have evaluated retention to HCC surveillance beyond initial screening. **METHODS:** We retrospectively evaluated all consecutive adults with cirrhosis from 2014 to 2017 at a single underserved safety net hospital system to determine rates of HCC surveillance at 6 months and at 1 year beyond initial screening. Rates of HCC surveillance was stratified by sex, race/ethnicity, and etiology of liver disease. Multivariate Cox proportional hazards models evaluated predictors of retention into HCC surveillance. **RESULTS:** Among 235 cirrhosis patients [hepatitis C virus: 35.7%, hepatitis B virus (HBV): 15.7%, alcoholic cirrhosis: 36.2%, nonalcoholic steatohepatitis (NASH): 8.1%], mean age of cirrhosis diagnosis was  $54.2 \pm 8.9$  years. Overall, 74.8% received initial screening within 1 year of cirrhosis diagnosis. Among those who completed initial

screening, 47.6% [95% confidence interval (CI), 41.4-54.2) received second surveillance within 1 year. On multivariate analyses, patients with NASH and HBV were significantly more likely to receive second HCC surveillance compared with hepatitis C virus, HBV (hazard ratio, 2.32; 95% CI, 1.18-4.56; P=0.014) and NASH (hazard ratio, 2.49; 95% CI, 1.22-5.11; P=0.012). No sex or race-specific/ethnicity-specific differences in HCC surveillance retention were observed.

**CONCLUSIONS:** Although overall rates of initial HCC screening among cirrhosis patients is nearly 75%, retention into continued HCC surveillance is poor, with less than half of patients undergoing subsequent HCC surveillance. Cirrhosis patients with HBV and NASH were more likely to be retained into HCC surveillance.

**microRNAs: Key players in virus-associated hepatocellular carcinoma.** Sadri Nahand J1, Bokharaei-Salim F1, Salmaninejad A2,3, et al. *J Cell Physiol.* 2018 Dec 7. doi: 10.1002/jcp.27956. [Epub ahead of print]

Hepatocellular carcinoma (HCC) is known as one of the major health problems worldwide. Pathological analysis indicated that a variety of risk factors including genetical (i.e., alteration of tumor suppressors and oncogenes) and environmental factors (i.e., viruses) are involved in beginning and development of HCC. The understanding of these risk factors could guide scientists and clinicians to design effective therapeutic options in HCC treatment. Various viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV) via targeting several cellular and molecular pathways involved in HCC pathogenesis. Among various cellular and molecular targets, microRNAs (miRNAs) have appeared as key players in HCC progression. miRNAs are short noncoding RNAs which could play important roles as oncogenes or tumor suppressors in several malignancies such as HCC. Deregulation of many miRNAs (i.e., miR-222, miR-25, miR-92a, miR-1, let-7f, and miR-21) could be associated with different stages of HCC. Besides miRNAs, exosomes are other particles which are involved in HCC pathogenesis via targeting different cargos, such as DNAs, RNAs, miRNAs, and proteins. In this review, we summarize the current knowledge of the role of miRNAs and exosomes as important players in HCC pathogenesis. Moreover, we highlighted HCV- and HBV-related miRNAs which led to HCC progression.