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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Real-world efficacy of glecaprevir plus pibrentasvir for chronic hepatitis C patient with previous direct-acting antiviral therapy failures.](#) Osawa M1,2, Imamura M1,2, Teraoka Y1,2, et al. J Gastroenterol. 2018 Oct 17. doi: 10.1007/s00535-018-1520-9. [Epub ahead of print]

BACKGROUND: Combination therapy with glecaprevir (GLE) and pibrentasvir (PIB) has high efficacy for pan-genotypic hepatitis C virus (HCV)-infected patients. However, the efficacy of the therapy for failures to prior direct-acting antiviral (DAA) regimens in real-world practice is not well known. **METHODS:** Thirty patients infected with HCV genotype 1b, 2a, 2b, or 3a who failed to respond during prior DAA therapies were treated with GLE/PIB for 12 weeks. HCV NS3 and NS5A drug resistance-associated variants (RAVs) were determined by direct sequencing. **RESULTS:** Twenty-eight out of 30 patients (93.3%) achieved SVR12 by GLE/PIB treatment. SVR12 rates were similar between patients with and without advanced liver fibrosis (94.7% and 91.0%, respectively). All 9 patients with genotype 2a, 2b, or 3a HCV infection achieved SVR12. However, two genotype 1b HCV-infected patients who failed previous daclatasvir plus asunaprevir treatment experienced HCV relapse after the end of GLE/PIB treatment. Direct sequence analysis showed the presence of NS3-D168E plus NS5A-L31I/P58S/Y93H RAVs in one patient and NS5A-L31F/P32del RAVs in another patient before GLE/PIB treatment. In the former patient, NS3-D168E plus NS5A-L31I/P58S/Y93H RAVs persisted, and additional NS5A-L28M/V75A variants emerged after HCV relapse.

CONCLUSIONS: GLE/PIB treatment for HCV-infected patients who did not respond to prior DAA treatments was highly effective regardless of liver fibrosis stage. However, some genotype 1b HCV-infected patients, especially those with NS5A-P32del, may have low susceptibility to the treatment.

[Impact of successful treatment with direct-acting antiviral agents on health-related quality of life in chronic hepatitis C patients.](#) Juanbeltz R1,2,3, Martínez-Baz I2,3, San Miguel R1, Goñi-Esarte S4, Cabasés JM5, Castilla J2,3. PLoS One. 2018 Oct 9;13(10):e0205277. doi: 10.1371/journal.pone.0205277. eCollection 2018.

BACKGROUND: Direct-acting antivirals (DAA) have demonstrated high efficacy to achieve sustained virological response (SVR) in chronic hepatitis C patients. We aim to assess the change in health-related quality of life (HRQoL) among patients successfully treated, and to identify predictors of this variation. **METHODS:** In a prospective observational study, patients

with chronic hepatitis C who started DAA therapy between May 2016 and April 2017 completed the EQ-5D-5L questionnaire at baseline and 12 weeks after the end of therapy before knowing the virological result. Analysis included all patients with SVR. **RESULTS:** Median baseline EQ-5D-5L scores of the 206 enrolled patients were 0.857 utility and 70.0 visual analogue scale (VAS). Following SVR, a reduction occurred in the proportion of patients with mobility problems (35% vs 24%, $p = 0.012$), pain/discomfort (60% vs 42%, $p < 0.001$) and anxiety/depression (57% vs 44%, $p = 0.012$), with an increase in utility (+0.053, $p < 0.001$) and VAS (+10, $p < 0.001$). Score improvements were also observed in cirrhotic (+0.048 utility, $p = 0.027$; +15 VAS, $p < 0.001$) and HIV co-infected patients (+0.039 utility, $p = 0.036$; +5 VAS, $p = 0.002$). In multivariate analyses, middle age (45-64 years) and baseline anxiety/depression were associated to greater improvement in utility after SVR, and moderate-advanced liver fibrosis and cirrhosis to greater increase in VAS score. Low baseline values were associated to greater improvements in utility value and VAS score. **CONCLUSIONS:** The cure of chronic hepatitis C infection with DAA has a short term positive impact on HRQoL with improvement in mobility, pain/discomfort, anxiety/depression, utility value and VAS score. Patients with poor baseline HRQoL were the most benefited.

Influence of Progenitor-Derived Regeneration Markers on Hepatitis C Virus-Related Cirrhosis Outcome (ANRS CO12 CirVir Cohort). Wendum D1,2, Layese R3,4, Ganne-Carrié N5,6,7, et al. *Hepatology*. 2018 Oct;68(4):1534-1548. doi: 10.1002/hep.29927.

Progenitor-derived regeneration gives rise to the aberrant expression of biliary markers such as cytokeratin 7 (K7) and epithelial cell adhesion molecule (EpCAM) in hepatocytes. We aimed to describe the expression of these molecules in patients with compensated hepatitis C virus (HCV)-related cirrhosis and to investigate its potential influence on cirrhosis complications. Among patients with Child-Pugh A uncomplicated HCV-related cirrhosis enrolled in the prospective ANRS CO12 CirVir cohort, we selected individuals with a liver biopsy collected within 2 years before inclusion in the study. K7 and EpCAM immunostaining identified intermediate hepatobiliary cells. The influence of biliary marker expression in hepatocytes on decompensation events and the occurrence of hepatocellular carcinoma (HCC) was studied using a multivariate Cox proportional hazards regression model. Among the 337 patients eligible for the study (men, 67%; median age, 52 years), 198 (58.8%) had biopsies with K7-positive hepatocytes including extensive staining in 40 (11.9%) and 203 had EpCAM-positive hepatocytes (60.6%). During follow-up (median, 54.2 months), 47 patients (14%) experienced a decompensation event, and HCC was diagnosed in 37 patients (11%). Extensive K7 staining was independently associated with the occurrence of a decompensation event (hazard ratio [HR], 3.00; 95% confidence interval [CI], 1.30-6.89; $P = 0.010$). EpCAM expression was independently associated with HCC occurrence (HR, 2.37; 95% CI, 1.07-5.23; $P = 0.033$) along with age and a low prothrombin ratio. **CONCLUSION:** Progenitor-derived regeneration depicted by K7 and EpCAM immunostaining of hepatocytes in liver biopsies of patients with compensated HCV-related cirrhosis marks a cirrhosis stage more prone to develop complications. (*HEPATOLOGY* 2018; 68:1534-1548).

Treatment of chronic hepatitis C viral infection with sofosbuvir and daclatasvir in kidney transplant recipients. Huang H1, Tang H1, Deng H1, Shen J1, Zhou Q1, Xie W1, Wu J1, Chen J1. *Transpl Infect Dis*. 2018 Oct 27:e13018. doi: 10.1111/tid.13018. [Epub ahead of print]

OBJECTIVES: To assess the efficacy and the risk of sofosbuvir-daclatasvir treatment among kidney transplant recipients (KTRs) with chronic hepatitis C virus (HCV) infection.

METHODS: A real-life retrospective cohort analysis was performed on KTRs treated with sofosbuvir-daclatasvir at our center between January 2016 and March 2018. We collected data from 19 KTRs (13 males; age 48.3±9.6 years; HCV genotype I, n=16; chronic active hepatitis B coinfection, n=8). Virological and clinical data were assessed. **RESULTS:** Overall, 100% of the patients had achieved a sustained virological response 12 weeks after treatment (SVR12). Their liver function improved notably, with a significant decline in the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (ALT 34.8 ± 18.6 IU/L pretreatment and 15.0 ± 6.8 IU/L posttreatment, p = 0.0003; AST: 35.05 ± 18.1 IU/L pretreatment and 19.1 ± 7.0 posttreatment, p = 0.001). A significant amelioration was observed in patients with proteinuria (n=12) [0.95 (0.35-3.31) g/g at baseline to 0.39 (0.27-1.02) g/g posttherapy, p = 0.048]. The serum creatinine, eGFR and tacrolimus levels were stable during therapy. **CONCLUSION:** The preliminary data demonstrated that sofosbuvir-daclatasvir was highly effective in treating HCV infection in KTRs with acceptable tolerance. This article is protected by copyright. All rights reserved.

Pan-Genotypic Hepatitis C Treatment with Glecaprevir and Pibrentasvir for 8 Weeks Resulted in Improved Cardiovascular and Metabolic Outcomes and Stable Renal

Function: A Post-Hoc Analysis of Phase 3 Clinical Trials. Tran TT1, Mehta D2,3, Mensa F3, Park C3, Bao Y3, Sanchez Gonzalez Y4. Infect Dis Ther. 2018 Oct 27. doi: 10.1007/s40121-018-0218-x. [Epub ahead of print]

INTRODUCTION: Chronic hepatitis C (CHC) infection is associated with extrahepatic manifestations (EHMs) which can affect renal, cardiovascular and other comorbidities. The effect of CHC treatment with short-duration regimens on these EHMs is not well defined. Hence, we examined longitudinal estimated glomerular filtration rate (eGFR), triglycerides and glucose values to assess the impact of short-duration CHC therapy on renal, cardiovascular and metabolic diseases, respectively. **METHODS:** We conducted analyses of all patients without cirrhosis treated with glecaprevir and pibrentasvir (G/P) for 8 weeks in two phase 3 clinical trials. In addition, one phase 3 trial was carried out to explore the effects of treatment on renal EHMs in patients with advanced renal impairment at baseline. As a sensitivity analysis, we included all CHC patients treated with G/P for 8 or 12 weeks enrolled across five phase 3 trials. Adjusting for baseline demographics and clinical properties via mixed regression models enabled evaluation of changes in EHMs through end of treatment. **RESULTS:** G/P treatment for 8 weeks resulted in statistically significant declines in triglycerides (- 28.6 mg/dl) and glucose (- 11.2 mg/dl), while there was no statistically significant decline in eGFR. Biomarker improvements were greatest among patients with elevated triglycerides and elevated glucose at baseline. Similar effects were observed across all patients treated with G/P for 8 or 12 weeks. **CONCLUSION:** Short-duration treatment with G/P resulted in stable renal function and improvements in cardiovascular and metabolic EHM markers, especially in patients with severe EHMs at baseline.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Functional Study of the C-Terminal Part of the Hepatitis C Virus E1 Ectodomain. Moustafa RI#1,2, Haddad JG#1,3, Linna L1, et al. J Virol. 2018 Sep 26;92(20). pii: e00939-18. doi: 10.1128/JVI.00939-18. Print 2018 Oct 15.

In the hepatitis C virus (HCV) envelope glycoproteins E1 and E2, which form a heterodimer, E2 is the receptor binding protein and the major target of neutralizing antibodies, whereas the function of E1 remains less characterized. To investigate E1 functions, we generated a series of mutants in the conserved residues of the C-terminal region of the E1 ectodomain in the context of an infectious clone. We focused our analyses on two regions of interest. The first region is located in the middle of the E1 glycoprotein (between amino acid [aa] 270 and aa 291), which contains a conserved hydrophobic sequence and was proposed to constitute a putative fusion peptide. The second series of mutants was generated in the region from aa 314 to aa 342 (the aa314-342 region), which has been shown to contain two α helices ($\alpha 2$ and $\alpha 3$) by nuclear magnetic resonance studies. Of the 22 generated mutants, 20 were either attenuated or noninfectious. Several mutations modulated the virus's dependence on claudin-1 and the scavenger receptor BI coreceptors for entry. Most of the mutations in the putative fusion peptide region affected virus assembly. Conversely, mutations in the α -helix aa 315 to 324 (315-324) residues M318, W320, D321, and M322 resulted in a complete loss of infectivity without any impact on E1E2 folding and on viral assembly. Further characterization of the W320A mutant in the HCVpp model indicated that the loss of infectivity was due to a defect in viral entry. Together, these results support a role for E1 in modulating HCV interaction with its coreceptors and in HCV assembly. They also highlight the involvement of α -helix 315-324 in a late step of HCV entry.

IMPORTANCE HCV is a major public health problem worldwide. The virion harbors two envelope proteins, E1 and E2, which are involved at different steps of the viral life cycle. Whereas E2 has been extensively characterized, the function of E1 remains poorly defined. We characterized here the function of the putative fusion peptide and the region containing α helices of the E1 ectodomain, which had been previously suggested to be important for virus entry. We could confirm the importance of these regions for the virus infectivity. Interestingly, we found several residues modulating the virus's dependence on several HCV receptors, thus highlighting the role of E1 in the interaction of the virus with cellular receptors. Whereas mutations in the putative fusion peptide affected HCV infectivity and morphogenesis, several mutations in the $\alpha 2$ -helix region led to a loss of infectivity with no effect on assembly, indicating a role of this region in virus entry.

[NS5A Promotes Constitutive Degradation of IP3R3 to Counteract Apoptosis Induced by Hepatitis C Virus.](#) Kuchay S1, Saeed M2, Giorgi C3, Li J4, Hoffmann HH2, Pinton P5, Rice CM6, Pagano M7. Cell Rep. 2018 Oct 23;25(4):833-840.e3. doi: 10.1016/j.celrep.2018.09.088.

FBXL2 targets IP3R3 for ubiquitin-mediated degradation to limit Ca²⁺ flux to mitochondria and, consequently, apoptosis. Efficient replication of hepatitis C virus (HCV) requires geranylgeranylation of FBXL2. Here, we show that the viral protein NS5A forms a trimeric complex with IP3R3 and FBXL2, unmasking IP3R3's degron in the absence of inositol 1,4,5-trisphosphate (IP3) stimulation. FBXL2 knockdown or expression of a stable IP3R3 mutant causes persistent Ca²⁺ flux and sensitizes cells to apoptosis, resulting in the inhibition of viral replication. Importantly, the effect of FBXL2 silencing is rescued by depleting IP3R3, but not p85 β , another established FBXL2 substrate, indicating that the anti-HCV effect of FBXL2 knockdown is largely due to IP3R3 stabilization. Finally, disruption of the FBXL2-NS5A-IP3R3 complex using somatic cell genetics or pharmacologic inhibition results in IP3R3 stabilization and suppression of HCV replication. This study reveals an IP3-independent molecular mechanism through which HCV promotes IP3R3 degradation, thereby inhibiting virus-induced apoptosis and establishing chronic infection.

[Genetic variants upstream of TNFAIP3 in the 6q23 region are associated with liver disease severity in HIV/HCV-coinfected patients: A cross-sectional study.](#) Jiménez-Sousa MA1, Berenguer J2, Rodríguez AF3, et al. *Infect Genet Evol.* 2018 Oct 15. pii: S1567-1348(18)30690-7. doi: 10.1016/j.meegid.2018.10.008. [Epub ahead of print]

BACKGROUND: TNFAIP3 is a crucial hepatoprotective factor due to its anti-inflammatory, anti-apoptotic, anti-oxidant and pro-regenerative functions. The aim of this study was to analyze the associations between genetic variants upstream of TNFAIP3 (rs675520, rs9376293 and rs6920220) and liver fibrosis severity and inflammation in HIV/HCV-coinfected patients. **METHODS:** A cross-sectional study was carried out in 215 HIV/HCV-coinfected patients, who underwent a liver biopsy. TNFAIP3 polymorphisms were genotyped using GoldenGate® assay. Outcome variables were: a) liver fibrosis (Metavir score) [fibrosis stage (F0, F1, F2, F3 and F4) and advanced fibrosis and cirrhosis ($F \geq 3$ and F4, respectively)]; b) non-invasive indexes [FIB-4, APRI, and their cut-offs ($FIB-4 \geq 3.25$ and $APRI \geq 1.5$)]; c) inflammation-related biomarkers (leptin, NGF, sFas, MIF, TIMP1 and MMP2). **RESULTS:** Patients with rs675520 AG/GG genotypes had decreased odds of having cirrhosis (F4) and advanced fibrosis ($FIB-4 \geq 3.25$ and $APRI \geq 1.5$) [adjusted Odd Ratio (aOR) = 0.30 ($p = 0.025$), aOR = 0.20 ($p = 0.014$), and aOR = 0.34 ($p = 0.017$), respectively] and lower levels of FIB-4 and APRI [adjusted arithmetic mean ratio (aAMR) = 0.76 ($p = 0.003$) and aAMR = 0.72 ($p = 0.006$), respectively]. Patients with rs9376293 CT/CC genotypes had decreased odds of $APRI \geq 1.5$ [aOR = 0.39 ($p = 0.030$)] and lower levels of APRI [aAMR = 0.77 ($p = 0.018$)]. Patients with rs6920220 AG/AA genotypes had higher odds of having $FIB-4 \geq 3.25$ [aOR = 3.72 ($p = 0.043$)]. Moreover, rs675520 AG/GG genotypes, compared to AA genotype, were associated with lower levels of leptin and NGF ($p = 0.002$ and $p = 0.001$, respectively) and higher levels of sFas, MIF, TIMP1 and MMP2 ($p = 0.004$, $p = 0.007$, $p = 0.020$ and $p = 0.036$, respectively). Also, rs9376293 CT/CC genotypes were related to lower leptin levels ($p = 0.026$) and higher sFas, MIF, TIMP1 and MMP2 levels ($p = 0.029$, $p = 0.040$, $p = 0.022$ and $p = 0.024$, respectively). **CONCLUSIONS:** Genetic variants upstream of TNFAIP3 were associated with the liver fibrosis severity and inflammation in HIV/HCV-coinfected patients.

[Regression of liver fibrosis after curing chronic hepatitis C with oral antivirals in patients with and without HIV coinfection.](#) Lledó GM1, Carrasco I2, Benítez-Gutiérrez LM1, et al. *AIDS.* 2018 Oct 23;32(16):2347-2352. doi: 10.1097/QAD.0000000000001966.

BACKGROUND: Treatment with direct-acting antivirals (DAA) eradicates hepatitis C virus (HCV) from most chronic carriers. Information on regression of liver fibrosis and the influence of HIV is scarce in cured patients. **METHODS:** All consecutive HCV-infected individuals treated with DAA at our institution were examined. Hepatic elastography was performed at baseline and at the time of SVR12. Liver fibrosis regression was defined as a shift from advanced fibrosis (Metavir F3-F4) to null-mild fibrosis (F0-F2) and/or a reduction greater than 30% kPa. AST to platelet ratio index (APRI) and fibrosis 4 (FIB-4) scores were calculated in parallel. **RESULTS:** A total of 260 patients were treated with DAA. All but 14 achieved SVR12 and represented the study population. HIV coinfection was present in 42%. At baseline, 57.2% had advanced liver fibrosis with a median of 11 kPa, FIB-4 of 2.4, and APRI of 0.95. At the time of SVR12, a median reduction of 2.1 kPa ($P < 0.001$) was recognized using elastography. A significant fibrosis regression was seen in 40%, being more frequent in patients with baseline

advanced fibrosis than in those with null-mild fibrosis (52.3 vs. 22.5%; $P < 0.001$). Even so, 41.2% of patients with baseline F3-F4 kept within cirrhotic scores. In multivariable analysis, only baseline stiffness was significantly associated with the extent of liver fibrosis regression. **CONCLUSION:** HCV cure with DAA is associated with regression of liver fibrosis in most patients treated with DAA, as measured using elastography, FIB-4 and APRI. This benefit is more pronounced in patients with baseline advanced fibrosis and cirrhosis. The dynamics of liver fibrosis regression are not influenced by HIV coinfection.

[Prediction of Liver Disease, AIDS, and Mortality Based on Discordant Absolute and Relative Peripheral CD4 T Lymphocytes in HIV/Hepatitis C Virus-Coinfected Individuals.](#)

Hansen S1, Kronborg G1,2, Benfield T1,2. AIDS Res Hum Retroviruses. 2018 Oct 23. doi:

10.1089/AID.2017.0058. [Epub ahead of print]

Hepatitis C virus (HCV)-induced liver fibrosis and splenomegaly may lead to discordance between absolute numbers and percentages of lymphocytes and subpopulations because of sequestration. We investigated lymphocyte discordance in HIV/HCV-coinfected individuals and its relationship to progression to liver disease, AIDS, and all-cause mortality. This is an observational retrospective cohort study. Adjusted hazard ratios (aHRs) with 95% confidence intervals (95% CIs) associated with liver disease, AIDS, or mortality were computed by time-updated Cox proportional hazards regression. Of 380 HIV/HCV-coinfected adult individuals followed for a median of 8.2 years, 360 individuals had a median of 11 discordant measurements corresponding to 5,080 of 9,091 paired samples (56%). Discordance alone was not associated with any of the outcomes. By multivariable analysis, a doubling of absolute or percentage CD4 cells was associated with comparable lower risks of mortality (aHR: 0.60, 95% CI: 0.53-0.67, $p < .0001$ and aHR: 0.67, 95% CI: 0.56-0.79, $p < .0001$, respectively). Higher CD4/CD8 ratio was associated with a lower mortality risk (aHR: 0.39, 95% CI: 0.22-0.71 per doubling, $p = .002$). Only absolute CD4 cell measurements predicted AIDS. Development of liver disease was not predicted by total lymphocyte count or subpopulations. Despite a high prevalence of lymphocyte-subpopulation discordance with HIV/HCV coinfection, absolute CD4 cell count predicted mortality and AIDS, whereas CD4 percentage only predicted mortality. Neither CD4 T lymphocyte count nor CD4 percentage was associated with liver disease in this cohort. These findings may be necessary and useful in countries where antiretroviral treatment is not initiated for all HIV-infected individuals.

[Effect of incident hepatitis C infection on CD4 count and HIV RNA trajectories based on a multinational HIV seroconversion cohort.](#)

van Santen DK1, van der Helm JJ1,2, Touloumi G3, et al. AIDS. 2018 Oct 15. doi: 10.1097/QAD.0000000000002040. [Epub ahead of print]

BACKGROUND: Most studies on hepatitis C virus (HCV)/HIV co-infection do not account for the order and duration of these two infections. We aimed to assess the effect of incident HCV infection, and its timing relative to HIV seroconversion (HIVsc) in HIV-positive men who have sex with men (MSM) on their subsequent CD4 T-cell count (CD4) and HIV-RNA viral load (VL) trajectories. **METHODS:** We included MSM with well-estimated dates of HIVsc from 17 cohorts within the CASCADE Collaboration. HCV co-infected MSM were matched to as many HIV mono-infected MSM as possible by HIV-infection duration and cART use. We used multilevel random-effects models stratified by cART use to assess differences in CD4 and VL trajectories by HCV co-infection status. **FINDINGS:** We matched 214 (ART-naïve) and 147 (on cART) HCV co-infected MSM to 5,384 and 3,954 respectively matched controls. The timing of

HCVsc relative to HIVsc had no demonstrable effect on VL or CD4 trajectories. In the first 2-3 years following HCVsc CD4 counts were lower among HCV co-infected MSM, but became comparable to HIV mono-infected MSM thereafter. In ART-naïve MSM, during the first two years after HCVsc, VL levels were lower or comparable to HIV mono-infected, tending to be higher thereafter. In MSM on cART, HCV had no significant effect on having a detectable VL. **INTERPRETATION:** Irrespective of the duration of HIV infection when HCV is acquired, CD4 counts were temporarily lower following HCVsc, even when on cART. The clinical implications of our findings remain to be further elucidated.

[The Effects of Hepatitis C Infection and Treatment on All-cause Mortality Among People Living With Human Immunodeficiency Virus.](#)

Breskin A1, Westreich D1, Cole SR1, Hudgens MG2, Hurt CB3, Seaberg EC4, Thio CL5, Tien PC6, Adimora AA1,3. Clin Infect Dis. 2018 Oct 12. doi: 10.1093/cid/ciy588. [Epub ahead of print]

BACKGROUND: Persons living with human immunodeficiency virus (HIV; PLwH) are commonly co-infected with hepatitis C virus (HCV). Most co-infected individuals can achieve a sustained HCV virologic response after treatment with direct-acting antivirals (DAA). However, the effect of HCV co-infection and DAA treatment on mortality after initiating antiretroviral therapy (ART) is unknown for PLwH. **METHODS:** We analyzed data from the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. Participants included those who had prevalent HIV or seroconverted during follow-up; all were antiretroviral-naïve and acquired immunodeficiency syndrome (AIDS)-free prior to their first visit after 1 October 1994. The follow-up lasted 10 years or until 30 September 2015. We used parametric g-computation to estimate the effects of HCV infection and DAA treatment on mortality had participants initiated ART at study entry. **RESULTS:** Of the 3056 eligible participants, 58% were female and 18% had HCV. The estimated 10-year all-cause mortality risk in the scenario in which no PLwH had HCV was 10.4% (95% confidence interval [CI] 6.0-18.0%). The 10-year mortality risk difference for HCV infection was 4.3% (95% CI 0.4-8.9%) and the risk ratio was 1.4 (95% CI 1.0-1.9). The risk difference for DAA treatment was -3.8% (95% CI -9.2-0.9%) and the risk ratio was 0.8 (95% CI 0.6-1.1). **CONCLUSIONS:** HCV co-infection remains an important risk factor for mortality among PLwH after initiating ART according to modern guidelines, and DAAs are effective at reducing mortality in this population. HCV prevention and treatment interventions should be prioritized to reduce mortality among PLwH.

[Regression of liver fibrosis after curing chronic hepatitis C with oral antivirals in patients with and without HIV coinfection.](#)

Lledó GM1, Carrasco I2, Benítez-Gutiérrez LM1, et al. AIDS. 2018 Oct 23;32(16):2347-2352. doi: 10.1097/QAD.0000000000001966.

Arias A1, Royuela A3, Requena S2, Cuervas-Mons V1, de Mendoza C2.

BACKGROUND: Treatment with direct-acting antivirals (DAA) eradicates hepatitis C virus (HCV) from most chronic carriers. Information on regression of liver fibrosis and the influence of HIV is scarce in cured patients. **METHODS:** All consecutive HCV-infected individuals treated with DAA at our institution were examined. Hepatic elastography was performed at baseline and at the time of SVR12. Liver fibrosis regression was defined as a shift from advanced fibrosis (Metavir F3-F4) to null-mild fibrosis (F0-F2) and/or a reduction greater than 30% kPa. AST to platelet ratio index (APRI) and fibrosis 4 (FIB-4) scores were calculated in parallel. **RESULTS:** A total of 260 patients were treated with DAA. All but 14 achieved SVR12 and represented the study population. HIV coinfection was present in 42%. At baseline, 57.2%

had advanced liver fibrosis with a median of 11 kPa, FIB-4 of 2.4, and APRI of 0.95. At the time of SVR12, a median reduction of 2.1 kPa ($P < 0.001$) was recognized using elastography. A significant fibrosis regression was seen in 40%, being more frequent in patients with baseline advanced fibrosis than in those with null-mild fibrosis (52.3 vs. 22.5%; $P < 0.001$). Even so, 41.2% of patients with baseline F3-F4 kept within cirrhotic scores. In multivariable analysis, only baseline stiffness was significantly associated with the extent of liver fibrosis regression. **CONCLUSION:** HCV cure with DAA is associated with regression of liver fibrosis in most patients treated with DAA, as measured using elastography, FIB-4 and APRI. This benefit is more pronounced in patients with baseline advanced fibrosis and cirrhosis. The dynamics of liver fibrosis regression are not influenced by HIV coinfection.

[Relationship between various hepatic function scores and the formation of esophageal varices in patients with HIV/HCV coinfection due to contaminated blood products for hemophilia.](#) Yoshimoto T1, Eguchi S1, Natsuda K1, et al. *Hepato Res.* 2018 Oct 25. doi: 10.1111/hepr.13279. [Epub ahead of print]

BACKGROUND: It was reported to be difficult to accurately assess the liver reserve capacity of patients with HIV/HCV coinfection through contaminated blood products by the Child-Pugh (CP) classification. Therefore, we investigated a clinically applicable scoring system in determining the risk of esophageal varices in HIV/HCV coinfecting patients, that is known as latent portal hypertension leading to esophageal varices. **PATIENTS AND METHODS:** Forty-three patients with HIV/HCV coinfection underwent clinical examinations, including endoscopy and assessment of hepatic reserve, in our department between 2009 and 2017. CP score, the recently developed Albumin-Bilirubin (ALBI) grade, and the Albumin-Indocyanine Green Evaluation (ALICE) were compared to evaluate the diagnostic accuracies for the detection of esophageal varices using the Area under the Receiver Operating Characteristic curve (AUROC). **RESULTS:** The patients were all male hemophiliacs and were positive for both HIV and HCV antibodies, with a median age of 45 years (range, 29-66 years). Thirty-seven patients (84.1%) were classified as CP A at the examination. The comparison of AUROCs showed a superior diagnostic accuracy for ALICE (AUROC= 0.814) to detect esophageal varices. The positive prediction rate was maximum with ALICE if -2.325 was set, while the negative prediction rate was maximum with ALBI if -2.575 was set. ALICE showed the most accuracy as compared to other 2 scores. **CONCLUSION:** ALICE scoring was found to be the most valuable system for portal hypertension in HIV/HCV coinfecting hemophilic patients. Because of its high specificity, ALICE for secondary surveillance could be used after other markers such as APRI and FIB-4 indices.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[Characteristics of Opioid Prescriptions to Veterans with Cirrhosis.](#) Rogal SS1, Beste LA2, Youk A3, et al. *Clin Gastroenterol Hepatol.* 2018 Oct 17. pii: S1542-3565(18)31142-X. doi: 10.1016/j.cgh.2018.10.021. [Epub ahead of print]

BACKGROUND & AIMS: Despite increased risks for adverse effects in patients with cirrhosis, little is known about opioid prescriptions for this population. We aimed to assess time

trends in opioid prescribing and factors associated with receiving opioids among patients with cirrhosis. **METHODS:** Among Veterans with cirrhosis, identified using national Veterans Health Administration data (2005-2014), we assessed characteristics of patients and their prescriptions for opioids. We calculated the annual proportion of patients receiving any opioid prescription. Among opioid recipients, we assessed prescriptions that were long-term (>90 days' supply), for high doses (>100 MME/day), or involved combinations of opioids and acetaminophen or benzodiazepine. We evaluated patient characteristics independently associated with long-term and any opioid prescriptions using mixed-effects regression models. **RESULTS:** Among 127,239 Veterans with cirrhosis, 97,974 (77.0%) received a prescription for an opioid. Annual opioid prescriptions increased from 36% in 2005 to 47% in 2014 ($P<.01$). Among recipients of opioids, the proportions of those receiving long-term prescriptions increased from 47% in 2005 to 54% in 2014 ($P<.01$), and 19%-21% received prescriptions for high-dose opioids. Prescriptions for combinations of opioids and acetaminophen decreased from 68% in 2005 to 50% in 2014 ($P<.01$) and for combinations of opioids and benzodiazepines decreased from 24% to 19% over this time ($P<.01$). Greater probability of long-term opioid prescriptions was independently associated with younger age, female sex, white race, hepatitis C, prior hepatic decompensation, hepatocellular carcinoma, mental health disorders, nicotine use disorders, medical comorbidities, surgery, and pain-related conditions. **CONCLUSION:** Among Veterans with cirrhosis, 36%-47% were prescribed opioids in each year. Mental health disorders and hepatic decompensation were independently associated with long-term opioid prescriptions.

[Pooled Resistance Analysis in Patients with Hepatitis C Virus Genotype 1 to 6 Infection Treated with Glecaprevir-Pibrentasvir in Phase 2 and 3 Clinical Trials.](#) Krishnan P1, Pilot-Matias T2, Schnell G2, et al. *Antimicrob Agents Chemother.* 2018 Sep 24;62(10). pii: e01249-18. doi: 10.1128/AAC.01249-18. Print 2018 Oct.

Over 2,200 patients infected with hepatitis C virus (HCV) genotypes (GT) 1 to 6, with or without cirrhosis, who were treatment naive or experienced to interferon, ribavirin, and/or sofosbuvir were treated with glecaprevir/pibrentasvir for 8, 12, or 16 weeks in eight registrational phase 2 and 3 clinical studies. High rates of sustained virologic response at 12 weeks postdosing (SVR12) were achieved with a <1% virologic failure (VF) rate. The prevalence of baseline polymorphisms (BPs) in NS3 at amino acid position 155 or 168 was low (<3%) in patients infected with GT1, GT2, GT3, GT4, and GT6, while 41.9% of the GT5-infected patients had NS3-D168E; BPs were not detected at position 156 in NS3. The prevalence of NS5A-BPs was high across genotypes, driven by common polymorphisms at amino acid position 30 or 31 in GT2, 58 in GT4, and 28 in GT6. The prevalence of NS5A T/Y93 polymorphisms was 5.5% in GT1, 4.9% in GT3, and 12.5% in GT6. Consistent with the activity of glecaprevir and pibrentasvir against most amino acid polymorphisms in vitro, BPs in NS3 and/or NS5A did not have an impact on treatment outcome for patients infected with GT1 to GT6, with the exception of treatment-experienced GT3-infected patients treated for 12 weeks, for whom a 16-week regimen of glecaprevir/pibrentasvir was required to achieve SVR12 rates of $\geq 95\%$. Among the 22 patients experiencing VF, treatment-emergent substitutions were detected in NS3 in 50% of patients and in NS5A in 82% of patients, frequently as a combination of substitutions that conferred resistance to glecaprevir and/or pibrentasvir. The glecaprevir/pibrentasvir regimen, when the recommended durations are used, allows for a pan-genotypic treatment option without the need for baseline resistance testing.

[Sofosbuvir based regimens in the treatment of chronic hepatitis C genotype 1 infection in African-American patients: a community-based retrospective cohort study.](#)

Gayam V1, Tionson B1, Khalid M1, et al. Eur J Gastroenterol Hepatol. 2018 Oct;30(10):1200-1207. doi: 10.1097/MEG.0000000000001233.

BACKGROUND: Direct-acting antiviral (DAA) drugs have been highly effective in the treatment of chronic hepatitis C (HCV) infection. Limited data exist comparing the safety, tolerability, and efficacy of DAAs in African-American (AA) patients with chronic hepatitis C genotype 1 (HCV GT-1) in the community practice setting. We aim to evaluate treatment response of DAAs in these patients. **PATIENTS AND METHODS:** All the HCV GT-1 patients treated with DAAs between January 2014 and January 2018 in a community clinic setting were retrospectively analyzed. Pretreatment baseline patient characteristics, treatment efficacy with a sustained virologic response at 12 weeks post-treatment (SVR12), and adverse reactions were assessed. **RESULTS:** Two-hundred seventy-eight patients of AA descent were included in the study. One-hundred sixty-two patients were treated with ledipasvir/sofosbuvir (SOF)±ribavirin, 38 were treated with simeprevir/SOF±ribavirin, and 38 patients were treated with SOF/velpatasvir. Overall, SVR at 12 weeks was achieved in 94.6% in patients who received one of the three DAA regimens (93.8% in ledipasvir/SOF group, 92.1% in simeprevir/SOF group, and 97.4% in SOF/velpatasvir group). Previous treatment experience, HCV RNA levels and HIV status had no statistical significance on overall SVR achievement (P=0.905, 0.680, and 0.425, respectively). Compensated cirrhosis in each of the treatment groups did not influence overall SVR of 12. The most common adverse effect was fatigue (27%). None of the patients discontinued the treatment because of adverse events. **CONCLUSION:** In the real-world setting, DAAs are safe, effective, and well tolerated in African-American patients with chronic HCV GT-1 infection with a high overall SVR rate of 94.6%. Treatment rates did not differ on the basis of previous treatment and compensated cirrhosis status.

[Functional MRI and delay discounting in patients infected with hepatitis C.](#) McCready H1,2,3, Kohno M1,2,3, Kolessar M1,4, et al. J Neurovirol. 2018 Oct 8. doi: 10.1007/s13365-018-0670-0. [Epub ahead of print]

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.

[Qualitative case study of needle exchange programs in the Central Appalachian region of the United States.](#) Davis SM1,2, Davidov D2,3, Kristjansson AL3, Zullig K3, Baus A3, Fisher M4. PLoS One. 2018 Oct 12;13(10):e0205466. doi: 10.1371/journal.pone.0205466. eCollection 2018.

BACKGROUND: The Central Appalachian region of the United States is in the midst of a hepatitis C virus epidemic driven by injection of opioids, particularly heroin, with contaminated syringes. In response to this epidemic, several needle exchange programs (NEP) have opened to provide clean needles and other supplies and services to people who inject drugs (PWID).

However, no studies have investigated the barriers and facilitators to implementing, operating, and expanding NEPs in less populous areas of the United States. **METHODS:** This qualitative case study consisted of interviews with program directors, police chiefs, law enforcement members, and PWID affiliated with two NEPs in the rural state of West Virginia. Interview transcripts were coded inductively and analyzed using qualitative data analysis software. Final common themes related to barriers and facilitators of past program openings, current program operations, and future program plans, were derived through a consensus of two data coders.

RESULTS: Both NEPs struggled to find existing model programs, but benefited from broad community support that facilitated implementation. The largest operational barrier was the legal conundrum created by paraphernalia laws that criminalize syringe possession. However, both PWID and law enforcement appreciated the comprehensive services provided by these programs. Program location and transportation difficulties were additional noted barriers. Future program operations are threatened by funding shortages and bans, but necessitated by unexpected program demand. **CONCLUSION:** Despite broad community support, program operations are threatened by growing participant volumes, funding shortages, and the federal government's prohibition on the use of funds to purchase needles. Paraphernalia laws create a legal conundrum in the form of criminal sanctions for the possession of needles, which may inadvertently promote needle sharing and disease transmission. Future studies should examine additional barriers to using clean needles provided by rural NEPs that may blunt the effectiveness of NEPs in preventing disease transmission.

[Patient Reaction to Telemedicine for Clinical Management of Hepatitis C Virus Integrated into an Opioid Treatment Program.](#) Talal AH1,2, McLeod A2, Andrews P2, et al. Telemed J E Health. 2018 Oct 16. doi: 10.1089/tmj.2018.0161. [Epub ahead of print]

BACKGROUND AND INTRODUCTION: Virtual integration of hepatitis C virus (HCV) infection management within the opioid treatment program (OTP) through telemedicine may overcome limited treatment uptake encountered when patients are referred offsite. To evaluate the diffusion of telemedicine within the OTP, we conducted a pilot study to assess acceptance of and satisfaction with telemedicine among 45 HCV-infected opioid use disorder (OUD) patients on methadone. **MATERIALS AND METHODS:** We administered a modified 11-item telemedicine satisfaction questionnaire after the initial HCV telemedicine evaluation, when initiating HCV treatment, and 3 months post-HCV treatment completion. Among a patient subset, a semistructured interview further assessed issues of participant referral to the telemedicine program as well as convenience and confidentiality with the telemedicine encounters. **RESULTS:** Patients demonstrated their acceptance of telemedicine-based

encounters by referral of additional participants. They highlighted the convenience of on-site treatment with a liver specialist through recognition of the benefit of "one-stop shopping." They also expressed confidence in the privacy and confidentiality of telemedicine encounters.

DISCUSSION: In this pilot study, telemedicine appears to be well accepted as a modality for HCV management among OUD patients on methadone. Virtual integration of medical and behavioral therapy through telemedicine warrants further investigation for its use in this population. **CONCLUSIONS:** In this pilot study, we found that a largely racial minority population of substance users grew to accept telemedicine over time with diminished privacy and confidentiality concerns. Telemedicine was well accepted within the OTP community as reflected by participant referral to the program.

[Integrated, Co-located, Telemedicine-based Treatment Approaches for Hepatitis C Virus \(HCV\) Management in Opioid Use Disorder Patients on Methadone.](#) Talal AH1,2, Andrews P2, Mcleod A2, Chen Y3, Sylvester C2, Markatou M3, Brown LS2. Clin Infect Dis. 2018 Oct 17. doi: 10.1093/cid/ciy899. [Epub ahead of print]

BACKGROUND AND AIMS: Despite high hepatitis C virus (HCV) prevalence, opioid use disorder (OUD) patients on methadone rarely engage in HCV treatment. We investigated the effectiveness of HCV management via telemedicine in an opioid substitution therapy (OST) program. **METHODS:** OUD patients on methadone underwent biweekly telemedicine sessions between a hepatologist and physician assistant during the entire HCV treatment course. All pretreatment labs (HCV RNA, genotype and noninvasive fibrosis assessments) were obtained onsite and direct acting antivirals were co-administered with methadone using modified directly observed therapy. We used multiple correspondence analysis, LASSO, and logistic regression to identify variables associated with pursuit of HCV care. **RESULTS:** Sixty-two HCV RNA-positive patients (24% HIV-infected, 61% male, 61% black/African-American, 25.8% Hispanic) were evaluated. All patients were stabilized on methadone and all except 4 were HCV genotype 1-infected. Advanced fibrosis/cirrhosis was present in 34.5% of patients. Of the 45 treated patients, 42 (93.3%) achieved viral eradication. Of 17 evaluated patients who were not treated, 5 were discontinued from the drug treatment program or did not follow-up after the evaluation, 2 had HIV adherence issues, and 10 had insurance authorization issues. Marriage and a mental health diagnosis other than depression were the strongest positive predictors of treatment pursuit while being divorced, separated, or widowed was the strongest negative predictor.

CONCLUSION: HCV management via telemedicine integrated into an OST program is a feasible model with excellent virologic effectiveness. Psychosocial and demographic variables can assist in identification of subgroups with a propensity or aversion to pursue HCV treatment.

[Drug Misuse and Hepatitis C Virus Infection Profiles for Three Generations of Patients Being Monitored for Prescription Drug Adherence.](#) McClure FL1, Niles JK, Kaufman HW, Gudin J. Addict Med. 2018 Oct 16. doi: 10.1097/ADM.0000000000000460. [Epub ahead of print]

OBJECTIVES: Two epidemics in the United States are related: opioid drug injection and hepatitis C virus (HCV) infection. This study quantifies the relationship between illicit/prescription drug misuse and HCV infection in 3 population generations: baby boomers (born 1945-1965, inclusive), pre-baby boomers, and post-baby boomers. **METHODS:** This retrospective study included prescription drug consistency (March-December 2015) and HCV (2011-2015) patient test results performed at a large national clinical reference laboratory. HCV

positivity, drug use consistency/inconsistency with prescribed drug information, type of inconsistent use, and inconsistent use of individual drug classes were assessed. **RESULTS:** This study evaluated 39,231 prescription drug monitoring and HCV sets of test results from 18,410 patients. Of these patients, 25.1% tested positive for HCV and 57.3% demonstrated drug test results that were inconsistent with the prescribed medication(s). The types of drug test inconsistency differed substantially between HCV-positive and -negative patients, particularly testing positive for both non-prescribed drugs and prescribed drugs. Specimens from HCV-positive baby boomer and post-baby boomers demonstrated non-prescribed use of opioids and many other drug classes more often than from HCV-negative patients. **CONCLUSIONS:** The rates of inconsistent drug test results and types of drugs misused suggest that HCV-positive patients are more likely than HCV-negative patients to display high-risk behavior, even beyond opioid use. This difference is most pronounced in the post-baby boomer generation. Healthcare professionals should consider these patterns and how they differ by generation when monitoring for both prescription and illicit drugs, the results of which can impact treatment decisions including prescribing analgesics. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. <http://creativecommons.org/licenses/by-nc-nd/4.0>.

[Using telehealth to improve access to hepatitis C treatment in the direct-acting antiviral](#)

[therapy era.](#) Schulz TR1,2, Kanhutu K1,2,3, Sasadeusz J1, Watkinson S1, Biggs BA1,2. J Telemed Telecare. 2018 Oct 18:1357633X18806651. doi: 10.1177/1357633X18806651. [Epub ahead of print]

INTRODUCTION: One-third of the Australian population lives outside major cities and this group has worse health outcomes. Telehealth is becoming an accepted way to improve patient access to specialist healthcare. Over 200,000 Australian's have hepatitis C virus (HCV) and new treatments are very effective and well tolerated. We aim to demonstrate that HCV treatment utilising telehealth support for care delivery has cure rates similar to onsite care in clinical trials. We also report length of consultation and calculate reductions in travel and carbon output. **Methods** Patient demographic, clinical, and treatment outcome data were collected prospectively from hospital software and analysed retrospectively. This was an audit of all patients treated for HCV in one year from a single tertiary hospital that included telehealth in their care delivery. **Results** Sustained virological response was achieved in 51/52 (98%) patients with completed treatment courses, and 51/58 (88%) of those who had a planned telehealth consultation as part of their management. A median of 634 km of patient travel was saved per telehealth consultation. **Discussion** We found that a telehealth-supported outreach programme for patients in regional Australia with HCV produced similar outcomes to clinical trials. There was a considerable saving in time and cost for the patients and significant environmental benefit through the reduction in carbon footprint associated with travel to distant specialist health services. We conclude that telehealth facilitated outreach is a feasible and effective way to access HCV treatment and cure in regional Australia.

[Funding Hepatitis C Treatment in Correctional Facilities by Using a Nominal Pricing](#)

[Mechanism.](#) Spaulding AC1,2, Chhatwal J3,4, Adee MG1, Lawrence RT5, Beckwith CG6,7,

Oehsen WV8. Correct Health Care. 2018 Oct 15:1078345818805770. doi: 10.1177/1078345818805770. [Epub ahead of print]

The cost of treating all incarcerated people who have hepatitis C with direct-acting antiviral agents (DAAs) greatly stresses correctional facility budgets. Complex federal laws bar pharmaceutical companies from simply discounting expensive medications to prices that facilities can afford. This article discusses means by which correctional facilities may qualify under federal law as "safety-net providers" to allow sale of DAAs at a price <10% of the average manufacturer price (AMP). No new laws would need to be enacted to implement this strategy. Using fiscal year 2018 pricing data from the Georgia Department of Corrections, we derived an estimate for the AMP and then used this estimate to calculate a nominal price. The United States would save ~\$3 billion if manufacturers sold DAAs at a nominal price to correctional facilities. Use of this strategy would help solve the conundrum of how state and county governments can pay for hepatitis C treatment and would ultimately save money for society.

HEPATOCELLULAR (LIVER) CANCER

[Liver transplant listing for hepatitis C associated cirrhosis and hepatocellular carcinoma has fallen in the United Kingdom since the introduction of direct acting antiviral therapy.](#)

Vaziri A1, Gimson A1, Agarwal K2, et al. J Viral Hepat. 2018 Oct 19. doi: 10.1111/jvh.13022. [Epub ahead of print]

Following the introduction of direct acting antivirals (DAA), there have been reports of declining incidence of hepatitis C (HCV) related liver disease as a liver transplantation indication. In this study we assessed the impact of DAA on liver transplant indications in the UK and waiting list outcomes for patients with HCV. We assessed UK adult elective liver transplant registrants between 2006 and 2017. The aetiology of liver disease at registration was reclassified using an accepted hierarchical system and changes were assessed over time and compared before and after the introduction of DAA. Registration UKELD scores and 1-year waiting list outcomes were also compared. The proportion of waiting list patients registered with HCV-related cirrhosis reduced after the introduction of DAA from 10.5% in 2013 to 4.7% in 2016 ($p < 0.001$). Alcohol related liver disease (ARLD) was the leading indication for liver transplantation followed by liver cancer (26.1% and 18.4% in 2016 respectively). The proportion of registrations with Hepatocellular carcinoma (HCC) associated with HCV reduced from 46.4% in 2013 to 33.7% in 2016 ($p = 0.002$). For patients with HCV-related cirrhosis at one year the outcomes death, transplantation, delisting due to improvement or deterioration and awaiting a graft at 1 year were similar. For patients with HCV-related HCC the proportion dying at one year reduced significantly from 2.9% to 0.0% ($p = 0.04$). These data demonstrate an association between DAA and reduced listing rates for HCV-related cirrhosis and HCC, but no significant changes in waiting list outcomes other than reduced mortality in the HCC group. his article is protected by copyright. All rights reserved.

[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. 2018 Oct 15. pii: S0168-8278(18)32454-1. doi: 10.1016/j.jhep.2018.09.029. [Epub ahead of print]
BACKGROUND AND AIMS: It remains controversial whether direct-acting antivirals (DAA) 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 DAA (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. Recurrence pattern was categorized as follows: intrahepatic recurrence with a single tumor < 2 cm (stage 0), a single tumor or up to three 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, multiple histories of HCC treatment, 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 HCC recurrence rates and patterns between patients who received IFN-based and DAA therapy after HCC treatment. High lens culinaris agglutinin-reactive fraction of alpha-fetoprotein level, short recurrence-free period, and multiple histories of HCC treatment were independent risk factors for early HCC recurrence after the initiation of antiviral therapy.

[Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study.](#) Hong TP1, Gow PJ2, Fink M3, et al. Med J Aust. 2018 Oct 15;209(8):348-354.

OBJECTIVES: To determine the factors associated with survival of patients with hepatocellular carcinoma (HCC) and the effect of HCC surveillance on survival. **DESIGN, SETTING AND PARTICIPANTS:** Prospective population-based cohort study of patients newly diagnosed with HCC in seven tertiary hospitals in Melbourne, 1 July 2012 - 30 June 2013. **MAIN OUTCOME MEASURES:** Overall survival (maximum follow-up, 24 months); factors associated with HCC surveillance participation and survival. **RESULTS:** 272 people were diagnosed with incident HCC during the study period; the most common risk factors were hepatitis C virus infection (41%), alcohol-related liver disease (39%), and hepatitis B virus infection (22%). Only 40% of patients participated in HCC surveillance at the time of diagnosis; participation was significantly higher among patients with smaller median tumour size (participants, 2.8 cm; non-participants, 6.0 cm; $P < 0.001$) and earlier Barcelona Clinic Liver Cancer (BCLC) stage disease (A/B, 59%; C/D, 25%; $P < 0.001$). Participation was higher among patients with compensated cirrhosis or hepatitis C infections; it was lower among those with alcohol-related liver disease or decompensated liver disease. Median overall survival time was 20.8 months; mean survival time was 18.1 months (95% CI, 16.6-19.6 months). Participation in HCC surveillance was associated with significantly lower mortality (adjusted hazard ratio [aHR], 0.60; 95% CI, 0.38-0.93; $P = 0.021$), as were curative therapies (aHR, 0.33; 95% CI, 0.19-0.58). Conversely, higher Child-Pugh class, alpha-fetoprotein levels over 400 kU/L, and later BCLC disease stages were each associated with higher mortality. **CONCLUSIONS:** Survival for patients with HCC is poor, but may be improved by surveillance, associated with the identification of earlier stage tumours, enabling curative therapies to be initiated.

[PNPLA3 and TM6SF2 variants as risk factors of hepatocellular carcinoma across various etiologies and severity of underlying liver diseases.](#) Yang J1, Trépo E1,2, Nahon P1,3,4, et al. *Int J Cancer*. 2018 Oct 5. doi: 10.1002/ijc.31910. [Epub ahead of print]

Few single nucleotide polymorphisms (SNPs) have been reproducibly associated with hepatocellular carcinoma (HCC). Our aim was to test the association between nine SNPs and HCC occurrence. SNPs in genes linked to HCC (DEPDC5, GRIK1, KIF1B, STAT4, MICA, DLC1, DDX18) or to liver damage (PNPLA3-rs738409, TM6SF2-rs58542926) in GWAS were genotyped in discovery cohorts including 1,020 HCC, 2,021 controls with chronic liver disease and 2,484 healthy individuals and replication was performed in prospective cohorts of cirrhotic patients with alcoholic liver disease (ALD, n=249) and hepatitis C (n=268). In the discovery cohort, PNPLA3 and TM6SF2 SNPs were associated with HCC (OR=1.67 [CI95%:1.16-2.40], p=0.005; OR=1.45 [CI95%:1.08-1.94], p=0.01) after adjustment for fibrosis, age, gender and etiology. In contrast, STAT4-rs7574865 was associated with HCC only in HBV infected patients (p=0.03) and the other tested SNP were not linked with HCC risk. PNPLA3 and TM6SF2 variants were independently associated with HCC in patients with ALD (OR=3.91 [CI95%:2.52-6.06], p=1.14E-09; OR=1.79 [CI95%:1.25-2.56], p=0.001) but not with other etiologies. PNPLA3 SNP was also significantly associated with HCC developed on a non-fibrotic liver (OR=2.19 [CI95%:1.22-3.92], p=0.007). The association of PNPLA3 and TM6SF2 with HCC risk was confirmed in the prospective cohort with ALD. A genetic score including PNPLA3 and TM6SF2 minor alleles showed a progressive significant increased risk of HCC in ALD patients. **In conclusion**, PNPLA3-rs738409 and TM6SF2-rs58542926 are inherited risk variants of HCC development in patients with ALD in a dose dependent manner. The link between PNPLA3 and HCC on non-fibrotic liver suggests a direct role in liver carcinogenesis. This article is protected by copyright. All rights reserved.

[A changing etiologic scenario in liver transplantation for hepatocellular carcinoma in a multicenter cohort study from Latin America.](#) Piñero F1, Costa P2, Boteon YL3, et al. *Clin Res Hepatol Gastroenterol*. 2018 Oct;42(5):443-452. doi: 10.1016/j.clinre.2018.03.014.

BACKGROUND AND AIM: Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of hepatocellular carcinoma (HCC) and liver transplantation (LT). Our study focused on changing trends of liver related HCC etiologies during the last years in Latin America.

METHODS: From a cohort of 2761 consecutive adult LT patients between 2005 and 2012 in 17 different centers, 435 with HCC were included. Different periods including years 2005-2006, 2007-2008, 2009-2010 and 2011-2012 were considered. Etiology of liver disease was confirmed in the explant. **RESULTS:** Participating LT centers per country included 2 from Brazil (n=191), 5 transplant programs from Argentina (n=98), 2 from Colombia (n=65), 4 from Chile (n=49), 2 from Mexico (n=12), and 1 from Peru (n=11) and Uruguay (n=9). Chronic hepatitis C infection was the leading cause of HCC in the overall cohort (37%), followed by HBV (25%) and alcoholic liver disease (17%). NAFLD and cryptogenic cirrhosis accounted for 6% and 7%, respectively. While HCV decreased from 48% in 2005-06 to 26% in 2011-12, NAFLD increased from 1.8% to 12.8% during the same period, accounting for the third cause of HCC. This represented a 6-fold increase in NAFLD-HCC, whereas HCV had a 2-fold decrease. Patients with NAFLD were older, had lower pre-LT serum AFP values and similar 5-year survival and recurrence rates than non-NAFLD. **CONCLUSION:** There might be a global changing figure

regarding etiologies of HCC in Latin America. This epidemiological change on the incidence of HCC in the world, although it has been reported, should still be confirmed in prospective studies.

Epidemiology and Management of Hepatocellular Carcinoma. Kulik L1, El-Serag HB2. Gastroenterology. 2018 Oct 24. pii: S0016-5085(18)35165-5. doi: 10.1053/j.gastro.2018.08.065. [Epub ahead of print]

The major risk factors for hepatocellular carcinoma (HCC) in a contemporary clinical practice is becoming increasingly related to post sustained virological response hepatitis C, suppressed hepatitis B virus on treatment, alcoholic and non-alcoholic fatty liver disease. We review the emerging data on the risk and determinants of HCC in these conditions, and the implications to HCC surveillance. However, from a public health perspective, active hepatitis C and B continue to drive most of the global burden of HCC. In United States, the age adjusted incidence rates of HCC in Hispanics have surpassed that of Asians. Prognosis in HCC is complex due to the competing risk imposed by underlying cirrhosis and presence of malignancy. In addition to tumor burden, liver function and performance status, additional parameters including tumor biopsy, serum markers and sub classification of current staging systems, taking into account patterns of tumor progression, may improve patient selection for therapy. Advancements in the treatment of HCC has included identification of patients that are most likely to derive a clinically significant benefit from the available therapeutic options. Additionally, the combination strategies of locoregional therapies and/or systemic therapy are being investigated.