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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

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Efficacy of 12 or 18 weeks of elbasvir plus grazoprevir with ribavirin in treatment-naïve, non-cirrhotic HCV genotype 3-infected patients.](#) Gane E1, Nahass R2, Luketic V3,4, Asante-Appiah E5, Hwang P5, Robertson M5, Wahl J5, Barr E5, Haber B5. J Viral Hepat. 2017 May 4. doi: 10.1111/jvh.12719. [Epub ahead of print]

Elbasvir (EBR; HCV NS5A inhibitor) and grazoprevir (GZR; HCV NS3/4A protease inhibitor) are approved as a fixed-dose combination to treat patients chronically infected with HCV genotypes 1 and 4. During the development program and supported by in vitro potency, the efficacy of EBR + GZR was assessed in HCV GT3-infected patients. This study's aim was to determine the efficacy and tolerability of 12 or 18 weeks of EBR+GZR with ribavirin (RBV) in treatment-naïve, non-cirrhotic HCV GT3-infected patients. Randomized patients received open-label EBR (50 mg once daily) + GZR (100 mg once daily) + RBV. The primary efficacy objective was to evaluate the sustained virologic response rates 12 weeks after the end of all study therapy (SVR12). SVR12 rates (95% confidence interval) were 45.0% (23.1, 68.5) and 57.1% (34.0, 78.2) after treatment with EBR+GZR+RBV for 12 weeks or 18 weeks, respectively. On-treatment virologic failure was observed in 41% (17/41) of patients. At virologic failure, resistance-associated substitutions (RASs) with a >5 fold shift in potency occurred in the NS3 region in 6 (35%) patients and in the NS5A region in 16 (94%) patients. The most common RAS at virologic failure was Y93H in NS5A which was identified in 13/17 (76%) patients. The efficacy of EBR+GZR+RBV was suboptimal in HCV GT3-infected patients due to a high rate of on-treatment virologic failure and treatment emergent RASs which demonstrates an inadequate barrier to the development of GT3 resistance. However, rapid viral clearance demonstrated the antiviral activity of EBR+GZR+RBV in GT3-infected patients.

[Effectiveness and safety of ledipasvir/sofosbuvir±ribavirin in the treatment of HCV infection: The real-world HARVEST study.](#) Flisiak R1, Łucejko M2, Mazur W3, et al. Adv Med Sci. 2017 May 26;62(2):387-392. doi: 10.1016/j.advms.2017.04.004. [Epub ahead of print]

BACKGROUND: To evaluate the effectiveness and safety of ledipasvir/sofosbuvir (LDV/SOF)±ribavirin (RBV) regimen in a real-world setting. **METHODS:** Patients received a fixed-dose combination tablet containing LDV and SOF with or without RBV, for 8, 12 or 24 weeks. Patients were assessed at baseline, end of treatment, and 12 weeks after the end of treatment. The primary effectiveness endpoint was sustained virologic response 12 weeks after

the end of treatment (SVR12). **RESULTS:** Of the 86 patients, aged 20-80 years, 82.6% were HCV genotype 1b-infected and 50.0% were cirrhotic. More than half (52.3%) had previously followed pegylated interferon-containing (PEG-IFN) treatment regimens, and 38.5% were non-responders. SVR12 was achieved by 94.2% of patients. All non-responders were cirrhotic: two demonstrated virologic breakthrough and the remaining three relapsed. All patients treated with an 8-week regimen achieved SVR12 despite having high viral load at baseline (HCV RNA of >1 million IU/mL in 8/10 patients, including one with a viral load of >6 million IU/mL). Adverse events were generally mild and transient. Most frequently, fatigue (22.1%), headache (15.1%), and arthralgia (7.0%) were observed. Laboratory abnormalities included anemia and hyperbilirubinemia. **CONCLUSIONS:** Treatment with LDV/SOF±RBV is an effective and safe option for patients with HCV, including those with advanced liver disease or a history of non-response to PEG-IFN-based therapy.

Sofosbuvir and Ribavirin in Adolescents 12 to 17 Years Old With Hepatitis C Virus

Genotype 2 or 3 Infection. Wirth S1, Rosenthal P2, Gonzalez-Peralta RP3, et al. *Hepatology*. 2017 May 22. doi: 10.1002/hep.29278. [Epub ahead of print]

BACKGROUND & AIMS: Children with chronic hepatitis C virus (HCV) infection have limited treatment options. We evaluated the all-oral combination of sofosbuvir and ribavirin in adolescents aged 12-17 with HCV genotype 2 or 3. **METHODS:** Fifty-two patients received sofosbuvir 400mg once daily and weight-based ribavirin twice daily for 12 (genotype 2) or 24 (genotype 3) weeks. The pharmacokinetics of sofosbuvir and its metabolite GS-331007 were evaluated by intensive plasma sampling at day 7 in the first 10 patients enrolled, and by sparse sampling in all patients throughout treatment. The primary efficacy endpoint was the percentage of patients with a sustained virologic response 12 weeks after treatment (SVR12). **RESULTS:** The median age of patients was 15 years, and 75% had genotype 3. Eighty-three percent of patients were treatment-naïve, and 73% were infected by vertical transmission. Forty percent were assessed as not having cirrhosis; the remainder did not have a cirrhosis determination. Overall, SVR12 was achieved by 98% of patients (51/52; 95% CI, 90%-100%). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR12 was lost to follow-up after achieving SVR4. The most commonly reported adverse events were nausea (27%) and headache (23%). When compared with the exposure in adults treated in Phase 2 and 3 sofosbuvir studies, the AUC_{tau} and C_{max} for sofosbuvir and GS-331007 in adolescents were within predefined pharmacokinetic equivalence boundaries of 50%-200%. **CONCLUSION:** Sofosbuvir and ribavirin was safe and highly effective in adolescents with chronic HCV genotype 2 or 3 infection. <http://ClinicalTrials.gov> NCT02175758. This article is protected by copyright. All rights reserved.

The Performance of Serum Biomarkers for Predicting Fibrosis in Patients with Chronic Viral Hepatitis.

Bang CS1, Kang HY2, Choi GH2, Kim SB2, Lee W3, Song IH2. *Korean J Gastroenterol*. 2017 May 25;69(5):298-307. doi: 10.4166/kjg.2017.69.5.298.

BACKGROUND/AIMS: The invasiveness of a liver biopsy and its inconsistent results have prompted efforts to develop noninvasive tools to evaluate the severity of chronic hepatitis. This study was intended to assess the performance of serum biomarkers for predicting liver fibrosis in patients with chronic viral hepatitis. **METHODS:** A total of 302 patients with chronic hepatitis

B or C, who had undergone liver biopsy, were retrospectively enrolled. We investigated the diagnostic accuracy of several clinical factors for predicting advanced fibrosis ($F \geq 3$).

RESULTS: The study population included 227 patients with chronic hepatitis B, 73 patients with chronic hepatitis C, and 2 patients with co-infection (hepatitis B and C). Histological cirrhosis was identified in 16.2% of the study population. The grade of porto-periportal activity was more correlated with the stage of chronic hepatitis compared with that of lobular activity ($r=0.640$ vs. $r=0.171$). Fibrosis stage was correlated with platelet count ($r=-0.520$), aspartate aminotransferase to platelet ratio index (APRI) ($r=0.390$), prothrombin time ($r=0.376$), and albumin ($r=-0.357$). For the diagnosis of advanced fibrosis, platelet count and APRI were the most predictive variables (AUROC=0.752, and 0.713, respectively). **CONCLUSIONS:** In a hepatitis B endemic region, platelet count and APRI could be considered as reliable non-invasive markers for predicting fibrosis of chronic viral hepatitis. However, it is necessary to validate the diagnostic accuracy of these markers in another population.

[Ledipasvir-Sofosbuvir Plus Ribavirin in Treatment-Naive Patients With Hepatitis C Virus Genotype 3 Infection: An Open-Label Study.](#)

Feld JJ1, Ramji A2, Shafran SD3, Willems B4, Marotta P5, Huchet E6, Vachon ML7, Svarovskaia ES8, Huang KC8, Hyland RH8, Yun C8, Massetto B8, Brainard DM8, McHutchison JG8, Tam E9, Bailey R10, et al. Clin Infect Dis. 2017 May 23. doi: 10.1093/cid/cix289. [Epub ahead of print]

BACKGROUND: Patients chronically infected with genotype 3 hepatitis C virus (HCV) have faster disease progression and are less responsive to current direct-acting antiviral regimens than patients infected with other genotypes. We conducted an open-label trial to evaluate the safety, tolerability, and efficacy of ledipasvir and sofosbuvir plus ribavirin in patients with genotype 3 HCV infection. **METHODS:** We enrolled treatment-naive patients with and without compensated cirrhosis at 15 sites in Canada. All patients were treated with ledipasvir-sofosbuvir (90 mg and 400 mg) plus weight-based ribavirin for 12 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). Secondary endpoints included evaluation of baseline and treatment-emergent drug resistance. **RESULTS:** Of the 111 patients enrolled, 105 (95%) had subtype 3a HCV and 39 (35%) had compensated cirrhosis. SVR12 was achieved by 99 of 111 patients (89%; 95% confidence interval, 82%-94%). Of the 39 patients with cirrhosis, 31 (79%) achieved SVR12, compared with 68 of 72 (94%) patients without cirrhosis. No treatment-emergent resistance mutations occurred in those who failed treatment. One patient discontinued treatment due to liver cancer and died 22 days after treatment discontinuation. The most common adverse events were fatigue (51%), headache (36%), and nausea (23%). **CONCLUSIONS:** In this multicenter trial involving treatment-naive patients with genotype 3 HCV, 12 weeks of ledipasvir-sofosbuvir provided a high level of SVR in those without cirrhosis.

[Liver stiffness reduction correlates with histological characteristics of Hepatitis C patients with sustained virological response.](#)

Tachi Y1, Hirai T1, Kojima Y1, Ishizu Y2, Honda T2, Kuzuya T2, Hayashi K2, Ishigami M2, Goto H2. Liver Int. 2017 May 30. doi: 10.1111/liv.13486. [Epub ahead of print]

BACKGROUND AND AIMS: We investigated the correlation between histological characteristics and changes in liver stiffness in patients with sustained virological response using acoustic radiation force impulse elastography. **METHODS:** In this prospective study, we

enrolled 176 Hepatitis C patients with sustained virological response who underwent acoustic radiation force impulse elastography and liver biopsy before antiviral treatment, and serial acoustic radiation force impulse elastography at the end of treatment and at 24 weeks after the end of treatment. To compare the long-term changes in liver stiffness in patients with sustained virological response using acoustic radiation force impulse elastography, another group of 140 patients who had undergone paired biopsy after achieving sustained virological response were included. **RESULTS:** Mean liver stiffness values were 1.60 ± 0.63 m/s, 1.48 ± 0.56 m/s and 1.37 ± 0.62 m/s at baseline, end of treatment, and 24 weeks after end of treatment, respectively, $P < 0.001$. Higher inflammatory activity at baseline was associated with an improvement in liver stiffness at the end of treatment, with an odds ratio of 1.940. Significant fibrosis at baseline was associated with an improvement in liver stiffness at 24 weeks after the end of treatment, with an odds ratio of 2.617. Among patients in the paired biopsy group with baseline fibrosis stage identical to the acoustic radiation force impulse group, liver stiffness values at 24 weeks after the end of treatment did not show any difference with values at 5 years after end of treatment. **CONCLUSIONS:** Pre-treatment histological characteristics influence liver stiffness reduction after sustained virological response is achieved. This article is protected by copyright. All rights reserved.

[Elbasvir plus grazoprevir in patients with hepatitis C virus infection and stage 4-5 chronic kidney disease: clinical, virological, and health-related quality-of-life outcomes from a phase 3, multicentre, randomised, double-blind, placebo-controlled trial.](#) Bruchfeld A1,

Roth D2, Martin P3, et al. *Lancet Gastroenterol Hepatol.* 2017 May 30. pii: S2468-1253(17)30116-4. doi: 10.1016/S2468-1253(17)30116-4. [Epub ahead of print]

BACKGROUND: In the C-SURFER study, therapy with the all-oral elbasvir plus grazoprevir regimen for 12 weeks in patients with chronic hepatitis C virus (HCV) infection and stage 4-5 chronic kidney disease resulted in a high rate of virological cure compared with placebo. Here, we report sustained virological response (SVR), safety data, health-related quality-of-life (HRQOL), and virological resistance analyses in patients in C-SURFER who received immediate antiviral therapy or who received placebo before therapy. **METHODS:** In this phase 3, multicentre, randomised, placebo-controlled study, we randomly assigned adults with HCV genotype 1 infection and stage 4-5 chronic kidney disease enrolled at 68 centres worldwide to either elbasvir 50 mg plus grazoprevir 100 mg once per day for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by elbasvir 50 mg plus grazoprevir 100 mg once per day for 12 weeks beginning at week 16 (deferred treatment group). The primary safety and efficacy endpoints for the immediate treatment group and placebo phase of the deferred treatment group have been reported previously. Here, we report safety and efficacy data for the treatment phase of the deferred treatment group, as well as HRQOL assessed using the 36-Item Short Form Health Survey for all groups, and baseline and treatment-emergent resistance-associated substitutions (RASs). SVR at 12 weeks (SVR12) was assessed in the modified full analysis set (FAS), defined as all patients excluding those who did not receive at least one dose of study drug, who died, or who discontinued the study before the end of treatment for reasons determined to be unrelated to HCV treatment. This trial is registered with ClinicalTrials.gov, Number NCT02092350. **FINDINGS:** Between March 30 and Nov 28, 2014, 235 patients were enrolled and received at least one dose of study drug. The modified FAS included 116 patients assigned to immediate treatment and 99 assigned to deferred treatment. 115 (99.1%; 95% CI 95.3-100.0) of 116 assigned to immediate treatment achieved SVR12 compared with 97 (98.0%;

92.9-99.7) of 99 assigned to deferred treatment. In patients with genotype 1a infections, SVR12 was achieved by 11 (84.6%) of 13 patients with detectable baseline NS5A RASs and in 98 (100%) of 98 without. HRQOL did not differ at week 12 between immediate treatment and the placebo phase of deferred treatment. Safety was generally similar between patients receiving immediate treatment and those receiving placebo in the deferred treatment group. One serious adverse event during deferred treatment (interstitial nephritis) and one during the placebo phase of deferred treatment (raised lipase concentration) were deemed related to study drug. Four patients died, one who received immediate treatment (cardiac arrest) and three who received deferred treatment (aortic aneurysm, pneumonia, and unknown cause); all four deaths were considered unrelated to study drugs. Of the three deaths in the deferred treatment group, one occurred during placebo treatment and two occurred before starting active treatment. There were no notable differences in aminotransferase elevations in the deferred treatment group compared with the immediate treatment group, and no patients in the deferred treatment group had total bilirubin elevations. **INTERPRETATION:** These data add to the growing body of clinical evidence for the fixed-dose combination regimen of elbasvir plus grazoprevir for 12 weeks and support use of this therapy in patients with HCV genotype 1 infection and stage 4-5 chronic kidney disease. **FUNDING:** Merck Sharp & Dohme.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Differential hepatitis C virus RNA target site selection and host factor activities of naturally occurring miR-122 3' variants.](#)

Yamane D^{1,2}, Selitsky S^{R1,3,4}, Shimakami T^{1,5}, Li Y^{1,2}, Zhou M^{1,3,4}, Honda M⁵, Sethupathy P^{1,3,4}, Lemon S^{M1,2}. *Nucleic Acids Res.* 2017 May 5;45(8):4743-4755. doi: 10.1093/nar/gkw1332.

In addition to suppressing cellular gene expression, certain miRNAs potently facilitate replication of specific positive-strand RNA viruses. miR-122, a pro-viral hepatitis C virus (HCV) host factor, binds and recruits Ago2 to tandem sites (S1 and S2) near the 5' end of the HCV genome, stabilizing it and promoting its synthesis. HCV target site selection follows canonical miRNA rules, but how non-templated 3' miR-122 modifications impact this unconventional miRNA action is unknown. High-throughput sequencing revealed that a 22 nt miRNA with 3'G ('22-3'G') comprised <63% of total miR-122 in human liver, whereas other variants (23-3'A, 23-3'U, 21-3'U) represented 11-17%. All loaded equivalently into Ago2, and when tested individually functioned comparably in suppressing gene expression. In contrast, 23-3'A and 23-3'U were more active than 22-3'G in stabilizing HCV RNA and promoting its replication, whereas 21-3'U was almost completely inactive. This lack of 21-3'U HCV host factor activity correlated with reduced recruitment of Ago2 to the HCV S1 site. Additional experiments demonstrated strong preference for guanosine at nt 22 of miR-122. Our findings reveal the importance of non-templated 3' miR-122 modifications to its HCV host factor activity, and identify unexpected differences in miRNA requirements for host gene suppression versus RNA virus replication.

[Usefulness of humanized cDNA-uPA/SCID mice for the study of hepatitis B virus and hepatitis C virus virology.](#)

Uchida T¹, Imamura M¹, Kan H¹, et al. *J Gen Virol.* 2017 May;98(5):1040-1047. doi: 10.1099/jgv.0.000726. Epub 2017 May 25.

Urokinase-type plasminogen activator/severe combined immunodeficiency (uPA/SCID) mice transplanted with human hepatocytes are permissive for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. However, one of the problems affecting uPA transgenic mice is the expansion of mouse hepatocyte colonies due to homologous recombination of the uPA gene. In this study, we attempted to infect HBV and HCV in humanized cDNA-uPA/SCID mice, a novel uPA transgenic mouse model designed to overcome this disadvantage. Three hundred and eighty-six uPA/SCID and 493 cDNA-uPA/SCID mice were transplanted with human hepatocytes and then injected with either HBV- or HCV-positive human serum samples or HBV-transfected cell culture medium. Twelve weeks after human hepatocyte transplantation, the mouse serum concentration of human albumin, which is correlated with the degree of repopulation by human hepatocytes, was significantly higher in cDNA-uPA/SCID mice compared with uPA/SCID mice. HBV-infected cDNA-uPA/SCID mice showed significantly greater and more persistent viraemia, and similar virological effects by entecavir treatment were achieved in both systems. HCV-infected cDNA-uPA/SCID mice developed more frequent and significantly higher viraemia compared with uPA/SCID mice. The present study using a large number of mice showed that cDNA-uPA/SCID mice transplanted with human hepatocytes developed high and long-term persistent viraemia following HBV and HCV infection, and a higher survival rate was observed in cDNA-uPA/SCID compared with uPA/SCID mice. These mice may be a useful animal model for the study of HBV and HCV virology and the analysis of the effect of antiviral drugs.

In Vitro Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS5A Inhibitor Pibrentasvir.

Ng TII, Krishnan P2, Pilot-Matias T2, et al. *Antimicrob Agents Chemother.* 2017 Apr 24;61(5). pii: e02558-16. doi: 10.1128/AAC.02558-16. Print 2017 May.

Pibrentasvir (ABT-530) is a novel and pan-genotypic hepatitis C virus (HCV) NS5A inhibitor with 50% effective concentration (EC₅₀) values ranging from 1.4 to 5.0 pM against HCV replicons containing NS5A from genotypes 1 to 6. Pibrentasvir demonstrated similar activity against a panel of chimeric replicons containing HCV NS5A of genotypes 1 to 6 from clinical samples. Resistance selection studies were conducted using HCV replicon cells with NS5A from genotype 1a, 1b, 2a, 2b, 3a, 4a, 5a, or 6a at a concentration of pibrentasvir that was 10- or 100-fold over its EC₅₀ for the respective replicon. With pibrentasvir at 10-fold over the respective EC₅₀, only a small number of colonies (0.00015 to 0.0065% of input cells) with resistance-associated amino acid substitutions were selected in replicons containing genotype 1a, 2a, or 3a NS5A, and no viable colonies were selected in replicons containing NS5A from other genotypes. With pibrentasvir at 100-fold over the respective EC₅₀, very few colonies (0.0002% of input cells) were selected by pibrentasvir in genotype 1a replicon cells while no colonies were selected in other replicons. Pibrentasvir is active against common resistance-conferring substitutions in HCV genotypes 1 to 6 that were identified for other NS5A inhibitors, including those at key amino acid positions 28, 30, 31, or 93. The combination of pibrentasvir with HCV inhibitors of other classes produced synergistic inhibition of HCV replication. In summary, pibrentasvir is a next-generation HCV NS5A inhibitor with potent and pan-genotypic activity, and it maintains activity against common amino acid substitutions of HCV genotypes 1 to 6 that are known to confer resistance to currently approved NS5A inhibitors.

[Diversity of the association of serum levels and genetic variants of MHC class I polypeptide-related chain A with liver fibrosis in chronic hepatitis C.](#) Huang CF^{1,2,3}, Huang CII, Yeh ML^{1,2}, et al. *Oncotarget*. 2017 May 16;8(20):32618-32625. doi: 10.18632/oncotarget.15941.

BACKGROUND/AIMS: Genetic variants of MHC class I polypeptide-related chain A (MICA) at rs2596542 have been associated with hepatocellular carcinoma. The linkage between serum MICA (sMICA) and liver fibrosis in chronic hepatitis C is elusive. **RESULTS:** Linear regression analysis revealed that sMICA were independently correlated to α -fetoprotein (β : 0.149; 95% confidence interval [CI]: 0.001, 0.003; $P = 0.007$) and MICA rs2596542 GG genotype (β : 0.209; 95% CI: 0.153, 0.483; $P < 0.001$). While patients were stratified by MICA genetic variants, advanced fibrosis was the only factor independently correlated to sMICA among A allele carriers (β : 0.234; 95% CI: 0.107, 0.543; $P = 0.004$) but not among non-A allele carriers. Logistic regression analysis revealed that factors associated with advanced liver fibrosis was sMICA (OR/CI: 2.996/1.428-6.287, $P = 0.004$) and platelet counts (OR/CI: 0.988/0.982-0.994, $P < 0.001$) in MICA rs2596542 A allele carriers. sMICA > 50 pg/mL provided a positive predictive value of 72 % in predicting advanced liver fibrosis (F3-4) and of 90% in significant fibrosis ($> F2$) in MICA rs2596542 A allele carriers. **MATERIALS AND METHODS:** Serum level and single nucleotide polymorphism at rs2596542 of MICA were tested for the association with liver fibrosis in 319 biopsy proven chronic hepatitis C patients. **CONCLUSIONS:** Levels of sMICA were highly correlated to liver disease severity in chronic hepatitis C patients who carried the MICA rs738409 A allele. Patients possessing the genetic predisposition had a higher likelihood of progressed liver fibrosis if they expressed higher sMICA levels.

[TCF1+ hepatitis C virus-specific CD8+ T cells are maintained after cessation of chronic antigen stimulation.](#) Wieland D^{1,2,3}, Kemming J^{1,3}, Schuch A^{1,3}, et al. *Nat Commun*. 2017 May 3;8:15050. doi: 10.1038/ncomms15050.

Differentiation and fate of virus-specific CD8+ T cells after cessation of chronic antigen stimulation is unclear. Here we show that a TCF1+CD127+PD1+ hepatitis C virus (HCV)-specific CD8+ T-cell subset exists in chronically infected patients with phenotypic features of T-cell exhaustion and memory, both before and after treatment with direct acting antiviral (DAA) agents. This subset is maintained during, and for a long duration after, HCV elimination. After antigen re-challenge the less differentiated TCF1+CD127+PD1+ population expands, which is accompanied by emergence of terminally exhausted TCF1-CD127-PD1hi HCV-specific CD8+ T cells. These results suggest the TCF1+CD127+PD1+ HCV-specific CD8+ T-cell subset has memory-like characteristics, including antigen-independent survival and recall proliferation. We thus provide evidence for the establishment of memory-like virus-specific CD8+ T cells in a clinically relevant setting of chronic viral infection and we uncover their fate after cessation of chronic antigen stimulation, implicating a potential strategy for antiviral immunotherapy.

[Broadly neutralizing antibodies with few somatic mutations and hepatitis C virus clearance.](#) Bailey JR, Flyak AI, Cohen VJ, et al. *JCI Insight*. 2017 May 4;2(9). pii: 92872. doi: 10.1172/jci.insight.92872. [Epub ahead of print]

Here, we report the isolation of broadly neutralizing mAbs (bNAbs) from persons with broadly neutralizing serum who spontaneously cleared hepatitis C virus (HCV) infection. We found that bNAbs from two donors bound the same epitope and were encoded by the same germline heavy chain variable gene segment. Remarkably, these bNAbs were encoded by antibody variable

genes with sparse somatic mutations. For one of the most potent bNAbs, these somatic mutations were critical for antibody neutralizing breadth and for binding to autologous envelope variants circulating late in infection. However, somatic mutations were not necessary for binding of the bNAb unmutated ancestor to envelope proteins of early autologous transmitted/founder viruses. This study identifies a public B cell clonotype favoring early recognition of a conserved HCV epitope, proving that anti-HCV bNAbs can achieve substantial neutralizing breadth with relatively few somatic mutations, and identifies HCV envelope variants that favored selection and maturation of an anti-HCV bNAb in vivo. These data provide insight into the molecular mechanisms of immune-mediated clearance of HCV infection and present a roadmap to guide development of a vaccine capable of stimulating anti-HCV bNAbs with a physiologic number of somatic mutations characteristic of vaccine responses.

HIV/HCV COINFECTION

[Spontaneous clearance of chronic hepatitis C is rare in HIV-infected patients after effective use of combination antiretroviral therapy.](#) Frias M1, Rivero-Juarez A1, Tellez F2, et al. PLoS One. 2017 May 4;12(5):e0177141. doi: 10.1371/journal.pone.0177141. eCollection 2017.

OBJECTIVE: To evaluate the rate of spontaneous resolution of chronic hepatitis C (CHC) infection in a cohort of HIV-infected patients. **METHODS:** A retrospective analysis of 509 HIV-infected patients with chronic HCV infection was performed at two reference hospitals in Andalusia. The main variable of the study was spontaneous clearance of CHC, defined as a negative HCV RNA result after at least two previous quantitative measurements of HCV RNA separated by a minimum of 12 months. **RESULTS:** Of 509 patients, 3 (0.59%; 95% CI: 0.15%-1.6%) experienced spontaneous clearance of CHC. After combination antiretroviral therapy (cART) initiation, two of three cases experienced an increased CD4+ count, coinciding with HCV viral clearance. All patients were IL28B CC carriers, 2 were co-infected with HCV genotype 3 (the HCV genotype of the remaining patient was not available). **CONCLUSIONS:** Spontaneous clearance of CHC is a rare event in the context of HIV/HCV co-infected patients and may be associated with the effective use of cART and thus HIV suppression.

[HIV-coinfected patients respond worse to direct-acting antiviral-based therapy against chronic hepatitis C in real life than HCV-monoinfected individuals: a prospective cohort study.](#) Neukam K1,2, Morano-Amado LE3, Rivero-Juárez A4, et al. HIV Clin Trials. 2017 May;18(3):126-134. doi: 10.1080/15284336.2017.1330801.

OBJECTIVE: HIV/HCV-coinfected patients and hepatitis C virus (HCV) monoinfected subjects are thought to respond equally to direct-acting antiviral (DAA)-based therapy despite the lack of data derived from clinical trials. This study is aimed to evaluate the impact of HIV coinfection on the response to DAA-based treatment against HCV infection in the clinical practice. **PATIENTS AND METHODS:** In a prospective multicohort study, patients who initiated DAA-based therapy at the Infectious Disease Units of 33 hospitals throughout Spain were included. The primary efficacy outcome variables were the achievement of sustained virologic response 12 weeks after the scheduled end of therapy date (SVR12). **RESULTS:** A total of 908 individuals had reached the SVR12 evaluation time-point, 426 (46.9%) were HIV/HCV-coinfected, and 472 (52%) received interferon (IFN)-free therapy. In an intention-to-treat analysis, SVR12 rates in subjects with and without HIV-coinfection were 55.3% (94/170 patients) versus 67.3% (179/266 subjects; $p = 0.012$) for IFN-based treatment and 86.3%

(221/256 subjects) versus 94.9% (205/216 patients, $p = 0.002$) for IFN-free regimens. Relapse after end-of-treatment response to IFN-free therapy was observed in 3/208 (1.4%) HCV-monoinfected subjects and 10/231 (4.4%) HIV/HCV-coinfected individuals ($p = 0.075$). In a multivariate analysis adjusted for age, sex, transmission route, body-mass index, HCV genotype, and cirrhosis, the absence of HIV-coinfection (adjusted odds ratio: 3.367; 95% confidence interval: 1.15-9.854; $p = 0.027$) was independently associated with SVR12 to IFN-free therapy. **CONCLUSIONS:** HIV-coinfection is associated with worse response to DAA-based therapy against HCV infection. In patients receiving IFN-free therapy, this fact seems to be mainly driven by a higher rate of relapses among HIV-coinfected subjects.

Patient-reported outcomes in patients co-infected with hepatitis C virus and human immunodeficiency virus treated with sofosbuvir and velpatasvir: The ASTRAL-5 study.

Younossi ZM1,2, Stepanova M3, Sulkowski M4, Wyles D5, Kottlilil S6, Hunt S3. Liver Int. 2017 May 4. doi: 10.1111/liv.13462. [Epub ahead of print]

BACKGROUND & AIM: The fixed-dose combination of sofosbuvir and velpatasvir (SOF/VEL) is a ribavirin-free pan-genotypic regimen with high efficacy. We assessed the impact of SOF/VEL on patient-reported outcomes (PRO) of HIV-HCV co-infected patients.

METHODS: HIV-HCV co-infected patients were treated with 12 weeks of SOF/VEL (400 mg/100 mg daily). All subjects completed four PRO questionnaires [CLDQ-HCV, SF-36, FACIT-F and WPAI:SHP] before, during and post-treatment. **RESULTS:** ASTRAL-5 enrolled 106 HIV-HCV co-infected patients on stable antiretroviral therapy (age: 54.2 ± 0.9 years, cirrhosis: 17.9%, HCV genotype 1: 73.6%). SVR-12 was achieved by 95.3% of subjects. By week 4 of treatment, PRO scores improved from the baselines levels in 12 out of 26 calculated PRO domains (on average, +1.9 to +7.4 points on a universal 0-100 PRO scale, all $P < .05$). By the end of treatment, improvements were seen in 20/26 PRO domains (+2.5% to +11.9%, $P < .03$). There were no significant decrements in any PRO domains during treatment. By follow-up week 12, patients who achieved SVR-12 experienced significant improvement in 19/26 of their PRO domains (+3.2% to +13.3%, $P < .05$). After controlling for baseline psychiatric co-morbidities, improvements in PRO scores during treatment with SOF/VEL were similar to those seen in matched HCV-mono-infected patients treated with the same regimen (ASTRAL-1 study). In multivariate analysis, pre-treatment anxiety and concomitant use of opioids were the most consistent significant ($P < .05$) predictors of PRO impairment in HIV-HCV patients.

CONCLUSIONS: Patients with HIV-HCV treated with SOF/VEL experience very high efficacy accompanied by early and sustained improvement of patient-reported outcomes covering all aspects of patients' experience.

A prognostic model for development of significant liver fibrosis in HIV-hepatitis C co-infection.

Moqueet N1, Kanagaratham C2, Gill MJ3, et al. PLoS One. 2017 May 3;12(5):e0176282. doi: 10.1371/journal.pone.0176282. eCollection 2017.

BACKGROUND: Liver fibrosis progresses rapidly in HIV-Hepatitis C virus (HCV) co-infected individuals partially due to heightened inflammation. Immune markers targeting stages of fibrogenesis could aid in prognosis of fibrosis. **METHODS:** A case-cohort study was nested in the prospective Canadian Co-infection Cohort ($n = 1119$). HCV RNA positive individuals without fibrosis, end-stage liver disease or chronic Hepatitis B at baseline ($n = 679$) were eligible. A random subcohort ($n = 236$) was selected from those eligible. Pro-fibrogenic markers and Interferon Lambda (IFNL) rs8099917 genotype were measured from first available sample

in all fibrosis cases (APRI \geq 1.5 during follow-up) and the subcohort. We used Cox proportional hazards and compared Model 1 (selected clinical predictors only) to Model 2 (Model 1 plus selected markers) for predicting 3-year risk of liver fibrosis using weighted Harrell's C and Net Reclassification Improvement indices. **RESULTS:** 113 individuals developed significant liver fibrosis over 1300 person-years (8.63 per 100 person-years 95% CI: 7.08, 10.60). Model 1 (age, sex, current alcohol use, HIV RNA, baseline APRI, HCV genotype) was nested in model 2, which also included IFNL genotype and IL-8, sICAM-1, RANTES, hsCRP, and sCD14. The C indexes (95% CI) for model 1 vs. model 2 were 0.720 (0.649, 0.791) and 0.756 (0.688, 0.825), respectively. Model 2 classified risk more appropriately (overall net reclassification improvement, $p < 0.05$). **CONCLUSIONS:** Including IFNL genotype and inflammatory markers IL-8, sICAM-1, RANTES, hs-CRP, and sCD14 enabled better prediction of the 3-year risk of significant liver fibrosis over clinical predictors alone. Whether this modest improvement in prediction justifies their additional cost requires further cost-benefit analyses.

[Increased incidence of cancer observed in HIV/hepatitis C virus-coinfected patients versus HIV-monoinfected.](#) Meijide H1, Pértega S, Rodríguez-Osorio I, et al. AIDS. 2017 May 15;31(8):1099-1107. doi: 10.1097/QAD.0000000000001448.

BACKGROUND: Cancer is a growing problem in persons living with HIV infection (PLWH) and hepatitis C virus (HCV) coinfection could play an additional role in carcinogenesis. Herein, all cancers in an HIV-mono and HIV/HCV-coinfected cohort were evaluated and compared to identify any differences between these two populations. **METHODS:** A retrospective cohort study was conducted including all cancers in PLWH between 1993 and 2014. Cancers were classified in two groups: AIDS-defining cancer (ADC) and non-AIDS-defining cancer (NADC). Cancer incidence rates were calculated and compared with that observed in the Spanish general population (GLOBOCAN, 2012), computing the standardized incidence ratios (SIRs). A competing risk approach was used to estimate the probability of cancer after HIV diagnosis. Cumulative incidence in HIV-monoinfected and HIV/HCV-coinfected patients was also compared using multivariable analysis. **RESULTS:** A total of 185 patients (117 HIV-monoinfected and 68 HIV/HCV) developed cancer in the 26580 patient-years cohort, with an incidence rate of 696 cancers per 100000 person-years, higher than in the general population (SIR=3.8). The incidence rate of NADC in HIV/HCV-coinfected patients was 415.0 (SIR=3.4), significantly higher than in monoinfected (377.3; SIR=1.8). After adjustments, HIV/HCV-coinfected patients had a higher cumulative incidence of NADC than HIV-monoinfected (adjusted hazard ratio=1.80), even when excluding hepatocellular carcinomas (adjusted hazard ratio=1.26). **CONCLUSION:** PLWH have a higher incidence of NADC than the general population and HCV-coinfection is associated with a higher incidence of NADC. These data justify the need for prevention strategies in these two populations and the importance of eradicating HCV.

[Modelling CD4 T Cell Recovery in Hepatitis C and HIV Co-infected Children Receiving Antiretroviral Therapy.](#) Majekodunmi AO1, Thorne C, Malyuta R, et al. Pediatr Infect Dis J. 2017 May;36(5):e123-e129. doi: 10.1097/INF.0000000000001478.

BACKGROUND: The effect of hepatitis C virus (HCV) coinfection on CD4 T cell recovery in treated HIV-infected children is poorly understood. **OBJECTIVE:** To compare CD4 T cell recovery in HIV/HCV coinfecting children with recovery in HIV monoinfected children.

METHOD: We studied 355 HIV monoinfected and 46 HIV/HCV coinfecting children receiving antiretroviral therapy (ART) during a median follow-up period of 4.2 years (interquartile range: 2.7-5.3 years). Our dataset came from the Ukraine pediatric HIV Cohort and the HIV/HCV coinfection study within the European Pregnancy and Paediatric HIV Cohort Collaboration. We fitted an asymptotic nonlinear mixed-effects model of CD4 T cell reconstitution to age-standardized CD4 counts in all 401 children and investigated factors predicting the speed and extent of recovery. **RESULTS:** We found no significant impact of HCV coinfection on either pre-ART or long-term age-adjusted CD4 counts (z scores). However, the rate of increase in CD4 z score was slower in HIV/HCV coinfecting children when compared with their monoinfected counterparts ($P < 0.001$). Both monoinfected and coinfecting children starting ART at younger ages had higher pre-ART ($P < 0.001$) and long-term ($P < 0.001$) CD4 z scores than those who started when they were older. **CONCLUSIONS:** HIV/HCV coinfecting children receiving ART had slower CD4 T cell recovery than HIV monoinfected children. HIV/HCV coinfection had no impact on pre-ART or long-term CD4 z scores. Early treatment of HIV/HCV coinfecting children with ART should be encouraged.

[Real-World Efficacy of Daclatasvir and Sofosbuvir, With and Without Ribavirin, in HIV/HCV Coinfecting Patients With Advanced Liver Disease in a French Early Access Cohort.](#) Lacombe K1, Fontaine H, Dhiver C, et al. *J Acquir Immune Defic Syndr.* 2017 May 1;75(1):97-107. doi: 10.1097/QAI.0000000000001342.

BACKGROUND: Efficacious, well-tolerated, direct antiviral agents have drastically changed the prognosis of hepatitis C virus (HCV) disease, but real-world data for oral treatments are limited in key populations such as HIV/HCV coinfection with advanced liver disease. Daclatasvir (DCV) efficacy and safety was assessed in the French "Autorisation Temporaire d'Utilisation" (ATU) program, providing DCV ahead of market authorization to patients with advanced HCV disease without other treatment options. **METHODS:** This was a subanalysis of HIV/HCV coinfecting ATU patients treated with DCV plus sofosbuvir (SOF). Recommended duration was 24 weeks; addition of ribavirin (RBV) and/or shorter treatment was at the physician's discretion. The primary efficacy analysis was sustained virologic response at posttreatment week 12 (SVR12; modified intention-to-treat). Safety was assessed by spontaneous adverse event reporting. **RESULTS:** The efficacy population ($N = 407$) was mostly cirrhotic (72%, of whom 18% were decompensated), HCV treatment-experienced (82%), and infected with genotypes 1 (69%), 3 (12%), or 4 (19%). Median CD4 was 555 cells/mm³; 95% had HIV RNA < 50 copies/mL. Most (74%) were treated for 24 weeks; 14% received RBV. SVR12 was 92% overall (95% confidence interval: 88.6% to 94.0%); 90% (86.4% to 93.2%) in patients with cirrhosis; 95% (88.9% to 97.5%) in patients without cirrhosis. SVR12 was consistent across HCV genotypes and antiretroviral regimens. Among 617 patients with safety data, 7 discontinued for an adverse event and 10 died. **CONCLUSIONS:** DCV+SOF±RBV achieved high SVR12 and was well tolerated in this large real-world cohort of HIV/HCV coinfecting patients with advanced liver disease.

[Active HCV infection is associated with increased circulating levels of interferon-gamma \(IFN- \$\gamma\$ \)-inducible protein-10 \(IP-10\), soluble CD163 and inflammatory monocytes regardless of liver fibrosis and HIV coinfection.](#) Mascia C1, Lichtner M2, Zuccalà P3, et al. *Clin Res Hepatol Gastroenterol.* 2017 May 31. pii: S2210-7401(17)30098-0. doi: 10.1016/j.clinre.2017.04.007. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: Interferon-gamma (IFN- γ)-inducible protein-10 (IP-10), soluble (s) CD163 and sCD14 play an important role in the pathogenesis of HCV and HIV infection and are involved in inflammation and liver fibrosis. The aim of the present study was to evaluate at a single time point, plasma soluble biomarkers and inflammatory monocytes subsets in different groups of subjects: (i) HIV monoinfected patients on suppressive ART; (ii) HIV/HCV coinfecting patients on ART, with undetectable HIV viremia (including either subjects who had active HCV replication or those who cleared HCV); (iii) HCV monoinfected individual with active viral replication. **METHODS:** Hundred and twenty-nine plasma samples were analyzed including HCV and HIV monoinfected patients, HIV/HCV coinfecting patients, with active HCV infection (AHI) or with HCV viral clearance (VHC) and healthy donors (HD). Levels of IP-10, sCD163 and sCD14 were measured by ELISA. Absolute cell counts of monocyte subpopulations were enumerated in whole blood by using flow cytometric analyses. **RESULTS:** IP-10 and sCD163 plasma levels were higher in HCV monoinfected and in AHI coinfecting pts compared to HIV monoinfected and HD, whereas sCD14 levels were higher only in HIV monoinfected patients. Considering the degree of fibrosis, sCD163 and sCD14 levels positively correlated with kPa values (as assessed by fibroscan) and FIB-4 in HCV monoinfected group. On the other hand, IP-10 did not correlate with the fibrosis stage and it was found increased also in patients with low fibrosis. Moreover, we found an increase of the inflammatory NCM subset, in non-cirrhotic HCV subjects, while no alterations were observed in HIV, AHI and VHC. **CONCLUSIONS:** Our study suggests a scenario in which active HCV infection is associated with a strong pro-inflammatory state, even in the initial stage of liver fibrosis, regardless the presence of HIV coinfection, thus underlying the need of an early anti-HCV treatment.

[Hepatic steatosis progresses faster in HIV mono-infected than HIV/HCV co-infected patients and is associated with liver fibrosis.](#) Pembroke T1, Deschenes M2, Lebouché B2, et al. J Hepatol. 2017 May 17. pii: S0168-8278(17)32047-0. doi: 10.1016/j.jhep.2017.05.011. [Epub ahead of print]

BACKGROUND & AIMS: Hepatic steatosis (HS) seems common in patients infected with human immunodeficiency virus (HIV). However, the relative effect of HIV, as well as hepatitis C virus (HCV) in those co-infected, and the influence of HS on liver fibrosis progression are unclear. **METHODS:** The LIVEr disease in HIV (LIVEHIV) is a Canadian prospective Cohort using transient elastography and associated controlled attenuation parameter (CAP) to screen for HS and liver fibrosis in unselected HIV-infected adults. HS progression was defined as development of any grade HS (CAP \geq 248 dB/m), or transition to severe HS (CAP \geq 292 dB/m) for those with any grade HS at baseline. Fibrosis progression was defined as development of significant liver fibrosis (liver stiffness measurement [LSM] \geq 7.1kPa), or transition to cirrhosis (LSM \geq 12.5kPa) for those with significant liver fibrosis at baseline. Cox regression analysis was used to assess predictors of HS and fibrosis progression. **RESULTS:** A prospective cohort study was conducted, which included 726 HIV-infected patients (22.7% HCV co-infected). Prevalence of any grade HS did not differ between HIV mono-infected and HIV/HCV co-infected patients (36.1% vs 38.6%, respectively). 313 patients were followed for a median of 15.4 (interquartile range 8.5-23.0) months. The rate of HS progression was 37.8 (95% confidence interval [CI] 29.2-49.0) and 21.9 (95% CI 15.6-30.7) per 100 person-years in HIV mono-infection and HIV/HCV co-infection, respectively. HCV co-infection was an independent negative predictor of HS progression (adjusted hazard ratio [aHR] 0.50, 95% CI 0.28-0.89). HS predicted liver fibrosis

progression in HIV mono-infection (aHR 4.18, 95% CI 1.21-14.5), but not in HIV/HCV co-infection. **CONCLUSION:** HS progresses faster and is associated with liver fibrosis progression in HIV mono-infection but not in HIV/HCV co-infection. **LAY SUMMARY:** Fatty liver is the most frequent liver disease in Western countries. People living with HIV seems at high risk for fatty liver due to frequent metabolic disorders and long-term effect of antiretroviral therapy. However, due to the invasiveness of liver biopsy, the traditional way to diagnose fatty liver, there are few data about its frequency in people living with HIV. In this work, we used a non-invasive diagnostic tool to study epidemiology of fatty liver in 726 HIV+ patients. We observed that fatty liver affects over one third of people living with HIV. When followed over time, we found that HIV+ patients without co-infection with HCV develops more frequently fatty liver than those co-infected with HCV.

[Men who have sex with men starting pre-exposure prophylaxis \(PrEP\) are at risk of HCV infection: evidence from the Amsterdam PrEP study.](#) Hoornenborg E1, Achterbergh RCA, Schim Van Der Loeff MF, et al. AIDS. 2017 May 1. doi: 10.1097/QAD.0000000000001522.

[Epub ahead of print]

OBJECTIVES AND DESIGN: Hepatitis C virus (HCV) has been recognised as an emerging sexually transmitted infection (STI) among HIV-positive men who have sex with men (MSM). However, HIV-negative MSM at high risk for HIV might also be at increased risk for HCV. We studied the HCV prevalence in HIV-negative MSM who start pre-exposure prophylaxis (PrEP) in Amsterdam. Phylogenetic analysis was used to compare HCV strains obtained from HIV-negative and HIV-positive MSM. **METHODS:** At enrolment in the Amsterdam PrEP (AMPrEP) demonstration project, HIV-negative MSM were tested for the presence of HCV antibodies and HCV RNA. If positive for HCV RNA, an HCV NS5B gene fragment (709bp) was sequenced and compared with HCV isolates from HIV-positive MSM (n=223) and risk groups other than MSM (n=153), using phylogenetic analysis. **RESULTS:** Of 375 HIV-negative MSM enrolled in AMPrEP, 18 (4.8%, 95% CI 2.9%-7.5%) of participants were anti-HCV and/or HCV RNA positive at enrolment; 15/18 (83%) had detectable HCV RNA. HCV genotyping showed genotype 1a (73%), 4d (20%) and 2b (7%). All HCV-positive MSM starting PrEP were part of MSM-specific HCV clusters containing MSM with and without HIV. **CONCLUSION:** HCV prevalence among HIV-negative MSM who started PrEP was higher than previously reported. All HIV-negative HCV-positive MSM were infected with HCV strains already circulating among HIV-positive MSM. The increasing overlap between sexual networks of HIV-positive and HIV-negative MSM might result in an expanding HCV-epidemic irrespective of HIV-status. Hence, routine HCV testing should be offered to MSM at high risk for HIV, especially for those enrolling in PrEP programs.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

[Coffee: The magical bean for liver diseases.](#) Heath RD1, Brahmabhatt M1, Tahan AC1, Ibdah JA1, Tahan V1. World J Hepatol. 2017 May 28;9(15):689-696. doi: 10.4254/wjh.v9.i15.689. Coffee has long been recognized as having hepatoprotective properties, however, the extent of any beneficial effect is still being elucidated. Coffee appears to reduce risk of hepatocellular carcinoma, reduce advancement of fibrotic disease in a variety of chronic liver diseases, and

perhaps reduce ability of hepatitis C virus to replicate. This review aims to catalog the evidence for coffee as universally beneficial across a spectrum of chronic liver diseases, as well as spotlight opportunities for future investigation into coffee and liver disease.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[Urgency to treat patients with chronic hepatitis C in Asia.](#) Kao JH1, Ahn SH2, Chien RN3, Cho M4, Chuang WL5, Jeong SH6, Liu CH7, Paik SW8. J Gastroenterol Hepatol. 2017 May;32(5):966-974. doi: 10.1111/jgh.13709.

Chronic hepatitis C (CHC) infection poses a global healthcare burden, being associated with serious complications if untreated. The prevalence of hepatitis C virus (HCV) infection is highest in areas of Central, South, and East Asia; over 50% of HCV patients worldwide live in the region, where HCV genotypes 1b, 2, 3, and 6 are the most prevalent. Treatment outcomes for chronic hepatitis C vary by ethnicity, and Asian patients achieve higher sustained virologic response rates following interferon (IFN)-based therapy than non-Asians. However, low efficacy, poor safety profile, and subcutaneous administration limit the use of IFN-based therapies. Superior virologic outcomes have been observed with different classes of direct-acting antivirals (DAAs) alone or in combination, and several all-oral DAA regimens are available in Asia. These regimens have shown excellent efficacy and favorable tolerability in clinical trials, yet there is a need for further studies of DAAs in a real world context, particularly in Asia. Furthermore, IFN-free treatment may not be accessible for many patients in the region, and IFN-based regimens remain an option in some countries. There is a need to improve current clinical practices for HCV management in Asia, including effective screening, disease awareness, and prevention programs, and to further understand the cost-effectiveness of IFN-free regimens. The evolution of potent treatments makes HCV eradication a possibility that should be available to all patients. However, access to these therapies in Asian countries has been slow, primarily because of economic barriers that continue to present a hurdle to optimal treatment.

[Pharmacist-initiated hepatitis C virus screening in a community pharmacy to increase awareness and link to care at the medical center.](#) Isho NY, Kachlic MD, Marcelo JC, Martin MT. J Am Pharm Assoc (2003). 2017 May - Jun;57(3S):S259-S264. doi: 10.1016/j.japh.2017.03.006.

OBJECTIVE: To describe the design and implementation of a pharmacist-led hepatitis C virus (HCV) screening and education program in a community pharmacy with a protocol for linkage to care at the affiliated hepatology clinic for patients born between 1945 and 1965. **SETTING:** Outpatient pharmacy affiliated with the University of Illinois Hospital and Health Sciences System. **PRACTICE DESCRIPTION:** The community pharmacist resident conducted the HCV screening at the health system-based community pharmacy. **PRACTICE INNOVATION:** Community pharmacists provided patients with HCV screening and education while patients waited for their prescriptions to be ready or upon appointment. Patients were given a questionnaire before and after HCV education to assess the impact of pharmacist-provided education on patient knowledge. A protocol was developed to link patients with a positive HCV antibody test result to care with a hepatologist for confirmatory testing at a follow-up appointment at the medical center. **EVALUATION:** Investigators assessed the feasibility of providing the screening and education, recorded the number of patients screened, and recorded the differences in the questionnaire responses before and after education. **RESULTS:**

Pharmacist-led HCV screening services were implemented successfully at the community pharmacy. All patients had a negative antibody result; therefore, linkage to care at the medical center, although available, was not necessary. The self-reported posttest HCV knowledge scores were significantly higher than pretest scores. **CONCLUSION:** This article outlines the methodology for providing a multidisciplinary HCV screening, education, and referral program in a community pharmacy affiliated with a medical center. Pharmacist-initiated HCV screening in a community pharmacy can assist with identifying patients at risk for HCV infection and provide patients with linkage to care in the health system. This report may encourage community pharmacists to conduct future prospective trials to evaluate clinical and economic outcomes of community-based HCV screenings.

Primary Care and Hepatology Provider-Perceived Barriers to and Facilitators of Hepatitis C Treatment Candidacy and Adherence. Rogal SS^{1,2,3}, McCarthy R⁴, Reid A⁵, et al. *Dig Dis Sci.* 2017 May 18. doi: 10.1007/s10620-017-4608-9. [Epub ahead of print]

BACKGROUND: Provider perceptions regarding barriers to and facilitators of hepatitis C (HCV) treatment initiation and adherence have not been fully evaluated in the interferon-free treatment era. New treatments have provided opportunities for non-specialists to treat HCV, underscoring the importance of understanding primary care provider (PCP) and specialist perspectives. **METHODS:** Based on qualitative sampling principles, 12 PCPs and 12 hepatology providers (HPs) from the VA Pittsburgh Healthcare System completed audio-recorded semi-structured interviews. Qualitative analysts coded perceived barriers and facilitators from the interviews with 100% double coding. Codes were thematized and analyzed using Atlas.ti. **RESULTS:** Key barriers to treatment described by HPs and PCPs included patients' substance use disorders, mental health, transportation availability, history of non-adherence, and concern about side effects. PCPs also focused on medication cost as a system-based barrier. The main facilitators of treatment initiation and adherence described by both HPs and PCPs were provider education and encouragement. HPs focused almost exclusively on provider-based facilitators, while PCPs noted patient-based facilitators including past adherence, media exposure to information about HCV medications, a desire to clear the virus, and positive feedback regarding treatment response. **CONCLUSIONS:** Providers generally focused on perceived patient-level barriers to HCV treatment initiation and adherence, as well as provider-level facilitators; PCPs additionally noted patient preferences and system-level issues that guide decision making regarding treatment initiation. While HPs focused almost exclusively on provider-level facilitators, PCPs additionally focused on patient-level facilitators of treatment. These data provide novel insights and suggest focusing on patient, provider, and system-level strategies to further improve HCV treatment initiation and adherence.

The societal cost of heroin use disorder in the United States. Jiang R¹, Lee I¹, Lee TA¹, Pickard AS^{1,2}. *PLoS One.* 2017 May 30;12(5):e0177323. doi: 10.1371/journal.pone.0177323. eCollection 2017.

OBJECTIVE: Heroin use in the United States has reached epidemic proportions. The objective of this paper is to estimate the annual societal cost of heroin use disorder in the United States in 2015 US dollars. **METHODS:** An analytic model was created that included incarceration and crime; treatment for heroin use disorder; chronic infectious diseases (HIV, Hepatitis B, Hepatitis C, and Tuberculosis) and their treatments; treatment of neonatal abstinence syndrome; lost productivity; and death by heroin overdose. **RESULTS:** Using literature-based estimates to

populate the model, the cost of heroin use disorder was estimated to be \$51.2 billion in 2015 US dollars (\$50,799 per heroin user). One-way sensitivity analyses showed that overall cost estimates were sensitive to the number of heroin users, cost of HCV treatment, and cost of incarcerating heroin users. **CONCLUSION:** The annual cost of heroin use disorder to society in the United States emphasizes the need for sustained investment in healthcare and non-healthcare related strategies that reduce the likelihood of abuse and provide care and support for users to overcome the disorder.

Diagnosis of viral hepatitis. Easterbrook PJ1, Roberts T, Sands A, Peeling R. *Curr Opin HIV AIDS*. 2017 May;12(3):302-314. doi: 10.1097/COH.0000000000000370.

PURPOSE OF REVIEW: Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and HIV-HBV and HCV coinfection are major causes of chronic liver disease worldwide. Testing and diagnosis is the gateway for access to both treatment and prevention services, but there remains a large burden of undiagnosed infection globally. We review the global epidemiology, key challenges in the current hepatitis testing response, new tools to support the hepatitis global response (2016-2020 Global Hepatitis Health Sector strategy, and 2017 WHO guidelines on hepatitis testing) and future directions and innovations in hepatitis diagnostics. **RECENT FINDINGS:** Key challenges in the current hepatitis testing response include lack of quality-assured serological and low-cost virological in-vitro diagnostics, limited facilities for testing, inadequate data to guide country-specific hepatitis testing approaches, stigmatization of those with or at risk of viral hepatitis and lack of guidelines on hepatitis testing for resource-limited settings. The new Global Hepatitis Health Sector strategy sets out goals for elimination of viral hepatitis as a public health threat by 2030 and gives outcome targets for reductions in new infections and mortality, as well as service delivery targets that include testing, diagnosis and treatment. The 2017 WHO hepatitis testing guidelines for adults, adolescents and children in low-income and middle-income countries outline the public health approach to strengthen and expand current testing practices for viral hepatitis and addresses who to test (testing approaches), which serological and virological assays to use (testing strategies) as well as interventions to promote linkage to prevention and care. **SUMMARY:** Future directions and innovations in hepatitis testing include strategies to improve access such as through use of existing facility and community-based testing opportunities for hepatitis testing, near-patient or point-of-care assays for virological markers (nucleic acid testing and HCV core antigen), dried blood spot specimens used with different serological and nucleic acid test assays, multiplex and multi-disease platforms to enable testing for multiple analytes/pathogens and potential self-testing for viral hepatitis.

The association between implementation strategy use and the uptake of hepatitis C treatment in a national sample. Rogal SS1,2,3, Yakovchenko V4, Waltz TJ5,6, et al.

Implement Sci. 2017 May 11;12(1):60. doi: 10.1186/s13012-017-0588-6.

BACKGROUND: Hepatitis C virus (HCV) is a common and highly morbid illness. New medications that have much higher cure rates have become the new evidence-based practice in the field. Understanding the implementation of these new medications nationally provides an opportunity to advance the understanding of the role of implementation strategies in clinical outcomes on a large scale. The Expert Recommendations for Implementing Change (ERIC) study defined discrete implementation strategies and clustered these strategies into groups. The present evaluation assessed the use of these strategies and clusters in the context of HCV

treatment across the US Department of Veterans Affairs (VA), Veterans Health Administration, the largest provider of HCV care nationally. **METHODS:** A 73-item survey was developed and sent to all VA sites treating HCV via electronic survey, to assess whether or not a site used each ERIC-defined implementation strategy related to employing the new HCV medication in 2014. VA national data regarding the number of Veterans starting on the new HCV medications at each site were collected. The associations between treatment starts and number and type of implementation strategies were assessed. **RESULTS:** A total of 80 (62%) sites responded. Respondents endorsed an average of 25 ± 14 strategies. The number of treatment starts was positively correlated with the total number of strategies endorsed ($r = 0.43, p < 0.001$). Quartile of treatment starts was significantly associated with the number of strategies endorsed ($p < 0.01$), with the top quartile endorsing a median of 33 strategies, compared to 15 strategies in the lowest quartile. There were significant differences in the types of strategies endorsed by sites in the highest and lowest quartiles of treatment starts. Four of the 10 top strategies for sites in the top quartile had significant correlations with treatment starts compared to only 1 of the 10 top strategies in the bottom quartile sites. Overall, only 3 of the top 15 most frequently used strategies were associated with treatment. **CONCLUSIONS:** These results suggest that sites that used a greater number of implementation strategies were able to deliver more evidence-based treatment in HCV. The current assessment also demonstrates the feasibility of electronic self-reporting to evaluate ERIC strategies on a large scale. These results provide initial evidence for the clinical relevance of the ERIC strategies in a real-world implementation setting on a large scale. This is an initial step in identifying which strategies are associated with the uptake of evidence-based practices in nationwide healthcare systems.

[Access to healthcare insurance and healthcare services among syringe exchange program clients in Massachusetts: qualitative findings from health navigators with the iDU \("I do"\) Care Collaborative.](#) Stopka TJ1, Hutcheson M2, Donahue A2. Harm Reduct J. 2017 May 18;14(1):26. doi: 10.1186/s12954-017-0151-4.

BACKGROUND: Little is known about access to health insurance among people who inject drugs (PWID) who attend syringe exchange programs (SEPs). The goal of the current study was to assess perceptions of SEP staff, including health navigators and program managers, on access to health insurance and healthcare access among SEP clients following implementation of state and federal policies to enhance universal healthcare access in Massachusetts. **METHODS:** Between December 2014 and January 2015, we conducted in-depth interviews ($n = 14$) with SEP staff, including both program managers and health navigators, to assess knowledge, attitudes, and beliefs related to health insurance enrollment and access to enhanced referrals among SEP clients. We developed a preliminary coding scheme from the interview guide and used a grounded theory approach to guide inclusion of subsequent thematic codes that emanated from the data. We analyzed the coded data thematically in an iterative fashion using a consensus-based approach. **RESULTS:** We identified five primary themes that emerged from the qualitative interviews, including high levels of health insurance enrollment among SEP clients; barriers to enrolling in health insurance; highly needed referrals to services, including improved access to substance use disorder treatment and hepatitis C virus treatment; barriers to referring clients to these highly needed services; and recommendations for policy change. **CONCLUSIONS:** While barriers to enrollment and highly needed referrals remain, access to and enrollment in healthcare insurance plans among PWID at SEPs in Massachusetts are high. With the uncertain stability of the Affordable Care Act following the US presidential election of

2016, our findings summarize the opportunities and challenges that are connected to health insurance and healthcare access in Massachusetts. SEPs can play an important role in facilitating access to health insurance and enhancing access to preventive health and primary care.

The Prevalence of Parkinson Disease Among Patients With Hepatitis C Infection. Golabi P1, Otgonsuren M1, Sayiner M1, Arsalla A1, Gogoll T1, Younossi ZM1. Ann Hepatol. 2017 May - Jun;16(3):342-348. doi: 10.5604/16652681.1235476.

INTRODUCTION: HCV has been suspected to potentially cause degenerations in the central nervous system. Parkinson's disease is the second most common neurodegenerative disorder. Our aim was to assess the prevalence of Parkinson's disease among patients with HCV infection.

MATERIAL AND METHODS: For this study, we used Medicare database from 2005-2010. Medicare database contains information on enrollment, coverage, diagnosis recorded with International Classification of Disease, Ninth Revision (ICD-9). From combined inpatient and outpatient files, Parkinson's disease was identified as the first diagnosis by ICD-9 code 332.0. Other study variables were; age, gender, race (White and No White), and Medicare eligibility status. Simple distribution comparison by HCV status examined with t-test for numerical variables and χ^2 test for categorical variables in the main analytical cohort as well as in the propensity score matched cohort. **RESULTS:** A total of 1,236,734 patients (median age 76 years, 41% male, and 85% White) was identified among over 47 million claims. Of these, 6040 patients (0.5%) were infected with HCV. Overall, 0.8% (N = 49) of the HCV group and 1.3% (N = 16,004) of the Non-HCV group had Parkinson's disease (P < 0.001). When the study groups matched for age, gender and race, the prevalence of Parkinson's disease was similar between HCV and Non-HCV groups (P > 0.05). **DISCUSSION:** This study revealed that, among Medicare population, HCV was not associated with Parkinson disease.

Multi-disciplinary Concurrent Management of Recurrent Hepatocellular Therapy is Superior to Sequential Therapy. Fields TD1, Philips P1, Scoggins CR1, Tatum C1, Kelly L1, McMasters KM1, Martin RCG2. World J Surg. 2017 May;41(5):1331-1339. doi: 10.1007/s00268-016-3844-z.

BACKGROUND: Recurrent hepatocellular carcinoma after a patient's initial therapy, whether it is transplantation, resection, or ablation, remains a challenging clinical problem. Since recurrence occurs in 70% of all initially treated disease within 5 years, optimal management to treat this recurrence is needed. Currently, a bias exists toward mono-therapy (i.e., ablation alone, hepatic arterial therapy alone, or sorafenib therapy alone) instead of concurrent sequential therapy-as is common in other primary and metastatic disease to the liver. Thus, the aim of our study was to evaluate the overall survival of recurrent HCC based on either mono-therapy or multimodality therapy. **METHODS:** A review of our prospective 2245 patient hepato-pancreatico-biliary database was performed for all patients who underwent treatment with curative intent for hepatocellular carcinoma and had complete recurrence treatment data from June 2002 to May 2015. Mono-therapy was defined as initiation of a solitary therapy until disease progression or intolerance. Multimodality therapy was defined as at least 2 therapies that occurred simultaneously or within 4 weeks of each therapy. **RESULTS:** A total of 281 patients underwent treatment with curative intent for hepatocellular carcinoma, in which 192 experienced recurrence. These patients were treated with either thermal ablation or liver resection (LR) (N = 51), transarterial chemoembolization (TACE) or radiation (N = 68), systemic therapy (N = 26), or multimodality therapy (N = 47). The extent of the first recurrence was similar in regard to the

number of tumors (median 1), the type of radiologic HCC, gender, BMI, and percentage of liver involvement. They differed in regard to size (MMT largest, median 5.6 cm, $p = 0.02$), and MMT had higher Hepatitis C involvement (37% of patients, $p = 0.001$). In evaluation of first recurrence treatment, after a median follow-up of 24 months, multimodality therapy has a significant improvement in overall survival (median 40 months, range 8-85), when compared to LR/Ablation (27 months, range 4-75), TACE/XRT (13 months, range 4-68), and systemic (26 months, range 3-59) ($p = 0.003$). **CONCLUSION:** Multimodality therapy should be considered in all patients with recurrent HCC based on tumor biology and underlying hepatic reserve. Hepatocellular cancer should be treated like other hepatic malignancies in which concurrent therapies are utilized simultaneously to optimize oncologic effects (response rates and overall survival) and minimize quality-of-life side effects. Multimodality therapy can lead to far superior overall survival and is well tolerated in the majority of recurrent HCC patients.

[Assessment of liver fibrosis with acoustic radiation force impulse imaging versus liver histology in patients with chronic hepatitis C: a pilot study.](#)

Kohla MAS1, Abbasy M, Abozeid M, El-Abd O, Ezzat S, Kohla S, Abdel-Rahman M. Eur J Gastroenterol Hepatol. 2017 May 3. doi: 10.1097/MEG.0000000000000903. [Epub ahead of print]

BACKGROUND: Acoustic radiation force impulse imaging (ARFI) involves the mechanical excitation of tissues using short-duration acoustic pulses to generate localized displacements in tissue. The displacements results in shear-wave propagation, tracked by ultrasonography (US) correlation-based methods and recorded in meters per seconds. **AIM:** To compare (ARFI) integrated into a conventional US with the standard histological examination of liver biopsy specimens for the assessment of liver fibrosis. **MATERIALS AND METHODS:** Histological fibrosis staging with standard liver biopsy using the Metavir scoring system as well as fibrosis assessment using ARFI were performed to 80 patients with chronic hepatitis C over a 3-month period. **RESULTS:** ARFI findings were identical to the biopsy findings in 61 (76.25%) patients. Fifty-eight (67.5%) patients with an early fibrosis stage (F0, F1, and F2) by histology had identical fibrosis stages using ARFI. Only 20 out of 26 patients with an advanced fibrosis stage (F3 and F4) using ARFI had advanced fibrosis histologically. In the advanced fibrosis stages, the sensitivity of ARFI was 70% and specificity was 80%, with positive and negative predictive values of 53.8 and 88.9%, respectively. The accuracy of detection of advanced fibrosis by ARFI was 77.5%. **CONCLUSION:** ARFI imaging is a promising noninvasive US-based method for the assessment of liver fibrosis.

[The Optimal Timing of Hepatitis C Therapy in Transplant Eligible Patients With Child B and C Cirrhosis: A Cost-Effectiveness Analysis.](#)

Tapper EB1, Hughes MS, Buti M, Dufour JF, Flamm S, Firdoos S, Curry MP, Afdhal NH. Transplantation. 2017 May;101(5):987-995. doi: 10.1097/TP.0000000000001400.

BACKGROUND: Ledipasvir (LDV)/sofosbuvir (SOF) has demonstrated high efficacy, safety, and tolerability in hepatitis C virus (HCV)-infected patients. There is limited data, however, regarding the optimal timing of therapy in the context of possible liver transplantation (LT). **METHODS:** We compared the cost-effectiveness of 12 weeks of HCV therapy before or after LT or nontreatment using a decision analytical microsimulation state-transition model for a simulated cohort of 10 000 patients with HCV Genotype 1 or 4 with Child B or C cirrhosis. All model parameters regarding the efficacy of therapy, adverse events and the effect of therapy on changes in model for end-stage liver disease (MELD) scores were derived from the SOLAR-1

and 2 trials. The simulations were repeated with 10 000 samples from the parameter distributions. The primary outcome was cost (2014 US dollars) per quality adjusted life year. **RESULTS:** Treatment before LT yielded more quality-adjusted life year for less money than treatment after LT or nontreatment. Treatment before LT was cost-effective in 100% of samples at a willingness-to-pay threshold of US \$100 000 in the base-case and when the analysis was restricted to Child B alone, Child C, or MELD > 15. Treatment before transplant was not cost-effective when MELD was 6-10. In sensitivity analyses, the MELD after which treatment before transplant was cost-effective was 13 and the maximum cost of LDV/SOF therapy at which treatment before LT is cost-effective is US \$177 381. **CONCLUSIONS:** From a societal perspective, HCV therapy using LDV/SOF with ribavirin before LT is the most cost-effective strategy for patients with decompensated cirrhosis and MELD score greater than 13.

[Exploration of potential mechanisms of hepatitis C virus resistance in exposed uninfected intravenous drug users.](#) Shawa IT1, Felmlee DJ1, Hegazy D1, Sheridan DA1, Cramp ME1. J Viral Hepat. 2017 May 5. doi: 10.1111/jvh.12720. [Epub ahead of print]

A rare outcome following exposure to hepatitis C virus (HCV) is a lack of observable infection as clinically measured by HCV RNA- or HCV-recognizing antibodies. The population who exhibit this trait is termed exposed uninfected (EU). Increasing evidence has refined characterization of these individuals, distinct from those who become infected but spontaneously clear HCV. Study of the EU population is highly pertinent for the discovery of antiviral mechanisms of resistance that can reveal antiviral therapeutic strategies. This review provides an overview of similarities and differences of the EU population relative to spontaneous resolvers and the majority whom develop chronic HCV infection, and focusses on possible mechanisms of resistance including innate and adaptive immunity, genetics and lipid interactions.

[Hepatitis C Virus Infection Among Women Giving Birth - Tennessee and United States, 2009-2014.](#) Patrick SW, Bauer AM, Warren MD, Jones TF, Wester C. MMWR Morb Mortal Wkly Rep. 2017 May 12;66(18):470-473. doi: 10.15585/mmwr.mm6618a3.

Hepatitis C virus (HCV) affects an estimated 3.5 million persons in the United States (1), making it the most common bloodborne infection in the country. Recent surveillance data showed increased rates of HCV infection among adolescents and adults who are predominantly white, live in nonurban areas, and have a history of injection drug use.* U.S. birth certificate data were used to analyze trends and geographic variations in rates of HCV infection among women giving birth during 2009-2014. Birth certificates from Tennessee were used to examine individual characteristics and outcomes associated with HCV infection, using a multivariable model to calculate adjusted odds of HCV-related diagnosis in pregnancy among women with live births. During 2009-2014, HCV infection present at the time of delivery among pregnant women from states reporting HCV on the birth certificate increased 89%, from 1.8 to 3.4 per 1,000 live births. The highest infection rate in 2014 (22.6 per 1,000 live births) was in West Virginia; the rate in Tennessee was 10.1. In adjusted analyses of Tennessee births, the odds of HCV infection were approximately threefold higher among women residing in rural counties than among those in large urban counties, 4.5-fold higher among women who smoked cigarettes during pregnancy, and nearly 17-fold higher among women with concurrent hepatitis B virus (HBV) infection. HCV infection among pregnant women is an increasing and potentially modifiable threat to maternal and child health. Clinicians and public health officials should consider individual and population-level opportunities for prevention and risk mitigation.

[State HCV Incidence and Policies Related to HCV Preventive and Treatment Services for Persons Who Inject Drugs - United States, 2015-2016.](#) Campbell CA1, Canary L1, Smith N1, Teshale E1, Ryerson AB1, Ward JW1. MMWR Morb Mortal Wkly Rep. 2017 May 12;66(18):465-469. doi: 10.15585/mmwr.mm6618a2.

Hepatitis C is associated with more deaths in the United States than 60 other infectious diseases reported to CDC combined. Despite curative hepatitis C virus (HCV) therapies and known preventive measures to interrupt transmission, new HCV infections have increased in recent years (1,2). Injection drug use is the primary risk factor for new HCV infections (2). One potential strategy to decrease the prevalence of HCV is to create and strengthen public health laws and policies aimed specifically at reducing transmission risks among persons who inject drugs. To evaluate factors affecting access to HCV preventive and treatment services, CDC assessed state laws governing access to safe injection equipment and Medicaid policies related to sobriety requirements for approval of HCV treatment for persons who inject drugs. Acute HCV incidence rates were obtained from CDC's National Notifiable Disease Surveillance System (NNDSS). States were categorized based on analysis of laws related to access to clean needles and syringes and Medicaid HCV treatment policies associated with sobriety requirements. In 2015, HCV incidence remained high in the United States, with rates in 17 states exceeding the national average. Three states were determined to have state laws and Medicaid policies capable of comprehensively preventing and treating HCV among persons who inject drugs. Opportunities exist for states to adopt laws and policies that could help increase access to HCV preventive and treatment services reducing the number of persons at risk for HCV transmission and disease.

[Hepatitis C Virus Infection Among Reproductive-Aged Women and Children in the United States, 2006 to 2014.](#) Ly KN1, Jiles RB1, Teshale EH1, Foster MA1, Pesano RL1, Holmberg SD1. Ann Intern Med. 2017 Jun 6;166(11):775-782. doi: 10.7326/M16-2350. Epub 2017 May 9.

BACKGROUND: In the United States, hepatitis C virus (HCV) infection has increased among young persons who inject drugs, but the extent of this epidemic among reproductive-aged women and their children is unknown. **OBJECTIVE:** To estimate numbers and describe characteristics of reproductive-aged women with HCV infection and of their offspring. **DESIGN:** Analysis of the National Notifiable Diseases Surveillance System (NNDSS) from 2006 to 2014 and the Quest Diagnostics Health Trends national database from 2011 to 2014. **SETTING:** United States. **PARTICIPANTS:** 171 801 women (aged 15 to 44 years) and 1859 children (aged 2 to 13 years) with HCV infection reported to the NNDSS; 2.1 million reproductive-aged women and 56 684 children who had HCV testing by Quest Diagnostics. **MEASUREMENTS:** NNDSS HCV case reports and Quest laboratory data regarding unique reproductive-aged women and children who were tested for HCV infection. **RESULTS:** The number of reproductive-aged women with acute and past or present HCV infection in the NNDSS doubled, from 15 550 in 2006 to 31 039 in 2014. Of 581 255 pregnant women tested by Quest from 2011 to 2014, 4232 (0.73% [95% CI, 0.71% to 0.75%]) had HCV infection. Of children tested by Quest, 0.76% (CI, 0.69% to 0.83%) had HCV infection, but the percentage was 3.2-fold higher among children aged 2 to 3 years (1.62% [CI, 1.34% to 1.96%]) than those aged 12 to 13 years (0.50% [CI, 0.41% to 0.62%]). Applying the Quest HCV infection rate to annual live births from 2011 to 2014 resulted in an estimated average of 29 000 women (CI, 27 400 to 30 900 women) with HCV infection, who gave birth to 1700 infants (CI, 1200 to 2200 infants) with the infection each year. **LIMITATIONS:** Only a fraction of HCV infections is

detected and reported to the NNDSS. Quest data are potentially biased, because women who are asymptomatic, do not access health care, or have unreported risks may be less likely to be tested for HCV infection. **CONCLUSION:** These data suggest a recent increase in HCV infection among reproductive-aged women and may inform deliberations regarding a role for routine HCV screening during pregnancy. **PRIMARY FUNDING SOURCE:** Centers for Disease Control and Prevention.

[A preliminary needs assessment of American Indians who inject drugs in northeastern Montana.](#) Anastario M1, FourStar K2, Ricker A3, Dick R4, Skewes MC5, Rink E6. Harm Reduct J. 2017 May 8;14(1):22. doi: 10.1186/s12954-017-0146-1.

BACKGROUND: Injection drug use has not been well documented in American Indians living in the USA. American Indian and Alaskan Natives (AI/ANs) show higher rates of substance use compared to the general population, and have historically been subject to a number of risk factors that are known to increase the likelihood of substance use. AI/ANs also experience increased risk for infectious diseases that are transmitted via injection drug use and/or sexual activity. Harm reduction approaches have been shown to be effective for decreasing risk of disease transmission in at-risk populations, and may be well suited for AI/AN injection drug users residing in rural reservation communities. In this study, we aimed to examine the characteristics of American Indians (AI) who use injection drugs (PWUID) in northeastern Montana to identify needs that could be addressed with harm reduction programming.

METHODS: For the present study, we used a respondent-driven sampling approach to generate a sample of 51 self-identified male and female injection drug users ≥ 18 years of age who were American Indians living on the Fort Peck Indian Reservation. Sampling weights were applied to all analyses using Respondent-Driven Sampling Analysis Tool (RDSAT). **RESULTS:** There were no strong recruitment patterns by age, sex, or ethnic identity status of the recruiter or participant, but there were strong within-group recruitment patterns by location within the reservation. The majority of the sample reported initiating substance use before the age of 18. Participants reported significant risk for HIV, hepatitis, and other infectious diseases through their drug use and/or risky sexual behavior. Sixty-five percent reported having reused syringes, and 53% reported drawing from the same filter. Seventy-five percent reported inconsistent condom use during the 3 months preceding the survey, and 53% reported injecting drugs during sex during the 3 months preceding the survey. Only 66% of participants reported having been tested for HIV in the 12 months preceding the survey. The vast majority (98%) of respondents expressed interest in a harm reduction program. Seventy-six percent reported that it was easy or very easy to obtain new syringes. **CONCLUSIONS:** We documented several risks for blood-borne pathogens, including elevated levels of syringe reuse. Further, we documented significant interest in harm reduction interventions in the present sample of AI/AN injection drug users. Findings suggest a need for increased access to harm reduction programming for AI/AN injection drug users to reduce the transmission of infectious disease and increase access to compassionate care.

[Lessons from Epidemiology: The Burden of Liver Disease.](#) Rowe IA1. Dig Dis. 2017;35(4):304-309. doi: 10.1159/000456580. Epub 2017 May 3.

Liver cirrhosis is responsible for more than 1 million deaths annually and the majority of these deaths are preventable. There is marked geographical variation in rates of mortality due to cirrhosis, and this variation in liver disease burden exemplifies the links between population risks

for liver disease and mortality. The differing geographical distribution of the major risks factors for the development of liver disease including alcohol consumption, hepatitis C virus (HCV) infection, hepatitis B virus infection, and obesity and the metabolic syndrome has the potential to highlight opportunities for intervention, while the evolution of these risk factors provides insights into understanding the future burden of liver disease. This review focuses on the use of population data to identify high-risk areas and populations that would benefit from preventative interventions to reduce the mortality from liver disease. Specific strategies that are effective at the policy and public health levels are discussed to illustrate the impact these can have if widely implemented. The impact of therapies that have the potential to change the natural history of liver disease, including direct acting antivirals for HCV infection is also described. Finally, the challenges of describing the epidemiology of non-alcoholic fatty liver disease are highlighted to illustrate the need to understand the natural history of disease to inform and influence the development of novel therapies.

[Increases in prescription opioid injection abuse among treatment admissions in the United States, 2004-2013.](#) Jones CM¹, Christensen A², Gladden RM². Drug Alcohol Depend. 2017 Jul 1;176:89-95. doi: 10.1016/j.drugalcdep.2017.03.011. Epub 2017 May 16.

BACKGROUND: The 2015 HIV outbreak in Indiana associated with prescription opioid injection coupled with rising rates of hepatitis C, especially in areas with long-standing opioid abuse, have raised concerns about prescription opioid injection. However, research on this topic is limited. We assessed trends in treatment admissions reporting injection, smoking, and inhalation abuse of prescription opioids and examined characteristics associated with non-oral routes of prescription opioid abuse in the U.S. **METHODS:** Prescription opioid abuse treatment admissions in the 2004-2013 Treatment Episode Data Set were used to calculate counts and percentages of prescription opioid treatment admissions reporting oral, injection, or smoking/inhalation abuse overall, by sex, age, and race/ethnicity. Multivariable multinomial logistic regression was used to identify demographic and substance use characteristics associated with injection or smoking/inhalation abuse. **RESULTS:** From 2004-2013, oral abuse decreased from 73.1% to 58.9%; injection abuse increased from 11.7% to 18.1%; and smoking/inhalation abuse increased from 15.3% of admissions to 23.0%. Among treatment admissions, the following were associated with injection abuse: male sex, 18-54 year-olds, non-Hispanic whites, non-Hispanic other, homeless or dependent living, less than full-time work, living in the Midwest or South, ≥ 1 prior treatment episodes, younger age of first opioid use, and reporting use of cocaine/crack, marijuana, heroin, or methamphetamine. **CONCLUSIONS:** The proportion of treatment admissions reporting prescription opioid injection and smoking/inhalation abuse increased significantly in the U.S. between 2004 and 2013. Expanding prevention efforts as well as access to medication-assisted treatment and risk reduction services for people who inject drugs is urgently needed.

HEPATOCELLULAR (LIVER) CANCER

[Immune Reconstitution After HCV Clearance With Direct Antiviral Agents: Potential Consequences for Patients With HCC?](#) Werner JM¹, Adenuga A, Protzer U. Transplantation. 2017 May;101(5):904-909. doi: 10.1097/TP.0000000000001606.

Recent introduction of all-oral direct-acting antiviral (DAA) treatment has revolutionized care of patients with chronic hepatitis C virus infection. Because patients with different liver disease

stages have been treated with great success including those awaiting liver transplantation, therapy has been extended to patients with hepatocellular carcinoma as well. From observational studies among compensated cirrhotic hepatitis C patients treated with interferon-containing regimens, it would have been expected that the rate of hepatocellular carcinoma occurrence is markedly decreased after a sustained virological response. However, recently 2 studies have been published reporting markedly increased rates of tumor recurrence and occurrence after viral clearance with DAA agents. Over the last decades, it has been established that chronic antigen stimulation during persistent infection with hepatitis C virus is associated with continuous activation and impaired function of several immune cell populations, such as natural killer cells and virus-specific T cells. This review therefore focuses on recent studies evaluating the restoration of adaptive and innate immune cell populations after DAA therapy in patients with chronic hepatitis C virus infection in the context of the immune responses in hepatocarcinogenesis.

Frequency and geographic distribution of TERT promoter mutations in primary hepatocellular carcinoma. Pezzuto F1, Buonaguro L1, Buonaguro FM1, Tornesello ML1. *Infect Agent Cancer*. 2017 May 19;12:27. doi: 10.1186/s13027-017-0138-5. eCollection 2017. Primary hepatocellular carcinoma (HCC) mainly develops in subjects chronically infected with hepatitis B (HBV) and C (HCV) viruses through a multistep process characterized by the accumulation of genetic alterations in the human genome. Nucleotide changes in coding regions (i.e. TP53, CTNNB1, ARID1A and ARID2) as well as in non-coding regions (i.e. TERT promoter) are considered cancer drivers for HCC development with variable frequencies in different geographic regions depending on the etiology and environmental factors. Recurrent hot spot mutations in TERT promoter (G > A at -124 bp; G > A at -146 bp), have shown to be common events in many tumor types including HCC and to up regulate the expression of telomerases. We performed a comprehensive review of the literature evaluating the differential distribution of TERT promoter mutations in 1939 primary HCC from four continents. Mutation rates were found higher in Europe (56.6%) and Africa (53.3%) than America (40%) and Asia (42.5%). In addition, HCV-related HCC were more frequently mutated (44.8% in US and 69.7% in Asia) than HBV-related HCC (21.4% in US and 45.5% in Africa). HCC cases associated to factors other than hepatitis viruses are also frequently mutated in TERT promoter (43.6%, 52.6% and 57.7% in USA, Asia and Europe, respectively). These results support a major role for telomere elongation in HCV-related and non-viral related hepatic carcinogenesis and suggest that TERT promoter mutations could represent a candidate biomarker for the early detection of liver cancer in subjects with HCV infection or with metabolic liver diseases.
PMCID: PMC5437489 Free PMC Article

Effect of smoking on survival of patients with hepatocellular carcinoma. Kolly P1,2, Knöpfli M2, Dufour JF1,2. *Liver Int*. 2017 May 3. doi: 10.1111/liv.13466. [Epub ahead of print] **BACKGROUND & AIMS:** Lifestyle factors such as smoking, obesity and physical activity have gained interest in the field of hepatocellular carcinoma. These factors play a significant role in the development of hepatocellular carcinoma. Several studies revealed the impact of tobacco consumption on the development of hepatocellular carcinoma and its synergistic effects with viral etiologies (hepatitis B and C). The effects of smoking on survival in patients with a diagnosed hepatocellular carcinoma have not yet been investigated in a Western cohort where hepatitis C infection is a major risk factor. **METHODS:** Using data from a prospective cohort of

patients with hepatocellular carcinoma who were followed at the University Hospital of Bern, Switzerland, survival was compared by Kaplan-Meier analysis in smokers and nonsmokers, and multivariate Cox regression was applied to control for confounding variables. **RESULTS:** Of 238 eligible hepatocellular carcinoma patients, 64 were smokers at the time of inclusion and 174 were nonsmokers. Smokers had a significant worse overall survival than nonsmokers (hazard ratio 1.77, 95% confidence interval: 1.22-2.58, P=.003). Analysis of patients according to their underlying liver disease, revealed that smoking, and not nonsmoking, affected survival of hepatitis B virus and C virus-infected patients only. In this subgroup, smoking was an independent predictor for survival (hazard ratio 2.99, 95% confidence interval: 1.7-5.23, P<.001) and remained independently predictive when adjusted for confounding variables. **CONCLUSIONS:** This study shows that smoking is an independent predictor of survival in hepatitis B virus/hepatitis C virus-infected patients with hepatocellular carcinoma.

Cirrhosis Patients with Nonalcoholic Steatohepatitis Are Significantly Less Likely to Receive Surveillance for Hepatocellular Carcinoma. Tavakoli H1, Robinson A1, Liu B2, Bhuket T2, Younossi Z3, Saab S4, Ahmed A5, Wong RJ6. Dig Dis Sci. 2017 May 4. doi: 10.1007/s10620-017-4595-x. [Epub ahead of print]

BACKGROUND: Disparities in receipt of hepatocellular carcinoma (HCC) surveillance contribute to disparities in overall survival outcomes. **AIM:** We aim to evaluate disparities in receipt of routine HCC surveillance among patients with cirrhosis in a large urban safety-net hospital. **METHODS:** Consecutive adults (age ≥ 18) with cirrhosis from July 1, 2014, to December 31, 2015, were retrospectively evaluated to determine rates of receiving appropriate HCC surveillance within 6 months and 1 year after diagnosis of cirrhosis. Rates of HCC surveillance were stratified by sex, race/ethnicity, and liver disease etiology. Multivariate Cox proportional hazards models were utilized to evaluate for predictors of receiving appropriate HCC surveillance. **RESULTS:** Among 157 cirrhosis patients enrolled [hepatitis C virus (HCV): 29.9%, hepatitis B virus: 13.4%, alcoholic cirrhosis: 44.6%, nonalcoholic steatohepatitis (NASH): 8.9%], mean age of cirrhosis diagnosis was 53.8 ± 9.0 years. Among these patients, 49% received (n = 77) HCC surveillance within 6 months and 78% (n = 123) were surveyed within 1 year of cirrhosis diagnosis. On multivariate analyses, patients with NASH cirrhosis were significantly less likely to receive HCC surveillance compared with chronic HCV cirrhosis patients (HR 0.44, 95% CI 0.19-0.99, p < 0.05). No significant sex-specific or race/ethnicity-specific disparities in receipt of HCC surveillance were observed. **CONCLUSION:** Among a diverse safety-net hospital population, sub-optimal HCC surveillance rates were observed: Only 49% of cirrhosis patients received HCC surveillance within 6 months, and 78% of cirrhosis patients received HCC surveillance within 1 year. Differences in rates of HCC screening by liver disease etiology were observed.

The Direct-Acting Antivirals for Hepatitis C Virus and the Risk for Hepatocellular Carcinoma. Chinchilla-López P1, Qi X2, Yoshida EM3, Méndez-Sánchez N1. Ann Hepatol. 2017 May - Jun;16(3):328-330. doi: 10.5604/16652681.1235473.

The increase of incidences of Hepatocellular Carcinoma (HCC) will continue in the next decades. The therapies about hepatitis C infection has been questioned as a risk factor. Some authors emphasized that sustained virologic response (SVR) with interferon-based therapy reduced the risk of developing HCC. In contrast, some publications that to suggest an increasing risk of HCC in patients treated with Direct-Acting Antivirals (DAA). Whether these therapies are

associated with an increased risk of HCC remains to be studied and continued long-term observational studies will be needed. The goal in HCV care needs to go beyond merely achieving an SVR.

[Association of hepatitis status with surgical outcomes in patients with dual hepatitis B and C related hepatocellular carcinoma.](#) Fu XT1, Shi YH1, Zhou J1,2, et al. Infect Agent Cancer. 2017 May 25;12:28. doi: 10.1186/s13027-017-0137-6. eCollection 2017.

BACKGROUND: The conception that serological hepatitis markers determined surgical prognosis of hepatocellular carcinoma (HCC) associated with hepatitis B (HBV) or hepatitis C (HCV) has been well defined. However, little is known about the relationship between surgical outcomes and serological hepatitis markers in patients with dual HBV and HCV related HCC. **METHODS:** A retrospective analysis of the clinical data of 39 HCC patients with HBV-HCV coinfection who underwent curative hepatectomy between 2001 and 2011 was performed. HBV DNA quantification, expression of HBV antigens, anti-HCV signal-to-cutoff ratio (S/CO) and some clinicopathological characteristics were investigated to show the potential relationship among them and the surgical prognosis. **RESULTS:** The Cox proportional hazards model identified that HBV DNA quantification of 1,000 IU/mL or higher, HBeAg seropositivity, tumor size of greater than 5 cm, multiple tumors, and vascular invasion were risk factors for HCC prognosis. Thus, HBV DNA quantification, HBsAg level, HBeAg status and HCV-Ab level which may reveal the hepatitis status were further analyzed. The overall survival time in the group with high ($\geq 1,000$ IU/mL) HBV DNA quantification was significantly lower than the group with low ($< 1,000$ IU/mL) HBV DNA quantification. Similarly, the high HBsAg level ($\geq 1,000$ IU/mL) was associated with poor survival compared with the low HBsAg level. Moreover, HBeAg seropositivity determined a higher cumulative risk for death. However, no significant difference was observed in overall survival time between the groups with low (< 10.9 S/CO) and high (≥ 10.9 S/CO) HCV-Ab level. Compared to HCV-Ab high-level group, the serological HBsAg level was observed significantly higher in HCV-Ab low-level group. Furthermore, the data we analyzed showed these 4 serological hepatitis markers were not correlated with cumulative recurrence rate. On multivariate analysis, none of serological hepatitis markers was an independent prognostic factor for HCC patients with dual hepatitis B and C. **CONCLUSION:** Among HCC patients with HBV-HCV coinfection, those who with preoperatively high HBV DNA quantification or HBeAg seropositivity had a short survival time and served as poor survival indicators. Serological expression of HBV status rather than HCV status might potentially dominate the surgical outcomes of the Chinese HCC patients with HBV-HCV coinfection.

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[Influence of higher BMI for hepatitis B- and C-related hepatocellular carcinomas.](#)

Hashimoto M1, Tashiro H2, Kobayashi T1, Kuroda S1, Hamaoka M1, Ohdan H1. Langenbecks Arch Surg. 2017 May 22. doi: 10.1007/s00423-017-1589-2. [Epub ahead of print]

PURPOSE: Although obesity is associated with hepatocellular carcinoma (HCC) development, its impact on the surgical outcomes of patients with hepatitis B virus (HBV)-and hepatitis C virus (HCV)-related HCC remains unclear. **METHODS:** We retrospectively analyzed 714 patients with HCC who underwent curative hepatectomy. Among them, the HBV-related HCC group (n = 125) and HCV-related HCC group (n = 426) were subdivided according to the presence of body mass index (BMI) ≥ 25 kg/m². The surgical outcomes were compared.

RESULTS: The 5-year overall survival rate after hepatectomy in the HBV-related HCC group was significantly better than that in the HCV-related HCC group. The 5-year overall survival rates of the HBV-related HCC with and without BMI \geq 25 kg/m² groups were 65 and 85%, respectively. The 5-year overall survival rates in the HCV-related HCC with and without BMI \geq 25 kg/m² groups were 75 and 65%, respectively. The HBV-related HCC with BMI \geq 25 kg/m² groups had a significantly worse prognosis than the HBV-related HCC without BMI \geq 25 kg/m² groups, while the HCV-related HCC with BMI \geq 25 kg/m² groups had a significantly better prognosis than the HCV-related HCC without BMI \geq 25 kg/m² groups. Multivariate analysis revealed that BMI \geq 25 kg/m² was the positive and negative prognostic factor for the surgical outcomes of patients with HBV- and HCV-related HCC, respectively. **CONCLUSIONS:** BMI \geq 25 kg/m² negatively affected the surgical outcomes of patients with HBV-related HCC and positively affected those of patients with HCV-related HCC.

[Potential ultrastructure predicting factors for hepatocellular carcinoma in HCV infected patients.](#)

Mansy SS1, El-Ahwany E2, Mahmoud S3, Hassan S1, et al. Ultrastruct Pathol. 2017 May-Jun;41(3):209-226. doi: 10.1080/01913123.2017.1316330. Epub 2017 May 11.

Hepatitis C virus represents one of the rising causes of hepatocellular carcinoma (HCC). Although the early diagnosis of HCC is vital for successful curative treatment, the majority of lesions are diagnosed in an irredeemable phase. This work deals with a comparative ultrastructural study of experimentally gradually induced HCC, surgically resected HCC, and potential premalignant lesions from HCV-infected patients, with the prospect to detect cellular criteria denoting premalignant transformation. Among the main detected pathological changes which are postulated to precede frank HCC: failure of normal hepatocyte regeneration with star shape clonal fragmentation, frequent elucidation of hepatic progenitor cells and Hering canals, hepatocytes of different electron density loaded with small sized rounded monotonous mitochondria, increase junctional complexes bordering bile canaliculi and in between hepatocyte membranes, abundant cellular proteinaceous material with hypertrophied or vesiculated rough endoplasmic reticulum (RER), sequestrated nucleus with proteinaceous granular material or hypertrophied RER, formation of lipolysosomes, large autophagosomes, and micro-vesicular fat deposition. In conclusion, the present work has visualized new hepatocytic division or regenerative process that mimic splitting or clonal fragmentation that occurs in primitive creature. Also, new observations that may be of value or assist in predicting HCC and identifying the appropriate patient for surveillance have been reported. Moreover, it has pointed to the possible malignant potentiality of liver stem/progenitor cells. For reliability, the results can be subjected to cohort longitudinal study.