



March 2016

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES  
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES  
HIV/HCV COINFECTION  
COMPLEMENTARY AND ALTERNATIVE MEDICINE  
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS  
LIVER CANCER

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**CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

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**[Simeprevir and Sofosbuvir \(SMV-SOF\) for 12 Weeks for the Treatment of Chronic Hepatitis C Genotype 1 Infection: A Real World \(Transplant\) Hepatology Practice Experience.](#)** Pillai AA1, Wedd J1, Norvell JP1, et al. Am J Gastroenterol. 2016 Feb;111(2):250-60. doi: 10.1038/ajg.2015.422. Epub 2016 Feb 2.

**OBJECTIVES:** The combination of simeprevir (SMV) and sofosbuvir (SOF) was found to be well-tolerated with high sustained virologic response (SVR) rates in patients with genotype 1 chronic hepatitis C in clinical trials. Previous experience with hepatitis C virus (HCV) therapy has shown that patient tolerability and treatment efficacy described in controlled clinical trials did not necessarily mirror the "real world" experience. The goal of this study was to define SVR rates in a "real world" analysis and to explore predictors of treatment response with SMV and SOF. **METHODS:** This is a retrospective study examining the "real world" treatment of 170 patients with chronic HCV genotype 1 using the combination of SMV and SOF with or without ribavirin (RBV) for a fixed 12-week duration irrespective of prior interferon therapy, transplant status or fibrosis stage. Differences between SVR cohorts were analyzed by both intention-to-treat (ITT) and per protocol. **RESULTS:** The vast majority of patients were genotype 1a, 77% were cirrhotic in the non-LT group, and 35% of the entire cohort was African-American. Combination treatment with SMV and SOF in genotype 1 chronic HCV patients achieved an overall SVR rate at 12 weeks after completion of therapy (SVR12) of 78% by ITT and 86% by per protocol (84% in non-liver transplant (LT) patients and 89% in post-LT recipients). The presence of hepatocellular carcinoma was found to be a significant negative predictor of SVR12, whereas an undetectable week eight VL was a significant positive predictor of SVR in the entire cohort. **CONCLUSIONS:** Our data confirm excellent SVR outcomes with favorable safety and tolerability profiles in patients who carry many traditional high-risk features for non-response, including post-LT recipients and patients with advanced liver disease.

**[Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial.](#)** Manns M1, Samuel D2, Gane EJ3, et al. Lancet Infect Dis. 2016 Feb 18. pii: S1473-3099(16)00052-9. doi: 10.1016/S1473-3099(16)00052-9. [Epub ahead of print]

**BACKGROUND:** Treatment options are limited for patients infected by hepatitis C virus (HCV) with advanced liver disease. We assessed the safety and efficacy of ledipasvir, sofosbuvir, and ribavirin in patients with HCV genotype 1 or 4 and advanced liver disease. **METHODS:** We did an open-label study at 34 sites in Europe, Canada, Australia, and New Zealand. Cohort A included patients with Child-Turcotte-Pugh class B (CTP-B) or CTP-C cirrhosis who had not undergone liver transplantation. Cohort B included post-transplantation patients who had either no cirrhosis; CTP-A, CTP-B, or CTP-C cirrhosis; or fibrosing cholestatic hepatitis. Patients in each group were randomly assigned (1:1) using a computer-generated randomisation sequence to receive 12 or 24 weeks of ledipasvir (90 mg) and sofosbuvir (400 mg) once daily (combination tablet), plus ribavirin (600-1200 mg daily). The primary endpoint was the proportion of patients achieving a sustained virological response 12 weeks after treatment (SVR12). All patients who received at least one dose of study drug were included in the safety analysis and all patients who received at least one dose of study drug and did not undergo liver transplantation during treatment were included in the efficacy analyses. Estimates of SVR12 and relapse rates and their two-sided 90% CI (Clopper-Pearson method) were provided. This exploratory phase 2 study was not powered for formal comparisons among treatment groups; no statistical hypothesis testing was planned or conducted. The trial is registered with EudraCT (number 2013-002802-30) and ClinicalTrials.gov (number NCT02010255). **FINDINGS:** Between Jan 14, 2014, and Aug 19, 2014, 398 patients were screened. Of 333 patients who received treatment, 296 had genotype 1 HCV and 37 had genotype 4 HCV. In cohort A, among patients with genotype 1 HCV, SVR12 was achieved by 20 (87%, 90% CI 70-96) of 23 CTP-B patients with 12 weeks of treatment; 22 (96%, 81-100) of 23 CTP-B patients with 24 weeks of treatment; 17 (85%, 66-96) of 20 CTP-C patients (12 weeks treatment); and 18 (78%, 60-91) of 23 CTP-C patients (24 weeks treatment). In cohort B, among patients with genotype 1 HCV, SVR12 was achieved by 42 (93%, 84-98) of 45 patients without cirrhosis (12 weeks treatment); 44 (100%, 93-100) of 44 patients without cirrhosis (24 weeks treatment); 30 (100%, 91-100) of 30 CTP-A patients (12 weeks treatment); 27 (96%, 84-100) of 28 CTP-A patients (24 weeks treatment); 19 (95%, 78-100) of 20 CTP-B patients (12 weeks treatment); 20 (100%, 86-100) of 20 CTP-B patients (24 weeks treatment); one (50%, 3-98) of two CTP-C patients (12 weeks treatment); and four (80%, 34-99) of five CTP-C patients (24 weeks treatment). All five patients with fibrosing cholestatic hepatitis achieved SVR12 (100%, 90% CI 55-100). Among all patients with genotype 4 HCV, SVR12 was achieved by 14 (78%, 56-92) of 18 patients (12 weeks treatment) and 16 (94%, 75-100) of 17 patients (24 weeks treatment). Seven patients (2%) discontinued ledipasvir-sofosbuvir prematurely due to adverse events. 17 patients died, mainly from complications of hepatic decompensation. **INTERPRETATION:** Ledipasvir-sofosbuvir and ribavirin provided high rates of SVR12 for patients with advanced liver disease, including those with decompensated cirrhosis before or after liver transplantation.

[On-treatment HCV RNA in patients with varying degrees of fibrosis and cirrhosis in the SOLAR-1 trial.](#) Welzel TM1, Reddy KR, Flamm SL, et al. *Antivir Ther.* 2016 Feb 18. doi: 10.3851/IMP3037. [Epub ahead of print]

**BACKGROUND:** In the phase 2 SOLAR-1 study, 12 or 24 weeks of ledipasvir-sofosbuvir and ribavirin yielded high SVR12 rates in patients with chronic hepatitis C virus (HCV) infection and advanced liver disease, included untransplanted patients with decompensated cirrhosis; and liver transplant recipients with all stages of liver disease. **METHODS:** We performed a posthoc analysis using data from this study to investigate associations between baseline characteristics

and early on-treatment HCV RNA, and to determine the utility of early virologic response (week 2 and 4) to predict SVR12. Serum HCV RNA was quantified using the Roche COBAS® Ampliprep®/Cobas TaqMan HCV Test, Version 2.0 (CAP/CTM HCV v2.0) v2.0 with a lower limit of quantitation (LLOQ) of 15 IU/mL. **RESULTS:** Most patients achieved HCV RNA <LLOQ by treatment week 4, and target not detected (TND) by week 6. Baseline factors significantly associated with HCV RNA < LLOQ at week 2 were low HCV RNA (<800,000 IU/mL), absence of cirrhosis, age <60 years, and no prior treatment experience. At week four, low HCV RNA, absence of cirrhosis, and IL28B CC were associated with < LLOQ,TND. No baseline factors were associated with week 6 response. There was no association between early on-treatment HCV RNA and SVR12. **CONCLUSIONS:** On treatment HCV RNA quantification is of limited clinical use in patients with advanced liver disease and/or liver transplantation and does not predict SVR12.

Important role of clinical pharmacists with DDI and how can we leverage partnerships, existing ECHO consultation, especially when many PCP offices do not work in conjunction with clinical pharm

**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, et al. Clin Pharmacokinet. 2016 Feb 19. [Epub ahead of print]

**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.

[CD4+CXCR5+ T cells activate CD27+IgG+ B cells via IL-21 in patients with hepatitis C virus infection.](#) Kong FY1, Feng B, Zhang HH, Rao HY, Wang JH, Cong X, Wei L.

Hepatobiliary Pancreat Dis Int. 2016 Feb;15(1):55-64.

**BACKGROUND:** Chronic hepatitis C virus (HCV) infection causes the skewing and activation of B cell subsets, but the characteristics of IgG+ B cells in patients with chronic hepatitis C (CHC) infection have not been thoroughly elucidated. CD4+CXCR5+ follicular helper T (Tfh) cells, via interleukin (IL)-21 secretion, activate B cells. However, the role of CD4+CXCR5+ T cells in the activation of IgG+ B cells in CHC patients is not clear. **METHODS:** The frequency of IgG+ B cells, including CD27-IgG+ B and CD27+IgG+ B cells, the expression of the activation markers (CD86 and CD95) in IgG+ B cells, and the percentage of circulating CD4+CXCR5+ T cells were detected by flow cytometry in CHC patients (n=70) and healthy controls (n=25). The concentrations of serum IL-21 were analyzed using ELISA. The role of CD4+CXCR5+ T cells in the activation of IgG+ B cells was investigated using a co-culture system. **RESULTS:** A significantly lower proportion of CD27+IgG+ B cells with increased expression of CD86 and CD95 was observed in CHC patients. The expression of CD95 was negatively correlated with the percentage of CD27+IgG+ B cells, and it contributed to CD27+IgG+ B cell apoptosis. Circulating CD4+CXCR5+ T cells and serum IL-21 were significantly increased in CHC patients. Moreover, circulating CD4+CXCR5+ T cells from CHC patients induced higher expressions of CD86 and CD95 in CD27+IgG+ B cells in a co-culture system; the blockade of the IL-21 decreased the expression levels of CD86 and CD95 in CD27+IgG+ B cells. **CONCLUSIONS:** HCV infection increased the frequency of CD4+CXCR5+ T cells and decreased the frequency of CD27+IgG+ B cells. CD4+CXCR5+ T cells activated CD27+IgG+ B cells via the secretion of IL-21.

[Plasma and intracellular ribavirin concentrations are not significantly altered by abacavir in hepatitis C virus-infected patients.](#) Fuchs EJ1, Kiser JJ2, Hendrix CW1, et al. J Antimicrob

Chemother. 2016 Feb 10. pii: dkw009. [Epub ahead of print]

**OBJECTIVES:** The objective of this study was to evaluate the effects of abacavir on intracellular ribavirin triphosphate and plasma ribavirin trough concentrations. **METHODS:** Hepatitis C virus-infected subjects who had been cured or failed prior treatment were randomized to 8 weeks of ribavirin alone (N=14; weight-based dosing) or weight-based ribavirin+abacavir (N=14; 300 mg orally every 12 h). Ribavirin trough concentrations were measured on days 14, 28, 42 and 56; PBMCs for ribavirin triphosphate determination were sampled on days 28 and 56, pre-dose and at 6 and 12 h post-dose. ClinicalTrials.gov: NCT01052701. **RESULTS:** Twenty-six subjects completed the study (24 males, 17 Caucasians, median age 52 years); 2 were excluded for missed pharmacokinetic visits. Fourteen subjects received ribavirin+abacavir and 12 received ribavirin alone. Mean±SD plasma ribavirin trough concentrations (µg/mL) on days 14, 28, 42 and 56, respectively, were not significantly different with coadministration of abacavir (1.54±0.60, 1.93±0.54, 2.14±0.73 and 2.54±1.05) compared with ribavirin alone (1.48±0.32, 2.08±0.41, 2.32±0.47 and 2.60±0.62) (P>0.40). Mean ribavirin triphosphate intracellular concentrations (pmol/106 cells) on days 28 and 56, respectively, did not differ statistically between abacavir users (11.98±9.86 and 15.87±12.52) and non-users (15.91±15.58 and 15.93±12.69) (P>0.4). Adverse events were mild or moderate, except for three grade 3 occurrences of transaminitis, cholecystitis and low absolute neutrophil



count that resolved and were judged not attributable to study medications. **CONCLUSIONS:** Abacavir did not significantly alter ribavirin or ribavirin triphosphate concentrations

**Alanine aminotransferase, HCV RNA levels and pro-inflammatory and pro-fibrogenic cytokines/chemokines during acute hepatitis C virus infection.**

Hajarizadeh B1, Lamoury FM2, Feld JJ3, et al. *Virology*. 2016 Feb 24;13(1):32. doi: 10.1186/s12985-016-0482-x.

**BACKGROUND:** This study assessed the association of alanine-aminotransferase (ALT) and hepatitis C virus (HCV) RNA levels with pro-inflammatory and pro-fibrogenic cytokines and chemokines during acute HCV infection to provide further insight into the potential HCV immunopathogenesis. **METHODS:** Participants in the ATACH study, a prospective study of recent HCV infection, with detectable HCV RNA at the time of HCV detection were included. Plasma levels of 27 cytokines and chemokines were measured and their correlation with ALT and HCV RNA levels were assessed. Log10 transformed cytokines and ALT values were used in the analysis. **RESULTS:** Among 117 individuals, the plasma levels of interferon-gamma inducible protein-10 (IP-10) and macrophage inflammatory protein-1beta (MIP-1β) were positively correlated with ALT levels (IP-10:  $r = 0.42$ ,  $P < 0.001$ ; MIP-1β:  $r = 0.29$ ,  $P = 0.001$ ) and HCV RNA levels (IP-10:  $r_s = 0.44$ ,  $P < 0.001$ ; MIP-1β:  $r_s = 0.43$ ,  $P < 0.001$ ). Using linear regression, after adjusting for sex, age, infection duration, symptomatic infection, HIV co-infection, interferon-lambda rs12979860 genotype, HCV genotype, and assay run, higher ALT levels ( $\beta = 0.20$ ; 95 % CI: 0.07, 0.32;  $P = 0.002$ ) and HCV RNA levels  $>400,000$  IU/mL (vs.  $<8,500$  IU/mL;  $\beta = 0.16$ ; 95 % CI: 0.03, 0.28;  $P = 0.014$ ) were independently associated with higher IP-10 levels. HCV RNA levels  $>400,000$  IU/mL (vs.  $<8,500$  IU/mL;  $\beta = 0.16$ ; 95 % CI: 0.01, 0.31;  $P = 0.036$ ) were associated with higher MIP-1β levels. **CONCLUSIONS:** During acute HCV infection, high ALT and HCV RNA levels were associated with increased IP-10 levels, while high HCV RNA levels were also associated with increased MIP-1β levels. These data suggest that IP-10 and MIP-1β may have a role in HCV immuno-pathogenesis starting early in acute HCV infection.

**Integrative role of vitamin D related and Interleukin-28B genes polymorphism in predicting treatment outcomes of Chronic Hepatitis C.**

El-Derany MO1, Hamdy NM2, Al-Ansari NL3, El-Mesallamy HO4. *BMC Gastroenterology*. 2016 Feb 24;16(1):19. doi: 10.1186/s12876-016-0440-5.

**BACKGROUND:** Improving prediction of treatment outcomes in chronic hepatitis C (CHC) genotype 4 (G4) is necessary to increase sustained viral response (SVR) rates. Vitamin D related and interferon stimulated genes are good candidates as they are recently crosstalk altering interferon response. Thus single nucleotide polymorphisms (SNPs) within some of these genes and multiple stepwise regression analysis including other independent predictors (IL28B(rs12979860), serum 25OH-vitamin D, serum alfa-fetoprotein (AFP)) were performed on a cohort of 200 Egyptian CHC patients treated with Pegylated interferon-alpha (Peg-IFN) plus ribavirin. **METHODS:** SNPs in cytochrome P-450 (CYP2R1)(rs10741657AG), vitamin D receptor (VDR)(rs2228570AG, rs1544410CT), oligoadenylate synthetases-like (OASL)(rs1169279CT) and adenosine deaminases acting on RNA (ADAR)(rs1127309TC) genes were analyzed by real-time PCR. **RESULTS:** The carrier state of A allele in VDR rs2228570 and CYP2R1 rs10741657 genes were independently associated with SVR [OR 6.453 & 3.536,  $p < 0.01$  respectively]. Combining carriers of A allele in CYP2R1 and VDR genes with IL28B C/C genotype increased the probability of SVR from 80 % to reach 87.8 %, 93 % and 100 %. No

relation was found between VDR rs1544410CT, ADAR rs1127309TC, OASL rs1169279CT polymorphisms and treatment outcome. Combining VDR rs2228570 A/A genotype with IL28B C/C genotype increased the probability of SVR from 82 % to reach 100 % and from 29 % to reach 80 % in C/T+ T/T IL28B genotype in none F4 liver disease patients. **CONCLUSION:** Vitamin D related (VDR rs2228570 and CYP2R1 rs10741657) and IL28B rs12979860 genes polymorphisms accurately assure SVR in naïve CHC G4 patients treated with low cost standard therapy.

**[Hepatitis C Virus Activates a Neuregulin-Driven Circuit to Modify Surface Expression of Growth Factor Receptors of the ErbB Family.](#)** Stindt S1, Cebula P1, Albrecht U1, et al. PLoS One. 2016 Feb 17;11(2):e0148711. doi: 10.1371/journal.pone.0148711. eCollection 2016.

Recently, the epidermal growth factor (EGF) receptor (EGFR), a member of the ErbB receptor family, and its down-stream signalling have been identified as co-factors for HCV entry and replication. Since EGFR also functions as a heterodimer with other ErbB receptor family members, the subject of the present study was to investigate a possible viral interference with these cellular components. By using genotype 1b replicon cells as well as an infection-based system we found that while transcript and protein levels of EGFR and ErbB2 were up-regulated or unaffected, respectively, HCV induced a substantial reduction of ErbB3 and ErbB4 expression. Down-regulation of ErbB3 expression by HCV involves specificity protein (Sp)1-mediated induction of Neuregulin (NRG)1 expression as well as activation of Akt. Consistently, at transcript level disruption of ErbB3 expression by HCV can be prevented by knockdown of NRG1 or Sp1 expression, whereas reconstitution of ErbB3 protein levels requires inhibition of HCV-induced NRG1 expression and of Akt activity. Interestingly, the NRG1-mediated suppression of ErbB3 expression by HCV results in an enhanced expression of EGFR and ErbB2 on the cell surface, which can be mimicked by siRNA-mediated knockdown of ErbB3 expression. These data delineate a novel mechanism enabling HCV to sway the composition of the ErbB family members on the surface of its host cell by an NRG1-driven circuit and unravels a yet unknown cross-regulation between ErbB3 and the two other family members ErbB2 and EGFR. The shift of the receptor surface expression of the ErbB family towards enhanced expression of ErbB2 and EGFR triggered by HCV was found to promote viral RNA replication and infectivity. This suggests that HCV rearranges expression of ErbB family members to adapt the cellular environment to its requirements.

**[PI3K-Akt signaling pathway upregulates hepatitis C virus RNA translation through the activation of SREBPs.](#)** Shi Q1, Hoffman B2, Liu Q3. Virology. 2016 Mar;490:99-108. doi: 10.1016/j.virol.2016.01.012. Epub 2016 Feb 6.

Hepatitis C virus (HCV) activates PI3K-Akt signaling to enhance entry and replication. Here, we found that this pathway also increased HCV translation. Knocking down the three Akt isoforms significantly decreased, whereas ectopic expression increased HCV translation. HCV translation upregulation by Akt required their kinase activities because Akt kinase-dead mutants downregulated HCV translation; and was dependent on PI3K activity since it was sensitive to PI3K inhibitor wortmannin. The viral 3'UTR was not involved in translation upregulation by Akt. HCV NS5A increased Akt phosphorylation/activity and HCV translation in the absence of the viral 3'UTR. Sterol regulatory element-binding proteins (SREBPs) were the downstream effectors of the PI3K-Akt pathway in regulating HCV translation because Akt1 and Akt2 activated both SREBP-1 and SREBP-2, whereas Akt3 upregulated SREBP-1. Knocking down

SREBPs significantly decreased, while ectopic expression of SREBPs increased HCV translation. Taken together, we showed that the PI3K-Akt signaling pathway positively regulates HCV translation through SREBPs.

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## HIV/HCV COINFECTION

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[IL15 polymorphism is associated with advanced fibrosis, inflammation-related biomarkers and virologic response in HIV/HCV coinfection.](#) Jiménez-Sousa MA<sup>1</sup>, Berenguer J<sup>2,3</sup>, Rallón N<sup>4,5</sup>, et al. *Liver Int.* 2016 Feb 2. doi: 10.1111/liv.13079. [Epub ahead of print]

**BACKGROUND & AIMS:** IL15 is an essential cytokine in both innate and adaptive immune response against HCV infection. The aim was to analyze whether IL15 rs10833 is associated with liver disease severity and response to pegylated-interferon-alpha plus ribavirin (pegIFN-alpha/RBV) therapy in human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients. **METHODS:** A retrospective study was performed in 315 patients who started pegIFN-alpha/RBV therapy. Liver fibrosis stage was characterized in 286 patients. IL15 rs10833 and IL28B rs12980275 were genotyped by GoldenGate. The primary outcomes were: a) advanced liver fibrosis evaluated by liver biopsy (F3-F4) or transient elastography (liver stiffness values  $\geq 9.5$  Kpa); b) sustained virological response (SVR). The secondary outcome variable was the levels of serum biomarkers of inflammation. **RESULTS:** Patients with rs10833 AA genotype had increased odds of having advanced fibrosis (adjusted odds ratio (aOR)=2.30; p=0.019), particularly in males (aOR=2.24; p=0.040), patients with HCV-RNA <500,000 IU/mL (aOR=5.14; p=0.018) and patients with IL28B rs12980275 AG/GG genotypes (aOR=2.51; p=0.046). Moreover, rs10833 AA genotype was significantly associated with higher levels of HGF (adjusted arithmetic mean ratio (aAMR)=1.50; p=0.016), sICAM-1 (aAMR=1.57; p=0.025) and sVCAM-1 (aAMR=1.56; p=0.007). Finally, patients with rs10833 AA genotype had increased odds of achieving SVR (aOR=3.12; p=0.006), particularly in males (aOR=3.69; p=0.005), GT1/4 patients (aOR=3.59; p=0.006), patients with advanced fibrosis (aOR=4.64; p=0.021), HCV-RNA  $\geq 500,000$  IU/mL (aOR=3.92; p=0.007) and patients with IL28B rs12980275 AG/GG genotype (aOR=2.98; p=0.041). **CONCLUSIONS:** The presence of IL15 rs10833 AA genotype in HIV/HCV-coinfected patients was associated with advanced liver fibrosis, inflammation-related biomarkers and increased rates of SVR to pegIFN-alpha/RBV therapy.

[Isolated Hepatitis B Core Antibody Status is not Associated with Accelerated Liver Disease Progression in HIV/Hepatitis C Coinfection.](#) French AL<sup>1</sup>, Hotton A, Young M, et al. *J Acquir Immune Defic Syndr.* 2016 Feb 24. [Epub ahead of print]

**BACKGROUND:** Isolated hepatitis B core antibody (anti-HBc) is a common serologic finding in HIV-infected persons but the clinical significance is uncertain. We studied HIV/HCV infected women over time to determine if the trajectory of liver disease progression (LDP) is affected by isolated anti-HBc serologic status. **METHODS:** We performed serial Enhanced Liver Fibrosis (ELF) markers on HIV/HCV coinfecting women to assess LDP trajectory over time comparing women with isolated anti-HBc to women with either negative HB serologies, anti-HBs alone or anti-HBc and anti-HBs. ELF, a serum marker that combines direct markers of extracellular matrix remodeling and fibrosis, was performed on serum stored biannually. Women with at least 3 ELF determinations and persistent HCV RNA positivity were included. **RESULTS:** 344 women, including 132 with isolated anti-HBc and 212 with other serologic findings were

included. A median of 6 (IQR 5-7) biannual ELF values were available for each woman, totaling 2119 visits. ELF increased over time from a median of 9.07 for women with isolated anti-HBc and 9.10 for those without to 9.83 and 9.88 respectively with no difference in degree of change or slope in the mixed effect model including age, race, CD4 count, antiretroviral therapy (ART), drug and alcohol use. Factors independently associated with LDP were older age, lower CD4, ART non-use and Hispanic ethnicity. **CONCLUSION:** Isolated anti-HBc serologic status was not associated with accelerated liver disease progression over a median of 9.5 years among HIV/HCV coinfecting women.

**Sofosbuvir and Ledipasvir for HIV/HCV Co-infected Patients.** Rosenthal ES1, Kottlilil S2, Polis MA3. Expert Opin Pharmacother. 2016 Feb 21. [Epub ahead of print]

**INTRODUCTION:** Hepatitis C virus (HCV) is a chronic infection that disproportionately impacts people living with HIV. In the past, HCV therapy was less effective in individuals with HIV co-infection. However, the advent of direct-acting antivirals has revolutionized HCV treatment with high rates of success in patients both with and without HIV. Areas covered: In this paper, we review the evidence supporting the use of ledipasvir and sofosbuvir (LDV/SOF) for the treatment of HCV in patients with HIV co-infection. Articles searchable on MEDLINE/PubMed were reviewed to provide context for use of LDV/SOF in individuals with HCV and HIV co-infection. Expert opinion: This treatment is highly effective in achieving HCV cure or sustained virologic response, however further studies need to be done to address efficacy of treatment in people with uncontrolled HIV, concerns regarding drug-interactions with antiretroviral therapy, and potential for shorter duration treatment.

**Soluble Adhesion Molecules in Patients Coinfected with HIV and HCV: A Predictor of Outcome.** Aldámiz-Echevarría T1,2, Berenguer J1,2, Miralles P1,2, et al. PLoS One. 2016 Feb 5;11(2):e0148537. doi: 10.1371/journal.pone.0148537. eCollection 2016.

**BACKGROUND:** Higher serum levels of adhesion molecules (sICAM-1 and sVCAM-1) are associated with advanced liver fibrosis in patients coinfecting with human immunodeficiency virus and hepatitis C virus. We assessed the relationship between serum levels of adhesion molecules and liver-related events (LRE) or death, in coinfecting patients. **METHODS:** We studied clinical characteristics and outcomes of 182 coinfecting patients with a baseline liver biopsy (58 with advanced fibrosis) and simultaneous plasma samples who were followed for median of 9 years. We used receiver-operating characteristic (ROC) curves to calculate optimized cutoff values (OCV) of sICAM-1 and sVCAM-1, defined as the values with the highest combination of sensitivity and specificity for LRE. We used multivariate regression analysis to test the association between OCVs of sICAM-1 and sVCAM-1 and outcomes. The variables for adjustment were age, HIV transmission category, liver fibrosis, baseline CD4+ T-cell counts, antiretroviral therapy, and sustained virologic response (SVR). **RESULTS:** During the study period 51 patients had SVR, 19 had LRE, and 16 died. The OCVs for LRE were 5.68 Log pg/mL for sICAM-1 and 6.25 Log pg/mL for sVCAM-1, respectively. The adjusted subhazard ratio (aSHR) (95% confidence interval [CI]) of death or LRE, whichever occurred first, for sICAM-1 and sVCAM-1 > OCV were 3.98 ([1.14; 13.89], P = 0.030) and 2.81 ([1.10; 7.19], respectively (P = 0.030). **CONCLUSIONS:** Serum levels of sICAM-1 and sVCAM-1 can serve as markers of outcome in HIV/HCV-coinfecting patients. Therapies targeting necroinflammatory damage and fibrogenesis may have a role in the management chronic hepatitis C.



### Impact of Hepatitis C Virus on the Circulating Levels of IL-7 in HIV-1 Coinfected Women.

Kerzerho J1, McIlvaine EJ, Anthony P, et al. J Acquir Immune Defic Syndr. 2016 Feb 1;71(2):172-80. doi: 10.1097/QAI.0000000000000832.

**OBJECTIVES:** Hepatitis C virus (HCV) infection causes an alteration in T-cell maturation and activation in patients coinfecting with human immunodeficiency virus (HIV). Because interleukin 7 (IL-7) is a major cytokine controlling T-cell homeostasis, we analyzed the potential influence of HCV coinfection on circulating IL-7 levels in HIV-infected women before and after highly active antiretroviral therapy (HAART). **DESIGN AND METHODS:** This prospective study included 56 HIV monoinfected, 55 HIV/HCV coinfecting without HCV viremia, 132 HIV/HCV coinfecting with HCV viremia, and 61 HIV/HCV-uninfected women for whom plasma levels of IL-7 were determined by enzyme-linked immunosorbent assay at 1 or more follow-up visits before and after HAART. Cross-sectional analyses of the associations between plasma IL-7 levels and HCV infection, demographic, clinical, and immunologic characteristics were evaluated using univariate and multivariate linear regression models before and after HAART. **RESULTS:** In multivariate models, IL-7 levels were significantly higher in coinfecting HCV viremic women than in HIV monoinfected women (multiplicative effect = 1.48; 95% confidence interval: 1.01 to 2.16;  $P = 0.04$ ) before HAART, but were similar between these two groups among women after HAART. In addition to HCV viremia, higher IL-7 levels were associated with older age ( $P = 0.02$ ), lower CD4 T-cell count ( $P = 0.0007$ ), and higher natural killer T-cell count ( $P = 0.02$ ) in women before HAART. Among HAART-treated women, only lower CD4 T-cell count was significantly associated with IL-7 level ( $P = 0.006$ ). **CONCLUSIONS:** Our data demonstrate that in HIV-infected women, circulating levels of IL-7 are strongly associated with CD4 T-cell depletion both before and after HAART. Our data also demonstrate that HCV viremia increases circulating IL-7 levels before HAART but not after HAART in coinfecting women. This suggests that the effect of HCV on lymphopenia is abrogated by HAART.

Knowing that HCV treatment can be a relatively short duration of time, what are the salient HCV knowledge points we would want to share with patients that may contribute to appointment-keeping behaviors? Do you see these knowledge points changing based on patient populations?

### Health Beliefs and Co-morbidities Associated with Appointment-Keeping Behavior Among HCV and HIV/HCV Patients.

Pundhir P1, North CS2, Fatunde O1, Jain MK3,4. J Community Health. 2016 Feb;41(1):30-7. doi: 10.1007/s10900-015-0059-4.

Appointment-keeping behavior is an important requisite for HCV linkage and treatment initiation. In this study we examine what impact hepatitis C (HCV) knowledge and attitudes has on appointment-keeping behavior among a cohort of HCV and HCV/HIV patients. Knowledge scores and attitude scales, obtained from a cross-sectional survey, were correlated with proportion of appointments kept 1 year prior to taking the survey. Independent risk factors for missing appointments were examined by multiple regression analysis. 292 HCV patients completed the survey, and 149 (51 %) were co-infected with HIV. HCV patients kept  $67.5 \pm 17.4$  % of their total appointments and a similar proportion ( $67 \pm 38.2$ ) of Liver Clinic appointments, but they attended a higher proportion ( $73 \pm 24.4$ ) of Primary Care Clinic appointments. However, certain health beliefs, psychiatric illness, and HIV co-infection were independently associated with lower levels of appointment-keeping behavior. HCV knowledge was not associated with appointment-keeping behavior. Health beliefs, psychiatric illness, and HIV co-infection are associated with missing appointments, but no link between knowledge and appointment keeping behavior is apparent. In order to increase engagement into HCV care, HCV

care coordination programs need to focus on addressing health beliefs and providing resources to those at highest risk for missing appointments.

[High serum HCV RNA in chronic hepatitis C patients coinfecting with HIV despite successful antiretroviral therapy.](#) Barreiro P1, Labarga P, de Mendoza C, et al. *Antivir Ther.* 2016 Feb 18. doi: 10.3851/IMP3038. [Epub ahead of print]

**BACKGROUND:** Baseline serum HCV-RNA predicts treatment success in chronic hepatitis C patients. Thresholds at 0.8, 2, 4 and 6 million IU/mL discriminate treatment outcomes using distinct antiviral regimens. Compared to the general population, immunosuppressed individuals exhibit greater viral load values. This has been confirmed in HIV-HCV coinfecting patients, although little is known about the influence of antiretroviral therapy. **METHODS:** Serum HCV-RNA results recorded from all chronic hepatitis C patients consecutively attended at our clinic were analyzed. **RESULTS:** A total of 813 patients with detectable HCV-RNA were identified. HIV coinfection was present in 78.7%, of whom 91% were on antiretroviral therapy. Overall, 467 (57%), 273 (34%), 170 (21%) and 127 (16%) had HCV-RNA >0.8, >2, >4 and >6 million IU/mL, respectively. These high viral load values were found in 60%/36%/23%/18% of HIV-positive versus 43%/25%/11%/6% of HIV-negatives ( $p < 0.01$ ). In multivariate analysis, the greatest HCV-RNA values were only significantly associated with HIV coinfection and HCV genotypes 1 or 4. Greater HCV-RNA values were paradoxically found in HIV patients on than off antiretroviral therapy. **CONCLUSIONS:** Serum HCV-RNA values above 0.8, 2, 4 and 6 million IU/mL are roughly seen in 43%, 25%, 11% and 6% of chronic hepatitis C mono-infected patients, respectively. Despite being on antiretroviral therapy, the corresponding figures are 1.3 to 3.0-fold greater in HIV-HCV coinfecting patients, who may benefit less frequently from shorter oral HCV treatment lengths.

[Daclatasvir and Sofosbuvir Versus Sofosbuvir and Ribavirin in Patients with Chronic Hepatitis C Coinfecting with HIV: A Matching-adjusted Indirect Comparison.](#) Swallow E1, Song J2, Yuan Y3, et al. *Clin Ther.* 2016 Feb;38(2):404-12. doi: 10.1016/j.clinthera.2015.12.017. Epub 2016 Feb 3.

**PURPOSE:** Our aim was to compare the efficacy and tolerability of daclatasvir plus sofosbuvir (DCV+SOF) versus SOF plus ribavirin (SOF+R) in patients coinfecting with HIV and hepatitis C virus (HCV). **METHODS:** A systematic literature review of Phase III clinical trials identified 2 trials of SOF+R-PHOTON-1 (A Phase 3, Open-Label Study to Investigate the Efficacy and Safety of GS-7977 Plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus [HCV] and Human Immunodeficiency Virus [HIV] Co-Infected Subjects) and PHOTON-2 (A Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Chronic Genotype 1, 2, 3 and 4 Hepatitis C Virus [HCV] and Human Immunodeficiency Virus [HIV] Co-Infected Subjects) suitable for comparison with the trial of DCV+SOF in patients coinfecting with HIV and HCV-ALLY-2 (A Phase 3 Evaluation of Daclatasvir Plus Sofosbuvir in Treatment-naïve and Treatment-experienced Chronic Hepatitis C [Genotype 1, 2, 3, 4, 5, or 6] Subjects Coinfecting With Human Immunodeficiency Virus [HIV]). Individual patient data from ALLY-2 were available; published summary data were extracted and pooled for the PHOTON trials. To adjust for cross-trial differences, ALLY-2 patients were subject to the inclusion and exclusion criteria reported in the PHOTON trials and were weighted to match all available summary baseline characteristics reported in both PHOTON trials. Sustained virologic response at week 12 post-treatment (SVR12) discontinuation due to adverse events (AEs) and rates of AEs were

compared. **FINDINGS:** The SVR12 rate was significantly higher among patients treated with DCV+SOF (n = 91) than among those treated with SOF+R (n = 455) both before (96.7% vs 84.6%; P = 0.002) and after (99.9% vs 84.6%; P < 0.001) adjusting for baseline characteristics. After adjustment, compared with patients treated with SOF+R, patients receiving DCV+SOF had a significantly lower rate of discontinuation due to AEs and significantly lower rates of the following specific AEs: cough, diarrhea, insomnia, nasopharyngitis, upper respiratory tract infection, and hemoglobin <10 g/dL. **IMPLICATIONS:** After adjustment for cross-trial differences in baseline characteristics, DCV+SOF was associated with a significantly higher SVR12 rate and lower rate of discontinuation due to AEs than SOF+R in patients coinfecting with HIV and HCV.

**Hepatitis C Screening in People With Human Immunodeficiency Virus: Lessons Learned From Syphilis Screening.** Wurcel AG1, Chen DD2, Fitzpatrick RE2, et al. Open Forum Infect Dis. 2016 Feb 12;3(1):ofv215. doi: 10.1093/ofid/ofv215. eCollection 2016.

**Background.** The incidence of hepatitis C virus (HCV) infection is increasing in human immunodeficiency virus (HIV)-positive men who have sex with men (MSM). New guidelines recommend annual screening for HCV, similar to recommendations for syphilis screening with rapid plasma reagin (RPR). **Methods.** This study compares the frequency of repeat HCV antibody (Ab) testing to repeat RPR testing in a retrospective chart review of 359 HCVAbs-negative people living with HIV (PLWH) observed in an Infectious Diseases clinic. Patients were classified into risk groups based on sexual risk factors. **Results.** Although 85% of PLWH had repeat syphilis screening, less than two thirds had repeat HCVAbs screening. The MSM status was associated with increased HCVAbs and RPR testing (adjusted odds ratio, 2.6 and 5.9, respectively). Seven persons had incident HCV infection: 3 were MSM, and 4 had symptoms or abnormal laboratory results to prompt testing. **Conclusions.** Failure to find incident HCV infection in PLWH represents missed opportunities to cure HCV infection and prevent progressive liver disease. Further quality improvement studies are necessary to develop physician-focused interventions to increase HCV screening rates in PLWH.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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**Anti-hepatitis C Virus Natural Product from a Fungus, Penicillium herquei.** Nishikori S, Takemoto K, Kamisuki S, et al. J Nat Prod. 2016 Feb 26;79(2):442-6. doi: 10.1021/acs.jnatprod.5b00555. Epub 2016 Feb 5.

New diazabicyclo[2.2.2]octane derivatives, penicilerquamides A-C (1-3), and a novel herqueinone derivative, neoherqueinone (5), were isolated from a fungal culture broth of *Penicillium herquei*. The structures of these novel compounds were determined by interpretation of spectroscopic data (1D/2D NMR, MS, and IR). Four known compounds, preparaherquamide (4), penicilerqueinone (6), and herqueinone/isoherqueinone (7/7a), were also obtained. The isolated compounds were tested for anti-hepatitis C virus (HCV) activity, and penicilerquamide C (3) was found to display an IC<sub>50</sub> value of 5.1 μM. To our knowledge, this is the first report of a diazabicyclo[2.2.2]octane derivative with anti-HCV activity.

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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[An assessment of concurrent drug and alcohol use among patients seeking treatment for hepatitis C.](#) Sims OT1, Pollio DE, Hong BA, Jain MK, Brown GR, North CS. *Ann Clin Psychiatry*. 2016 Feb;28(1):31-6.

**BACKGROUND:** The purpose of this study was to assess the one-year prevalence of drug use and of concurrent alcohol use among hepatitis C (HCV) patients seeking treatment from specialty HCV clinics. **METHODS:** Patients with confirmed HCV RNA considering HCV treatment (N = 309) were recruited from university-affiliated and Veterans Affairs medical centers. **RESULTS:** The prevalence of current drug use in the last year was 65% (201/309) among patients considering HCV treatment. More than one-fourth of the sample used drugs at some time in their lives but none in the last year. Only 7% (22/309) of patients reported no lifetime drug use. The prevalence of concurrent drug and alcohol use in the last year was 72% (145/201) and 52% (105/201) in the last month. **CONCLUSIONS:** More than half of current drug users were still consuming alcohol in the last month despite the fact that they had all been informed of the potential for accelerated liver damage from continued alcohol use. This finding suggests that achieving abstinence from drug use does not necessarily imply that abstinence from alcohol has been obtained. Integration of substance treatment and HCV treatment into a unified disease management approach might increase treatment eligibility and compliance and improve disease outcomes.

Individualized clinical information improved adherence...what specific elements should be considered in an individualised plan for a patient? Should that too change based on patient?

[Listening to both sides: A qualitative comparison between patients with hepatitis C and their healthcare professionals' perceptions of the facilitators and barriers to hepatitis C treatment adherence and completion.](#) Sublette VA1, Smith SK2, George J1, McCaffery K3, Douglas MW4. *J Health Psychol*. 2016 Feb 8. pii: 1359105315626786. [Epub ahead of print]

This qualitative study compares and contrasts the perspectives of healthcare professionals who treat hepatitis C with those of patients in treatment. Comparative analysis of semi-structured interviews with 20 healthcare professionals and 20 patients undergoing treatment for hepatitis C concluded that patients and healthcare professionals disagreed on the source of communication breakdowns, but both felt that individualised clinical information improved adherence. Stigma was recognised as a barrier to treatment adherence by both patients and healthcare professionals. Limitations of the healthcare system, such as patients receiving inconsistent information and long wait times, negatively impacted both patients and providers.

[Spouse-to-Spouse Transmission and Evolution of Hypervariable Region 1 and 5' Untranslated Region of Hepatitis C Virus Analyzed by Next-Generation Sequencing.](#)

Caraballo Cortes K1, Zagordi O2, Jabłońska J3, et al. *PLoS One*. 2016 Feb 26;11(2):e0150311. doi: 10.1371/journal.pone.0150311.

Hepatitis C virus (HCV) transmission between spouses remains poorly characterized, largely due to the limited availability of samples from the early stage of infection, as well as methodological constraints. A fifty-eight year-old male developed acute hepatitis C infection and his 53-year old spouse has been HCV-positive for over 10 years. Serum samples were collected from both at the time of acute hepatitis C diagnosis in male (baseline) and then at 9 and 13 months. Hypervariable region 1 (HVR1) and 5' untranslated region (5'UTR) sequences were amplified and subjected to next generation sequencing (NGS) using a pyrosequencing platform. Genetic variants were inferred by Shorah reconstruction method and compared by phylogenetic and sequence diversity analysis. As the sequencing error of the procedure was previously determined to be  $\leq 1.5\%$ , the



analysis was conducted with and without the 1.5% cut-off with regard to the frequency of variants. No identical HVR1 variants were identified in spouses at baseline and follow-up samples regardless whether the cut-off was applied or not. However, there was high similarity (98.3%) between a minor baseline donor variant (1.7% frequency) and the most abundant baseline recipient variant (62.5% frequency). Furthermore, donor and recipient strains clustered together when compared to 10 control subjects from the same area and infected with the same HCV subtype. There was an increase in HVR1 complexity (number of genetic variants) over time in both spouses. In contrast, the 5'UTR region was stable and of low complexity throughout the study. In conclusion, intrafamilial HCV transmission may be established by a very minor variant and investigation of this phenomenon requires high-sensitivity assays, such as NGS.

Issues of access to patient chart; impact of testing and informing of result if no treatment, or difficult to access treatment, is the only thing available?

**Awareness of Hepatitis C Virus Seropositivity and Chronic Infection in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).** Kuniholm MH1, Jung M2, Del Amo J3, et al. J Immigr Minor Health. 2016 Feb 10. [Epub ahead of print]

Few population-based studies have assessed awareness of hepatitis C virus (HCV) seropositivity and chronic infection. We report awareness of HCV seropositivity and chronic infection and correlates of awareness in a multi-city (Bronx, Miami, Chicago, and San Diego) community-dwelling population sample of United States (US) Hispanics/Latinos recruited during 2008-2011. Included were 260 HCV-seropositive participants, among whom 190 had chronic HCV. Among those with chronic HCV, 46 % had been told by a doctor that they had liver disease and 32 % had been told that they had HCV-related liver disease. Among those with chronic HCV who also lacked health insurance (37 % of those with chronic HCV), only 8 % had been told that they had HCV-related liver disease. As compared with the uninsured, those with insurance were over five times more likely to be aware of having HCV-related liver disease (44 %). Sex, age, education, city of residence, and birthplace were not associated with HCV awareness. Less than half of Hispanics/Latinos were aware of their HCV chronic infection. Lack of health insurance may be an important barrier to HCV awareness in this population.

**Streamlining Screening to Treatment: The Hepatitis C Cascade of Care at Kaiser Permanente Mid-Atlantic States.** Jonas MC1, Rodriguez CV2, Redd J3, Sloane DA3, Winston BJ3, Loftus BC4. Clin Infect Dis. 2016 Feb 16. pii: ciw086. [Epub ahead of print]

Hepatitis C virus (HCV) screening is recommended for patients at-risk and/or born 1945-1965, but screening gaps persist. This new program screens target populations and enhances care linkage for chronically HCV-infected patients. Kaiser Permanente Mid-Atlantic States created a comprehensive HCV screening pathway, supported by a HCV Care Coordinator. The testing pathway includes HCV antibody (Ab), automatic HCV RNA for Ab+ patients, co-infection and liver health tests, vibration controlled transient elastography (VCTE), and a physician referral. 11,200 patients were screened. 3.25% were HCV Ab+; 100% of Ab+ patients received HCV RNA testing. 75.3% of HCV Ab+ had chronic HCV, of which 80.8% underwent VCTE. HCV diagnosis was communicated to 94% of patients. 70.9% had HCV documented in the electronic health record. The pathway shows promise in closing gaps, including improving HCV RNA testing, communicating diagnoses, and assessing liver fibrosis. Improved testing and linkage could increase curative treatment access.

### [HCV kinetic and modeling analyses indicate similar time to cure among sofosbuvir combination regimens with daclatasvir, simeprevir or ledipasvir.](#)

Dahari H1, Canini L2, Graw F3, et al. J Hepatol. 2016 Feb 20. pii: S0168-8278(16)00153-7. doi: 10.1016/j.jhep.2016.02.022. [Epub ahead of print]

**BACKGROUND&AIMS:** Recent clinical trials of direct-acting-antiviral agents (DAAs) against hepatitis C virus (HCV) achieved >90% sustained-virological response (SVR) rates, suggesting that cure often took place before the end of treatment (EOT). We sought to evaluate retrospectively whether early response kinetics can provide the basis to individualize therapy to achieve optimal results while reducing duration and cost. **METHODS:** 58 chronic-HCV patients were treated with 12-week sofosbuvir+simeprevir(n=19), sofosbuvir+daclatasvir(n=19), or sofosbuvir+ledipasvir in three French referral centers. HCV was measured at baseline, day 2, every other week, EOT and 12 weeks post EOT. Mathematical modeling was used to predict the time to cure, i.e., <1 virus copy in the entire extracellular-body fluid. **RESULTS:** All but one patient who relapsed achieved SVR. Mean age was 60±11 years, 53% were male, 86% HCV genotype-1, 9% HIV coinfecting, 43% advanced fibrosis (F3), and 57% had cirrhosis. At weeks 2, 4 and 6, 48%, 88% and 100% of patients had HCV<15 IU/ml, with 27%, 74% and 91% of observations having target-not-detected, respectively. Modeling results predicted that 23(43%), 16(30%), 7(13%), 5(9%) and 3(5%) subjects were predicted to reach cure within 6, 8, 10, 12 and 13 weeks of therapy, respectively. The modeling suggested that the patient who relapsed would have benefitted from an additional week of sofosbuvir+ledipasvir. Adjusting duration of treatment according to the modeling predicts reduced medication costs of 43%-45% and 17%-30% in subjects who had HCV<15 IU/ml at weeks 2 and 4, respectively. **CONCLUSIONS:** The use of early viral-kinetic analysis has the potential to individualize duration of DAA therapy with a projected average cost-saving of 16%-20% per 100-treated persons.

### [Broad anti-HCV antibody responses are associated with improved clinical disease parameters in chronic HCV infection.](#)

Swann RE1, Cowton VM1, Robinson MW2, et al. J Virol. 2016 Feb 24. pii: JVI.02669-15. [Epub ahead of print]

During hepatitis C virus (HCV) infection broadly neutralizing antibody (bNAbs) responses targeting E1E2 envelope glycoproteins are generated in many individuals. It is unclear if these antibodies play a protective or a pathogenic role during chronic infection. In this study, we investigated whether bNAbs responses in individuals with chronic infection were associated with differences in clinical presentation. Patient-derived purified serum IgG was used to assess the breadth of HCV E1E2 binding and neutralization activity of HCV pseudoparticles. Two panels were compared, bearing viral envelope proteins representing either an inter-genotype or an intra-genotype (gt) 1 group. We found that HCV viral load was negatively associated with strong cross-genotypic E1E2 binding (P=0.03). Overall we observed only modest correlation between total E1E2 binding and neutralizing ability. The breadth of inter-genotype neutralization did not correlate with any clinical parameters, however, analysis of individuals with gt 1 HCV infection (n=20), using an intra-genotype pseudoparticle panel, found a strong association between neutralization breadth and reduced liver fibrosis (P=0.006). Broad bNAbs response in our chronic cohort was associated with a single nucleotide polymorphism (SNP) in the HLA-DQB1 gene (P=0.038) as previously reported in an acute cohort. Furthermore bNAbs in these individuals targeted more than one region of E2 neutralizing epitopes as assessed through cross-competition of patient bNAbs with well-characterized E2 antibodies. We conclude that bNAbs responses in chronic gt1 infection are associated with lower rates of fibrosis and host genetics may play a role

in the ability to raise such responses. **IMPORTANCE:** Globally there are 130-150 million people with chronic HCV infection. Typically the disease is progressive and is a major cause of severe liver cirrhosis and hepatocellular carcinoma. While it is known that neutralizing antibodies have a role in spontaneous clearance during acute infection, little is known about their role in chronic infection. In the present work we investigate the antibody response in a cohort of chronically infected individuals and find that a broad neutralizing antibody response is protective, with reduced levels of liver fibrosis and cirrhosis. We also find an association with SNPs in class II HLA genes and the presence of a broad neutralizing response indicating that antigen presentation may be important for production of HCV neutralizing antibodies.

**[Addressing barriers to the prevention, diagnosis and treatment of hepatitis B and C in the face of persisting fiscal constraints in Europe: report from a high level conference.](#)**

Papatheodoridis G1, Thomas HC2, Golna C3, et al. J Viral Hepat. 2016 Feb;23 Suppl 1:1-12. doi: 10.1111/jvh.12493.

In the WHO-EURO region, around 28 million people are currently living with chronic viral hepatitis, and 120 000 people die every year because of it. Lack of awareness and understanding combined with the social stigma and discrimination exacerbate barriers related to access to prevention, diagnosis and treatment services for those most in need. In addition, the persisting economic crisis has impacted on public health spending, thus posing challenges on the sustainable investment in promotion, primary and secondary prevention, diagnosis and treatment of viral hepatitis across European countries. The Hepatitis B and C Public Policy Association in cooperation with the Hellenic Center for Disease Prevention and Control together with 10 partner organizations discussed at the Athens High Level Meeting held in June 2014 recent policy developments, persisting and emerging challenges related to the prevention and management of viral hepatitis and the need for a de minimis framework of urgent priorities for action, reflected in a Call to Action (Appendix S1). The discussion confirmed that persisting barriers do not allow the full realisation of the public health potential of diagnosing and preventing hepatitis B and C, treating hepatitis B and curing hepatitis C. Such barriers are related to (a) lack of evidence-based knowledge of hepatitis B and C, (b) limited access to prevention, diagnosis and treatment services with poor patient pathways, (c) declining resources and (d) the presence of social stigma and discrimination. The discussion also confirmed the emerging importance of fiscal constraints on the ability of policymakers to adequately address viral hepatitis challenges, particularly through increasing coverage of newer therapies. In Europe, it is critical that public policy bodies urgently agree on a conceptual framework for addressing the existing and emerging barriers to managing viral hepatitis. Such a framework would ensure all health systems share a common understanding of definitions and indicators and look to integrate their responses to manage policy spillovers in the most cost-effective manner, while forging wide partnerships to sustainably and successfully address viral hepatitis.

**[Public health clinic-based hepatitis C testing and linkage to care in Baltimore.](#)**

Falade-Nwulia O1,2, Mehta SH3, Lasola J1, et al. J Viral Hepat. 2016 Feb 3. doi: 10.1111/jvh.12507. [Epub ahead of print]

Testing and linkage to care are important determinants of hepatitis C virus (HCV) treatment effectiveness. Public health clinics serve populations at high risk of HCV. We investigated their potential to serve as sites for HCV testing, initiation of and linkage to HCV care. Cross-sectional study of patients accessing sexually transmitted infection (STI) care at the Baltimore City Health

Department (BCHD) STI clinics, from June 2013 through April 2014 was conducted. Logistic regression was used to assess factors associated with HCV infection and specialist linkage to care. Between 24 June 2013 and 15 April 2014, 2681 patients were screened for HCV infection. Overall, 189 (7%) were anti-HCV positive, of whom 185 (98%) received follow-up HCV RNA testing, with 155 (84%) testing RNA positive. Of 155 RNA-positive individuals, 138 (89%) returned to the STI clinic for HCV RNA results and initial HCV care including counselling regarding transmission and harm reduction in alcohol, and 132 (85%) were referred to a specialist for HCV care. With provision of patient navigation services, 81 (52%) attended an offsite HCV specialist appointment. Alcohol use and lack of insurance coverage were associated with lower rates of specialist linkage (OR 0.4 [95% CI 0.1-0.9] and OR 0.4 [95% CI 0.1-0.9], respectively). We identified a high prevalence of HCV infection in BCHD STI clinics. With availability of patient navigation services, a large proportion of HCV-infected patients linked to off-site specialist care.

[New prospects for the treatment and prevention of hepatitis C in children.](#) Ohmer S1, Honegger J. *Curr Opin Pediatr.* 2016 Feb;28(1):93-100. doi: 10.1097/MOP.0000000000000313. **PURPOSE OF REVIEW:** Combined pegylated interferon- $\alpha$  and ribavirin remains the standard therapy for pediatric hepatitis C virus (HCV) infections in 2016, but direct-acting antivirals (DAAs) with greatly improved efficacy and safety are now approved for adults. Here we review the major classes of DAAs and their anticipated use for treatment and potentially prevention of HCV in children. **RECENT FINDINGS:** Currently approved DAAs target the viral protease, polymerase, and NS5A, a protein involved in viral replication and assembly. In combination, DAAs have lifted sustained virologic response rates in adults to more than 90% for multiple HCV genotypes, and the rich DAA pipeline promises further improvements. Clinical trials of interferon-free DAA regimens have been initiated for children ages 3-17 years. In 2016, the first efficacy trial of a preventive HCV vaccine is also underway. While awaiting a vaccine, there is hope that increased DAA utilization may prevent pediatric HCV infections by shrinking the pool of infectious persons. **SUMMARY:** Interferon-free DAA regimens have revolutionized therapy for HCV-infected adults and, pending results of pediatric trials, will likely do the same for HCV-infected children. If widely deployed, DAA therapies may also help to reduce the number of new vertically and horizontally acquired pediatric infections.

[Drug-Drug Interactions with the NS3/4A Protease Inhibitor Simeprevir.](#) Ouwerkerk-Mahadevan S1, Snoeys J2, Peeters M3, Beumont-Mauviel M3, Simion A3. *Clin Pharmacokinet.* 2016 Feb;55(2):197-208. doi: 10.1007/s40262-015-0314-y. Simeprevir is an NS3/4A protease inhibitor approved for the treatment of hepatitis C infection, as a component of combination therapy. Simeprevir is metabolized by the cytochrome P450 (CYP) system, primarily CYP3A, and is a substrate for several drug transporters, including the organic anion transporting polypeptides (OATPs). It is susceptible to metabolic drug-drug interactions with drugs that are moderate or strong CYP3A inhibitors (e.g. ritonavir and erythromycin) or CYP3A inducers (e.g. rifampin and efavirenz); coadministration of these drugs may increase or decrease plasma concentrations of simeprevir, respectively, and should be avoided. Clinical studies have shown that simeprevir is a mild inhibitor of CYP1A2 and intestinal CYP3A but does not inhibit hepatic CYP3A. The effects of simeprevir on these enzymes are of clinical relevance only for narrow-therapeutic-index drugs that are metabolized solely by these enzymes (e.g. oral midazolam). Simeprevir does not have a clinically relevant



effect on the pharmacokinetics of rilpivirine, tacrolimus, oral contraceptives and several other drugs metabolized by CYP enzymes. Simeprevir is a substrate and inhibitor of the transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and OATP1B1/3. Cyclosporine is an inhibitor of OATP1B1/3, BCRP and P-gp, and a mild inhibitor of CYP3A; cyclosporine causes a significant increase in simeprevir plasma concentrations, and coadministration is not recommended. Clinical studies have demonstrated increases in coadministered drug concentrations for drugs that are substrates of the OATP1B1/3, BCRP (e.g. rosuvastatin) and P-gp (e.g. digoxin) transporters; these drugs should be administered with dose titration and or/close monitoring.

**Symptoms of anxiety and depression are frequent in patients with acute hepatitis C and are not associated with disease severity.**

Deterding K1, Grüner N, Buggisch P, et al. Eur J Gastroenterol Hepatol. 2016 Feb;28(2):187-92. doi: 10.1097/MEG.0000000000000517.

**OBJECTIVE:** Neuropsychiatric symptoms of hepatitis C virus (HCV) infection and during peginterferon  $\alpha$  therapy have been investigated in the chronic stage of the infection, but have not been described during the acute phase of the disease so far. We therefore evaluated anxiety and depression in patients with acute hepatitis C by the Hospital Anxiety and Depression Scale (HADS) within a clinical trial. **METHODS:** Data were analysed from the German Hep-Net Acute HCV-III study. Anxiety and depression were characterized by an anxiety (HADS-A) and a depression subscale (HADS-D). More than eight points in each subscale were considered clinically relevant. Data were prospectively collected at baseline, end of treatment and at the end of the study. **RESULTS:** At baseline, a HADS-A above eight points was observed significantly more frequently than a HADS-D above eight points [n=23/103 (22%) vs. n=12/103 (12%); P=0.041]. A pathological HADS-A or HADS-D score did not correlate with age, sex, IL28B genotype, the probable mode of infection, HCV genotype or severity of disease as investigated by alanine aminotransferase and bilirubin levels. Antiviral therapy did not influence anxiety as 12/50 (24%) of patients had HADS-A above 8 at the end of therapy. The proportion of patients with HADS-D above eight points increased from 12% at baseline to 24% (n=12/50) at the end of therapy (P=0.06). HADS results were not associated with lost to follow-up or sustained virological response rates. **CONCLUSION:** HADS data in acute HCV infection indicate that anxiety and depression do not correlate with severity of the disease, mode of acquisition, lost to follow-up and sustained virological response rates.

**Relationship of hepatic fibrosis, cirrhosis, and mortality with cholecystectomy in patients with hepatitis C virus infection.**

Martin DJ1, Weideman R, Crook T, Brown G. Eur J Gastroenterol Hepatol. 2016 Feb;28(2):181-6. doi: 10.1097/MEG.0000000000000512.

**OBJECTIVES:** Studies have suggested that cholecystectomy is a risk factor for nonalcoholic fatty liver disease, but it is not known whether cholecystectomy is a risk factor for the progression of other chronic liver diseases such as hepatitis C virus (HCV) infection. The aim of this study was to assess whether cholecystectomy is associated with an increase in fibrosis, cirrhosis, and cirrhosis-related complications in patients with chronic HCV infection. **METHODS:** Among a total of 3989 HCV-positive patients at the VA North Texas Health Care System, we retrospectively reviewed the records of 88 patients who had undergone cholecystectomy between 1998 and 2013, followed up for a median of 4.9 years. We compared the outcomes of these patients with those of two age-matched, race-matched, and sex-matched cohorts: a cohort consisting of 129 HCV-positive patients without gallbladder disease (GBD) and

a second cohort consisting of 178 HCV-positive patients with GBD who had not undergone cholecystectomy. Demographics, presence of metabolic syndrome, alcohol use, laboratory data, and clinical progression of liver disease were compared at study entry and 5 years later.

**RESULTS:** Controlling for multiple factors associated with increase in liver fibrosis, analyses confirmed that there was an increase in the proportion of patients who developed cirrhosis [odds ratio (OR)=3.24, 95% confidence interval (CI) 1.57-6.68, P=0.001] and ascites (OR=3.01, 95% CI 1.14-7.97, P=0.026) as well as in the incidence of death (OR=6.29, 95% CI 2.13-18.59, P=0.001) 5 years after cohort entry among HCV-positive patients with cholecystectomy compared with HCV-positive controls. The HCV-positive patient group with previous cholecystectomy showed an increased incidence of cirrhosis (OR=2.43, 95% CI 1.34-4.41, P=0.004), hepatocellular carcinoma (OR=2.85, 95% CI 1.11-7.36, P=0.030), and death (OR=3.31, 95% CI 1.50-7.28, P=0.003) 5 years after cohort entry compared with HCV-positive controls with GBD who had not undergone cholecystectomy. **CONCLUSION:** holecystectomy among HCV-positive patients is associated an increased incidence of fibrosis, cirrhosis, and its complications (ascites, hepatocellular carcinoma, and death) compared with HCV-positive controls and HCV-positive patients with GBD who have not undergone cholecystectomy.

**Conditions for eradicating hepatitis C in people who inject drugs: A fibrosis aware model of hepatitis C virus transmission.** Rozada II, Coombs D2, Lima VD3. J Theor Biol. 2016 Feb 1;395:31-39. doi: 10.1016/j.jtbi.2016.01.030. [Epub ahead of print]

It is estimated that 80% of new hepatitis C virus (HCV) infections occur among people who inject drugs (PWID). Eradicating HCV from this population is key for the complete eradication of the disease, and the advent of simple to use, high efficacy treatments could conceivably make this scenario possible. This paper presents a mathematical model where transmission of HCV is studied in a simulated population of PWID where fibrosis progression is explicitly tracked. The stability thresholds that determine whether HCV will remain endemic or become eradicated were established numerically, and analytically on a reduced version of the model. Conditions on testing and treatment rates for eradication to occur were determined, within the context of the new high efficacy therapies. The results show that HCV eradication in the PWID population of the Vancouver, BC test scenario is achievable, but testing and especially treatment rates will need to increase significantly from current rates. Parameter estimates were drawn from published data.

**Extrahepatic manifestations of chronic hepatitis C virus infection.** Cacoub P1, Comarmond C, Domont F, Savey L1, Desbois AC, Saadoun D1. Ther Adv Infect Dis. 2016 Feb;3(1):3-14. doi: 10.1177/2049936115585942.

During hepatitis C virus (HCV) chronic infection, extrahepatic manifestations are frequent and polymorphous. This article reports on a large cohort of patients with HCV-related autoimmune or lymphoproliferative disorders, from mixed cryoglobulinemia vasculitis to frank lymphomas. The relationship between HCV infection and such immune-related diseases has been formally demonstrated by epidemiological, clinical, immunological and pathological data, and results of therapeutic trials. More recently, other nonliver-related HCV disorders have been reported, including cardiovascular (i.e. stroke, ischemic heart disease), renal, metabolic and central nervous system diseases. For these manifestations, most evidence comes from large epidemiological studies; there is a need for mechanistic studies and therapeutic trials for confirmation. Beyond the risk of developing liver complications, that is, cirrhosis and liver

cancer, patients with HCV infection have an increased risk of morbidity and mortality related to nonliver diseases. HCV chronic infection should be analyzed as a systemic disease in which extrahepatic consequences increase the weight of its pathological burden. The need for effective viral eradication measures is underlined.

**[The Patient-Provider Relationship Is Associated with Hepatitis C Treatment Eligibility: A Prospective Mixed-Methods Cohort Study.](#)**

Rogal SS1,2, Arnold RM3, Chapko M4, et al. PLoS One. 2016 Feb 22;11(2):e0148596. doi: 10.1371/journal.pone.0148596. eCollection 2016. Hepatitis C virus (HCV) treatment has the potential to cure the leading cause of cirrhosis and hepatocellular carcinoma. However, only those deemed eligible for treatment have the possibility of this cure. Therefore, understanding the determinants of HCV treatment eligibility is critical. Given that effective communication with and trust in healthcare providers significantly influences treatment eligibility decisions in other diseases, we aimed to understand patient-provider interactions in the HCV treatment eligibility process. This prospective cohort study was conducted in the VA Pittsburgh Healthcare System. Patients were recruited after referral for gastroenterology consultation for HCV treatment with interferon and ribavirin. Consented patients completed semi-structured interviews and validated measures of depression, substance and alcohol use, and HCV knowledge. Two coders analyzed the semi-structured interviews. Factors associated with patient eligibility for interferon-based therapy were assessed using multivariate logistic regression. Of 339 subjects included in this analysis, only 56 (16.5%) were deemed eligible for HCV therapy by gastroenterology (GI) providers. In the multivariate logistic regression, patients who were older (OR = 0.96, 95%CI = 0.92-0.99, p = .049), reported concerns about the GI provider (OR = 0.40, 95%CI = 0.10-0.87, p = 0.02) and had depression symptoms (OR = 0.32, 95%CI = 0.17-0.63, p = 0.001) were less likely to be eligible. Patients described barriers that included feeling stigmatized and poor provider interpersonal or communication skills. In conclusion, we found that patients' perceptions of the relationship with their GI providers were associated with treatment eligibility. Establishing trust and effective communication channels between patients and providers may lower barriers to potential HCV cure.

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## LIVER CANCER

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**[Kaempferol induces apoptosis in HepG2 cells via activation of the endoplasmic reticulum stress pathway.](#)**

Guo H1, Ren F2, Zhang L3, et al. Mol Med Rep. 2016 Feb 2. doi: 10.3892/mmr.2016.4845. [Epub ahead of print]

Kaempferol is a flavonoid compound that has gained importance due to its antitumor properties; however, the underlying mechanisms remain to be fully understood. The present study aimed to investigate the molecular mechanisms of the antitumor function of kaempferol in HepG2 hepatocellular carcinoma cells. Kaempferol was determined to reduce cell viability, increase lactate dehydrogenase activity and induce apoptosis in a concentration and time dependent manner in HepG2 cells. Additionally, kaempferol induced apoptosis possibly acts via the endoplasmic reticulum (ER) stress pathway, due to the significant increase in the protein expression levels of glucose regulated protein 78, glucose regulated protein 94, protein kinase R like ER kinase, inositol requiring enzyme 1 $\alpha$ , partial activating transcription factor 6 cleavage, caspase 4, C/EBP homologous protein (CHOP) and cleaved caspase 3. The pro apoptotic activity of kaempferol was determined to be due to induction of the ER stress CHOP pathway, as: i) ER

stress was blocked by 4 phenyl butyric acid (4 PBA) pretreatment and knockdown of CHOP with small interfering RNA, which resulted in alleviation of kaempferol induced HepG2 cell apoptosis; and ii) transfection with plasmid overexpressing CHOP reversed the protective effect of 4 PBA in kaempferol induced HepG2 cells and increased the apoptotic rate. Thus, kaempferol promoted HepG2 cell apoptosis via induction of the ER stress CHOP signaling pathway. These observations indicate that kaempferol may be used as a potential chemopreventive treatment strategy for patients with hepatocellular carcinoma.

[Influence of insulin resistance on the development of hepatocellular carcinoma after antiviral treatment for non-cirrhotic patients with chronic hepatitis C.](#) Hayashi T1, Ogawa E1, Furusyo N1, Murata M1, Hayashi J2. *Infect Agent Cancer*. 2016 Feb 24;11:9. doi: 10.1186/s13027-016-0056-y. eCollection 2016.

**BACKGROUND:** Insulin resistance is considered to be an important factor in the progression of fibrosis and the enhancement of the risk of hepatocellular carcinoma (HCC) for chronic hepatitis C patients. The aim of this study was to assess the effect of insulin resistance on the development of HCC by non-cirrhotic chronic hepatitis C patients treated with pegylated interferon alpha-2b (PEG-IFN $\alpha$ 2b) and ribavirin. **METHODS:** This retrospective study consisted of 474 Japanese non-cirrhotic patients with chronic hepatitis C. The cumulative incidence of HCC was estimated using the Kaplan-Meier method, according to insulin resistance by the homeostasis model assessment of insulin resistance (HOMA-IR) and treatment outcome. **RESULTS:** The overall sustained virological response (SVR) rate was 45.1 % (214/474, genotype 1: 35.4 % [129/364] and genotype 2: 77.3 % [85/110]). Twenty-one (4.4 %) patients developed HCC during the follow-up period. The 5-year cumulative incidence of HCC of the SVR group (2.6 %) was significantly lower than that of the non-SVR group (9.7 %) (log-rank test:  $P = 0.025$ ). In multivariable logistic regression analysis, HOMA-IR ( $\geq 2.5$ ) (hazard ratio [HR] 12.8,  $P = 0.0006$ ), fibrosis status (F3) (HR 8.85,  $P < 0.0001$ ), and post-treatment alanine aminotransferase (ALT) level ( $\geq 40$  U/L) (HR 4.33,  $P = 0.036$ ) were independently correlated to the development of HCC. Receiver operating characteristic analysis to determine the optimal threshold value of HOMA-IR for predicting the development of HCC in the non-SVR group showed that the areas under the curve was high (0.80, cutoff value: 3.0). Only three patients (1.4 %) who achieved SVR developed HCC. Two of them had severe insulin resistance and did not show improvement in HOMA-IR after achieving SVR. **CONCLUSIONS:** Insulin resistance has a strong impact on the development of HCC by non-cirrhotic patients who have PEG-IFN $\alpha$ 2b and ribavirin treatment failure.

[Diminished viral replication and compartmentalization of hepatitis C virus in hepatocellular carcinoma tissue.](#) Harouaka D1, Engle RE1, Wollenberg K2, et al. *Proc Natl Acad Sci U S A*. 2016 Feb 2;113(5):1375-80. doi: 10.1073/pnas.1516879113. Epub 2016 Jan 19. Analysis of hepatitis C virus (HCV) replication and quasispecies distribution within the tumor of patients with HCV-associated hepatocellular carcinoma (HCC) can provide insight into the role of HCV in hepatocarcinogenesis and, conversely, the effect of HCC on the HCV lifecycle. In a comprehensive study of serum and multiple liver specimens from patients with HCC who underwent liver transplantation, we found a sharp and significant decrease in HCV RNA in the tumor compared with surrounding nontumorous tissues, but found no differences in multiple areas of control non-HCC cirrhotic livers. Diminished HCV replication was not associated with changes in miR-122 expression. HCV genetic diversity was significantly higher in livers



containing HCC compared with control non-HCC cirrhotic livers. Tracking of individual variants demonstrated changes in the viral population between tumorous and nontumorous areas, the extent of which correlated with the decline in HCV RNA, suggesting HCV compartmentalization within the tumor. In contrast, compartmentalization was not observed between nontumorous areas and serum, or in controls between different areas of the cirrhotic liver or between liver and serum. Our findings indicate that HCV replication within the tumor is restricted and compartmentalized, suggesting segregation of specific viral variants in malignant hepatocytes.

**[Predictors of Benign Status in Liver Tumors Under 3 cm in Diameter Misdiagnosed as Hepatocellular Carcinoma.](#)** Kimura K1, Itoh S2, Kurihara T2, et al. *Anticancer Res.* 2016 Feb;36(2):793-7.

**BACKGROUND:** The clinical features of benign liver lesions misdiagnosed as hepatocellular carcinoma have not been fully described. **PATIENTS AND METHODS:** This study included 187 patients who underwent hepatectomy at the Kyushu University Hospital following a diagnosis of solitary HCC of  $\leq 3$  cm in diameter. **RESULTS:** Following hepatectomy, 9.6% patients were pathologically diagnosed with benign liver lesions. Univariate analysis showed that patient age  $\leq 67$  years, negativity for hepatitis C virus antigen, lesion size  $\leq 1.5$  cm, normal level of tumor markers, and absence of increase in tumor size were associated with benign lesions. Patient age  $\leq 67$  years and absence of tumor size increase were independent predictors of benign lesions. **CONCLUSION:** Benign liver lesions misdiagnosed as HCC were not infrequent, accounting for approximately 10% of resected cases. Age  $\leq 67$  years and absence of tumor size increase were independent predictors of benign liver lesions, and may help in the correct diagnosis of HCC.

**[Comparison of transarterial chemoembolization with radiofrequency ablation for unresectable Barcelona Clinic Liver Cancer stage 0/A hepatocellular carcinoma: a propensity score matching.](#)** Chen RX1, Gan YH1, Ge NL1, et al. *J Gastroenterol Hepatol.* 2016 Feb;31(2):442-9. doi: 10.1111/jgh.13077.

**BACKGROUND AND AIM:** Radiofrequency ablation (RFA) is recommended as one of the standard treatments for early hepatocellular carcinoma (HCC). Because of high-risk tumor locations unfit for RFA, transarterial chemoembolization (TACE) is served as an alternative option in these settings. To define the role of TACE on early HCC, we retrospectively compared the efficacies of TACE with RFA in patients with unresectable Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC. **MATERIALS AND METHODS:** Treatment-naïve patients with unresectable BCLC stage 0/A HCC who underwent TACE or RFA were recruited from 2007 to 2011. In all, 208 patients who underwent TACE and 235 patients who underwent RFA were included in the final analysis. Using the propensity model to correct selection bias, 103 patients were selected from each treatment arm. Cumulative overall survival (OS) as the primary end point was compared after adjustment with propensity score matching. **RESULTS:** In all patients, the OS rate was significantly higher in patients treated with RFA than that in those who received TACE (1-, 3-, and 5-year OS rates, 93.7%, 72.6%, and 58.1% vs 88.1%, 50.3%, and 30.4%, respectively;  $P < 0.001$ ). However, adjustment with propensity score matching yielded comparable OS between the two groups ( $P = 0.207$ ). Subgroup analysis showed that RFA provided better OS than TACE in patients with serum  $\gamma$ -glutamyltranspeptidase  $< 75$  IU/L ( $P = 0.035$ ). Univariate and subsequent multivariate analyses revealed that Child-Pugh class B (hazard ratio = 1.805; 95% confidence interval, 1.805-3.003;  $P = 0.023$ ) and hepatitis C virus

positivity (hazard ratio = 2.478; 95% confidence interval, 1.136-5.404; P = 0.023) were independent predictors of poor prognosis. **CONCLUSION:** Transarterial chemoembolization is an effective alternative treatment for unresectable BCLC stage 0/A HCC when RFA is not feasible.

**[How have the recent advances in antiviral therapy impacted the management of virus-related hepatocellular carcinoma?](#)** Wang CC1, Kao JH2. Expert Opin Pharmacother. 2016 Feb 25:1-9. [Epub ahead of print]

**INTRODUCTION:** Whether the recent advances in antiviral therapy including nucleos(t)ide analogue (NA) or interferon (IFN) impacts the management of patients with virus-related hepatocellular carcinoma (HCC) remains unclear. Area covered: The beneficial effects of antiviral therapy on HCC patients receiving curative treatment, transhepatic arterial chemoembolization (TACE), or radiotherapy are reviewed and discussed. Expert opinion: For patients with HCV-related HCC after curative treatment, interferon (IFN)-based therapy has been shown to improve the survival and reduces the risk of HCC recurrence. However, it carries the risk of adverse effects, especially in cirrhotic patients. Therefore, the benefit of IFN should be weighted against its risk in each individual. For patients with HBV-related HCC after curative treatments, antiviral treatment with NA has been found to improve liver function, overall survival, and possibly reduce the risk of HCC recurrence. In contrast, these benefits were not consistently observed in those receiving IFN treatment. In HCC patients receiving palliative TACE or radiotherapy, HBV reactivation occurs in a small proportion of them, and preemptive NA treatment can reduce the risk of hepatitis flare due to viral reactivation. Therefore, NA treatment after curative treatments or TACE is strongly recommended for HCC patients with high viral load (HBV DNA > 2000 IU/mL).

**[Long-Term Outcomes of Hepatitis-C-Infected Patients Achieving a Sustained Virological Response and Undergoing Radical Treatment for Hepatocellular Carcinoma.](#)**

Kunimoto H, Ikeda K, Sorin Y, et al. Oncology. 2016 Feb 23;90(3). [Epub ahead of print]

**BACKGROUND AND AIMS:** A sustained virological response (SVR) decreases the incidence of hepatocellular carcinoma (HCC) in patients with hepatitis C. We investigated the long-term outcomes of patients who developed HCC after achieving SVR with interferon therapy.

**PATIENTS:** Of 75 patients who developed HCC after SVR, 40 patients underwent radical therapies (SVR group). From 436 patients undergoing surgical resection for hepatitis C virus-positive HCC, 80 patients were randomly chosen as a control cohort, after adjusting for age, gender, and extent of hepatic fibrosis (non-SVR group). Patients were observed for a median of 5.08 years. **RESULTS:** HCC recurrence was found in 16 SVR patients and in 66 non-SVR patients. The respective HCC recurrence rates of SVR and non-SVR patients were 23 and 56% at 3 years, 42 and 77% at 5 years, and 53 and 90% at 10 years (p = 0.001). The respective overall survival rates in the SVR and non-SVR groups were 93 and 68% at 5 years, 88 and 34% at 10 years, and 53 and 21% at 15 years (p = 0.001). **CONCLUSION:** Although SVR patients had a significantly lower HCC recurrence rate than the non-SVR patients, the cumulative recurrence rate of SVR patients increased to 86% at 15 years.

**[TNF- \$\alpha\$  and IL-10 polymorphisms increase the risk to hepatocellular carcinoma in HCV infected individuals.](#)** Aroucha DC1,2, Carmo RF3,4, Vasconcelos LR1,5, et al. J Med Virol. 2016 Feb 17. doi: 10.1002/jmv.24501. [Epub ahead of print]

Hepatitis C virus (HCV) is the major cause of hepatocellular carcinoma (HCC). The risk to develop HCC increases with the severity of liver inflammation and hepatic fibrosis. It is believed that a balance between the releases of pro- and anti-inflammatory cytokines will determine the clinical course of HCV and the risk to develop HCC. The interleukin-10 (IL-10) and the tumor necrosis factor alpha (TNF- $\alpha$ ) play key roles in the Th1 and Th2 balance during the inflammatory response against HCV. The aim of the present study was to investigate the association between polymorphisms in TNF- $\alpha$  -308 G > A (rs1800629), IL-10 -1082 G > A (rs1800896) and -819/-592 (rs1800871/rs1800872) with HCC risk in individuals with HCV. The present study evaluated 388 chronic HCV patients. Polymorphisms were determined by Real-time PCR. Diplotypes associated with low IL-10 production and the TNF- $\alpha$  GG genotype were significantly associated with HCC occurrence after multivariate logistic regression analysis ( $p = 0.027$  and  $p = 0.029$ , respectively). Additionally, the IL-10 -819 (-592) TT (AA) genotype was significantly associated with multiple nodules and HCC severity according to BCLC staging ( $p = 0.044$  and  $p = 0.025$ , respectively). Patients carrying low production haplotypes of IL-10 and the TNF- $\alpha$  GG genotype have higher risk to develop HCC.

**Differential association of STAT3 and HK-II expression in hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma.** Li M1,2, Wang W3, Jin R4, Zhang T2, Li N1, Han Q1, Wei P1, Liu Z1. J Med Virol. 2016 Feb 17. doi: 10.1002/jmv.24498. [Epub ahead of print] STAT3 and hexokinase II (HK-II) are involved in viral infection and carcinogenesis of various cancers including hepatocellular carcinoma (HCC). The roles of STAT3 and HK-II in hepatitis B virus (HBV)- and hepatitis C virus (HCV)-related HCC remain largely unclear. This study examined STAT3 and HK-II expression in HBV- and HCV-related HCC, HBV-related liver fibrosis and normal control liver by using tissue microarray and immunohistochemical method. Results showed that STAT3 expression in HBV-related HCC, HCV-related HCC and HBV-related liver fibrosis was significantly higher than in control liver ( $P < 0.001$ ,  $P = 0.016$  and  $P = 0.005$ , respectively) and had no significant differences between these three diseased liver tissues. The HK-II expression in HBV-related HCC was significantly higher than that in HCV-related HCC, HBV-related liver fibrosis and control liver ( $P = 0.007$ ,  $P = 0.029$  and  $P = 0.008$ , respectively) but had no significant elevation in and no significant differences between HCV-related HCC, HBV-related liver fibrosis and control liver. The HK-II expression was significantly correlated to STAT3 expression in HBV-related HCC ( $P = 0.022$ ) but no correlation was observed in HCV-related HCC, HBV-related liver fibrosis and control liver. In conclusion, STAT3 expression is upregulated in both HBV- and HCV-related HCC, while HK-II is predominantly upregulated and correlated to STAT3 in HBV-related HCC. These differential expression and association may suggest the distinct roles of STAT3 and HK-II in hepatocarcinogenesis of HBV and HCV infection. Studies are needed to confirm the relationship of STAT3 and HK-II and to examine the underlying mechanisms.

**Statin use and survival with early stage hepatocellular carcinoma.** Jeon CY1, Goodman MT2, Cook-Wiens G3, Sundaram V4. Cancer Epidemiol Biomarkers Prev. 2016 Feb 9. pii: cebp.1040.2015. [Epub ahead of print]

**BACKGROUND:** Limited clinical and epidemiological data suggest that statins may improve the outcomes of hepatocellular carcinoma (HCC), which has poor prognosis. **METHODS:** We identified 1036 stage I or II HCC patients, diagnosed between 2007-2009, through the linked Surveillance, Epidemiology, and End Results (SEER) Program and Medicare claims database.

Of these, 363 patients were using statin either at the time of their HCC diagnosis or afterwards. We conducted multivariable Cox regression analysis to estimate the time-dependent effect of statin on survival. The analysis included age, sex, resection, trans-arterial chemoembolization, transplantation, cirrhosis, cardiovascular disease, diabetes, dyslipidemia, hepatitis B and C.

**RESULTS:** Over a median follow-up time of 21 months, 584 HCC patients died. Statin users had a longer median survival compared to non-users: 23.9 vs. 18.9 months ( $p = 0.047$ ). However, after accounting for immortal time bias and confounding, statin use was not associated with survival: hazard ratio = 0.98, 95% confidence interval (0.80, 1.20) The associations did not vary by hepatitis C, or intensity of statin use. **CONCLUSIONS:** Statin treatment after HCC diagnosis was not associated with survival in elderly patients with stage I/II disease.