Caring Ambassadors Program
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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Neuroplastic Effects of Transcranial Direct Current Stimulation on Painful Symptoms Reduction in Chronic Hepatitis C: A Phase II Randomized, Double Blind, Sham Controlled Trial. Brietzke AP1, Rozisky JR1, Dussan-Sarria JA1, et al. Front Neurosci. 2016 Jan 11;9:498. doi: 10.3389/fnins.2015.00498. eCollection 2015.
INTRODUCTION: Pegylated Interferon Alpha (Peg-IFN) in combination with other drugs is the standard treatment for chronic hepatitis C infection (HCV) and is related to severe painful symptoms. The aim of this study was access the efficacy of transcranial direct current stimulation (tDCS) in controlling the painful symptoms related to Peg-IFN side effects. **MATERIALS AND METHODS:** In this phase II double-blind trial, twenty eight (n = 28) HCV subjects were randomized to receive either 5 consecutive days of active tDCS (n = 14) or sham (n = 14) during 5 consecutive days with anodal stimulation over the primary motor cortex region using 2 mA for 20 min. The primary outcomes were visual analogue scale (VAS) pain and brain-derived neurotrophic factor (BDNF) serum levels. Secondary outcomes were the pressure-pain threshold (PPT), the Brazilian Profile of Chronic Pain: Screen (B-PCP:S), and drug analgesics use. **RESULTS:** tDCS reduced the VAS scores ($P < 0.003$), with a mean pain drop of 56% ($p < 0.001$). Furthermore, tDCS was able to enhance BDNF levels ($p < 0.01$). The mean increase was 37.48% in the active group. Finally, tDCS raised PPT ($p < 0.001$) and reduced the B-PCP:S scores and analgesic use ($p < 0.05$). **CONCLUSIONS:** Five sessions of tDCS were effective in reducing the painful symptoms in HCV patients undergoing Peg-IFN treatment. These findings support the efficacy of tDCS as a promising therapeutic tool to improve the tolerance of the side effects related to the use of Peg-IFN. Future larger studies (phase III and IV trials) are needed to confirm the clinical use of the therapeutic effects of tDCS in such condition.

Hepatitis E Virus Does Not Contribute To Hepatic Decompensation Among Patients with Advanced Chronic Hepatitis C. Samala N1, Wright EC2, Buckler AG3, et al. Clin Gastroenterol Hepatol. 2016 Jan 25. pii: S1542-3565(16)00055-0. doi: 10.1016/j.cgh.2015.12.048. [Epub ahead of print]
BACKGROUND & AIMS: Hepatitis E (HEV) can cause acute-on-chronic liver failure in persons with pre-existing liver disease. We investigated whether HEV infection contributes to hepatic decompensation in patients with previously stable, advanced chronic hepatitis C.

METHODS: We performed a case-control study using stored serum samples from subjects enrolled in the randomized phase of the hepatitis C antiviral long-term treatment against cirrhosis trial (n=1050; mean age, 51 years; 70% male; 40% with cirrhosis at baseline). Cases were subjects who developed hepatic decompensation within a 24 week period. Controls (3/case) were subjects without hepatic decompensation matched for fibrosis stage and followed for a similar period. A serum sample obtained within 6 months after the decompensation event in cases and same follow-up period in controls were tested for anti-HEV immunoglobulin (Ig)G. Subjects with a positive result had a baseline sample were similarly tested. We measured levels of anti-HEV IgM and HEV RNA in blood samples from incident cases. **RESULTS:** Of the 1050 subjects analyzed, 314 (30%) experienced a clinical event. Of the 314 subjects who experienced decompensation, as defined, 89 (28%) were tested for anti-HEV, along with 267 controls (without decompensation). Similar proportions of cases and controls tested positive for anti-HEV (22.5% and 20.6%; P=.70). Ten incident HEV infections were identified-4 in cases (4.5%) and 6 in controls (2.2%) (P=.28). HEV RNA was not detected in blood samples from the 10 incident infections. Only 2 of the 4 incident infections among cases were temporally related to the decompensation event. **CONCLUSION:** HEV does not appear to be a significant cause of hepatic decompensation among persons with previously stable, advanced chronic hepatitis C in the US.

Patient-Reported Outcomes of Elderly Adults with Chronic Hepatitis C Treated with Interferon- and Ribavirin-Free Regimens. Younossi ZM1, Stepanova M2, Nader F1,3, Henry L2,3. J Am Geriatr Soc. 2016 Jan 30. doi: 10.1111/jgs.13928. [Epub ahead of print]
The purpose of the study was to assess the effect of different treatment regimens for chronic hepatitis C on patient-reported outcomes (PROs) of individuals aged 65 and older with chronic hepatitis C. PRO data from eight multinational multicenter Phase 2 and 3 clinical trials were included. Of 3,120 participants in these clinical trials, 229 were aged 65 and older (67.8 ± 3.2, 57% male, 75% treatment-naïve, 22% cirrhotic), and 90 of those received ledipasvir plus sofosbuvir (LDV + SOF), 119 received SOF plus ribavirin (SOF + RBV), and 20 received pegylated IFN, SOF, and RBV (IFN + SOF + RBV). Participants aged 65 and older had slightly more pretreatment PRO impairment in their physical functioning than younger individuals (-3.1% on a normalized 0-100% PRO scale, P < .001). Despite this, these participants experienced significant PRO improvement during treatment with IFN-free RBV-free regimens (up to +8.0%, P < .001), similar to improvements in younger participants. In contrast, participants aged 65 and older experienced substantial decline in PROs while receiving IFN- or RBV-containing regimens (up to -18.9% in IFN + SOF + RBV, -10.4% in IFN-free SOF+RBV, P < .001), and some were greater than in the younger group. Nevertheless, after achieving sustained viral clearance at Posttreatment Week 12, PROs in participants aged 65 and older improved regardless of the regimen (up to +10.4%, P < .001). In multivariate analysis of the cohort aged 65 and older, the use of IFN and RBV was consistently associated with PRO impairment during treatment. The use of an IFN- and RBV-free anti-HCV regimen in older adults with hepatitis C results in significant improvement of PROs.

Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Abergel A1, Asselah T2, Metivier S3, et al. Lancet Infect Dis. 2016 Jan 20. pii: S1473-3099(15)00529-0. doi: 10.1016/S1473-3099(15)00529-0. [Epub ahead of print]

BACKGROUND: Data about the response of hepatitis C virus (HCV) genotype 5 to approved and experimental treatment regimens are scarce. We assessed the efficacy and safety of combination therapy with the NS5A inhibitor ledipasvir and the NS5B polymerase inhibitor sofosbuvir in patients with HCV genotype 5. **METHODS:** We did this open-label, multicentre, single-arm, phase 2 trial at five hospitals in France. Eligible patients were at least 18 years old and had chronic infection with HCV genotype 5, with plasma HCV RNA of at least 10 000 IU/mL. We used BLAST analyses of NS5B partial sequences to establish the genotype and subtype at screening. Patients were given a fixed-dose combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir orally once per day for 12 weeks. The primary endpoint was the proportion of patients with a sustained viral response, defined as HCV RNA concentration less than 15 IU/mL at 12 weeks after the end of treatment (SVR12). We analysed efficacy and safety in all patients who received at least one dose of ledipasvir-sofosbuvir. This trial is registered with EudraCT, number 2013-003978-27, and with ClinicalTrials.gov, number NCT02081079. **FINDINGS:** From March 7 to June 10, 2014, we recruited 41 patients, including 21 who were treatment naive and 20 who were treatment experienced. All patients were of white ethnic origins. All 41 patients who started treatment completed the full 12 weeks of treatment and had undetectable HCV RNA at their final treatment visit. In the overall study population, 39 (95%, 95% CI 83-99) of 41 patients achieved SVR12. SVR12 was achieved by 20 (95%, 76-100) of the 21 patients who were treatment naive and 19 (95%, 75-100) of the 20 patients who were treatment experienced. Eight (89%) of nine patients with cirrhosis achieved SVR12, whereas 31 (97%) of the 32 patients without cirrhosis achieved SVR12. The two patients who did not reach SVR12 both had IL28B TT genotype and had viral relapse within 4 weeks of the end of treatment. The most common adverse events were asthenia (16 [39%] patients), headache (11 [27%] patients), and fatigue (four [10%] patients). One patient had a serious adverse event, worsening depression, which we judged to be unrelated to study treatment. **INTERPRETATION:** The oral regimen of ledipasvir-sofosbuvir is an effective and well-tolerated treatment for patients with HCV genotype 5 infection who are treatment naive or treatment experienced. **FUNDING:** Gilead Sciences.

Simeprevir Plus Sofosbuvir (12 and 8 Weeks) in HCV Genotype 1-Infected Patients Without Cirrhosis: OPTIMIST-1, a Phase 3, Randomized Study. Kwo P1, Gitlin N2, Nahass R3, et al. Hepatology. 2016 Jan 22. doi: 10.1002/hep.28467. [Epub ahead of print]
Effective antiviral therapy is essential for achieving sustained virological response (SVR) in hepatitis C virus (HCV)-infected patients. The phase 2 COSMOS study reported high SVR rates in treatment-naïve and prior null-responder HCV genotype (GT)1-infected patients receiving simeprevir+sofosbuvir±ribavirin for 12/24 weeks. OPTIMIST-1 (NCT02114177) was a multicenter, randomized, open-label study assessing the efficacy and safety of 12 and 8 weeks of simeprevir+sofosbuvir in HCV GT1-infected treatment-naïve and -experienced patients without cirrhosis. Patients were randomly assigned (1:1; stratified by HCV GT/subtype and presence/absence of NS3 Q80K polymorphism [GT1b, GT1a with Q80K, GT1a without Q80K]), prior HCV treatment history, and IL28B GT [CC, non-CC]) to simeprevir 150 mg once daily (QD)+sofosbuvir 400 mg QD for 12 or 8 weeks. Primary efficacy endpoint: SVR rate 12 weeks after end of treatment (SVR12). Superiority in SVR12 was assessed for simeprevir+sofosbuvir at 12 and 8 weeks versus a composite historical control SVR rate. 310 patients were enrolled, randomized, and received treatment (n=155 in each arm). SVR12 with simeprevir+sofosbuvir for 12 weeks (97% [150/155; 95% CI 94-100%]) was superior to the historical control (87%).

SVR12 with simeprevir+sofosbuvir for 8 weeks (83% [128/155; 95% CI 76-89%]) was not superior to the historical control (83%). The most frequent adverse events (AEs) were nausea, headache, and fatigue (12-week arm: 15% [23/155]), 14% [22/155], and 12% [19/155]; 8-week arm: 9% [14/155], 17% [26/155], and 15% [23/155], respectively). No patients discontinued treatment due to an AE. One (1%; 12-week arm) and three (2%; 8-week arm) patients experienced a serious AE (all unrelated to study treatment).

Some Medicaid programs restrict HCV treatment to genotype 1 patients. With the release of new DAA's that effectively treat genotype 3 patients there may still be access issues because of unnecessary restrictions. The number of people with genotype 3 is relatively small in the US, but their impact in advocating for access to effective medications to G3 patients may have significant impact on patients with other genotypes. How can this small group of patients come together to advocate and create bigger change?

Daclatasvir, Sofosbuvir, and Ribavirin for Hepatitis C Virus Genotype 3 and Advanced Liver Disease: A Randomized Phase III Study (ALLY-3+). Leroy V1, Angus P2, Bronowicki JP3, et al. Hepatology. 2016 Jan 28. doi: 10.1002/hep.28473. [Epub ahead of print]
Patients with hepatitis C virus (HCV) genotype 3 infection, especially with advanced liver disease, are a challenging population in urgent need of optimally effective therapies. The combination of daclatasvir (DCV; pangenotypic NS5A inhibitor) and sofosbuvir (SOF; nucleotide NS5B inhibitor) for 12 weeks previously showed high efficacy (96%) in noncirrhotic genotype 3 infection. The phase III ALLY-3+ study (N = 50) evaluated DCV-SOF with ribavirin (RBV) in treatment-naive (n = 13) or treatment-experienced (n = 37) genotype 3 patients with advanced fibrosis (n = 14) or compensated cirrhosis (n = 36). Patients were randomized 1:1 to receive open-label DCV-SOF (60 + 400 mg daily) with weight-based RBV for 12 or 16 weeks. The primary endpoint was sustained virologic response at posttreatment week 12 (SVR12). SVR12 (intention-to-treat) was 90% overall (45/50): 88% (21/24) in the 12-week (91% observed) and 92% (24/26) in the 16-week group. All patients with advanced fibrosis achieved SVR12. SVR12 in patients with cirrhosis was 86% overall (31/36): 83% (15/18) in the 12-week (88% observed) and 89% (16/18) in the 16-week group; for treatment-experienced patients with cirrhosis, these values were 87% (26/30), 88% (14/16; 93% observed) and 86% (12/14), respectively. One patient (12-week group) did not enter posttreatment follow-up (death unrelated to treatment). There were 4 relapses (2 per group) and no virologic breakthroughs. The most common adverse events (AEs) were insomnia, fatigue and headache. There were no discontinuations for AEs, and no treatment-related serious AEs. **CONCLUSION:** The all-oral regimen of DCV-SOF-RBV was well tolerated and resulted in high and similar SVR12 after 12 or 16 weeks of treatment among genotype 3-infected patients with advanced liver disease, irrespective of prior HCV treatment experience.

Rapid decrease in hepatitis C viremia by direct acting antivirals improves the natural killer cell response to IFNα. Serti E1, Park H1, Keane M1, et al. Gut. 2016 Jan 4. pii: gutjnl-2015-310033. doi: 10.1136/gutjnl-2015-310033. [Epub ahead of print]
OBJECTIVE: Chronic HCV infection is characterised by innate immune activation with increased interferon-stimulated genes (ISG) expression and by an altered phenotype of interferon-responsive natural killer (NK) cells. Here, we asked whether a rapid reduction in viremia by daclatasvir (DCV) and asunaprevir (ASV) improves the response to pegylated interferon (PegIFN) in patients who had previously failed a standard course of PegIFN/ribavirin (RBV) therapy. **DESIGN:** Twenty-two HCV-infected non-responders to previous PegIFN/RBV

therapy were studied for IFN-responsiveness of NK cells during quadruple (QUAD) therapy with DCV, ASV, PegIFN and RBV. A direct comparison of early NK cell responses in PegIFN/RBV therapy and QUAD therapy was performed for seven patients using paired cryopreserved peripheral blood mononuclear cells (PBMC) from both treatment courses. As a validation cohort, nine DCV/ASV-treated patients were studied for their NK cell response to in vitro stimulation with IFNα. **RESULTS:** The 24 h virological response to QUAD therapy correlated with an increase in signal transducer and activator of transcription 1 (STAT1), phosphorylated STAT1 (pSTAT1) and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) expression in NK cells, and the STAT1/pSTAT1/TRAIL induction was greater during QUAD therapy than during previous PegIFN/RBV therapy. Successful QUAD therapy as well as successful IFN-free DCV/ASV regimen resulted in an improved functional NK cell response (degranulation and TRAIL expression) to in vitro stimulation with IFNα. **CONCLUSIONS:** IFN-responsiveness can be improved by inhibiting HCV replication and reducing the HCV-induced activation of the innate immune response. This may provide a rationale for clinical trials of a brief period of direct acting antiviral therapy followed by PegIFN/RBV therapy to reduce the overall treatment costs in low-income and middle-income countries.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Artesunate, an anti-malarial drug, has a potential to inhibit HCV replication. Dai R1, Xiao X1, Peng F1, Li M1, Gong G2. Virus Genes. 2016 Jan 6. [Epub ahead of print]
Hepatitis C virus (HCV) infection is a major global health issue. Although the search for HCV treatments has resulted in great achievements, the current treatment methods have limitations, and new methods and drugs for hepatitis C treatment are still required. The aim of the present study was to investigate the effects of artesunate (ART) on HCV replication and compared these effects with those of ribavirin (RBV) and interferon-2b (IFN). The study was performed in HCV-infection cell models (JFH1-infected Huh7.5.1 and OR6 cell lines). Our results showed that the antimalarial drug ART inhibited HCV replicon replication in a dose- and time-dependent manner at a concentration that had no effect on the proliferation of exponentially growing host cells, and the inhibitory effect on HCV replication was stronger than RBV but weaker than IFN, as determined by qPCR, luciferase assays, and Western blot analysis. Furthermore, the combination of ART and IFN resulted in a greater inhibition of HCV replication. These findings demonstrated that ART had an inhibitive effect on HCV replication and may be a novel supplemental co-therapy with IFN and RBV for HCV and as an alternative strategy to combat resistance mechanisms that have emerged in the presence of DAA agents.

The growing heroin epidemic has drastically impacted younger populations creating a new group of HCV patients. The results of this study will be interesting in identifying the use of computers and technology in HCV prevention in younger adults. How might the increased use of technology among this population provide avenues for prevention messaging? And, how effective do you think those strategies are in connecting to those at risk?

Computerized Tailored Interventions to Enhance Prevention and Screening for Hepatitis C Virus Among People Who Inject Drugs: Protocol for a Randomized Pilot Study.
Westergaard RP1, Hull SJ, Merkow A, Stephens LK, Hochstatter KR, Olson-Streed HK, Baker LM, Hess TM. JMIR Res Protoc. 2016 Jan 22;5(1):e15. doi: 10.2196/resprot.4830.

BACKGROUND: Hepatitis C virus (HCV) infection is a growing problem among people who inject drugs. Strategies to reduce disease transmission (eg, syringe exchange programs) and facilitate HCV screening and linkage are available but are under-utilized in many communities affected by injection drug use. Novel approaches to increasing the use of these strategies are needed. **OBJECTIVE:** The goals of this project are to (1) develop and pilot test a computerized tailored intervention for increasing HCV screening and decreasing risky drug use behavior among people who inject drugs and (2) determine the feasibility of disseminating such an intervention using peer-based referrals in the setting of a community-based syringe exchange program. **METHODS:** This 2-arm, randomized pilot study is being conducted in a large-volume, multisite syringe exchange program in southern Wisconsin. A social network-based strategy was used to recruit a total of 235 adults who reported past-month injection of opioids, cocaine, or methamphetamine. Network recruiters were identified among clients requesting services from the syringe exchange program and were enlisted to refer eligible peers to the study. All participants completed a computer-adapted questionnaire eliciting information about risk behaviors and their knowledge, attitudes, and prior experiences related to HCV screening. Subjects were then randomly assigned to receive usual care, consisting of standard counseling by syringe exchange staff, or the Hep-Net intervention, which provides algorithm-based, real-time tailored feedback and recommendations for behavior change in the style of motivational interviewing. Changes in drug use behaviors and attitudes will be assessed during a second session between 90 and 180 days after the baseline visit. Frequency of repeat HCV testing and HCV incidence will be assessed through a database search 1 year after study completion. **RESULTS:** Recruitment for this study was completed in April 2015. Follow-up of enrolled participants is expected to continue until March 2016. Network recruiters were enrolled who referred a total of 195 eligible peers (overall N=235). At baseline, the median age was 34 years; 41.3% (97/235) were non-white; and 86.4% (203/235) reported predominantly injecting heroin. Most participants (161/234, 68.8%) reported sharing injection equipment in the past and of these, 30.4% (49/161) had never been tested for HCV. **CONCLUSIONS:** This study will provide preliminary evidence to determine whether incorporating computerized behavioral interventions into existing prevention services at syringe exchange programs can lead to adoption of healthier behaviors.

Peripheral loss of CD8(+) CD161(++) TCRVα7·2(+) mucosal-associated invariant T cells in chronic hepatitis C virus-infected patients. Barathan M1, Mohamed R2, Vadivelu J1, et al. Eur J Clin Invest. 2016 Feb;46(2):170-80. doi: 10.1111/eci.12581. Epub 2016 Jan 5.
BACKGROUND: Mucosal-associated invariant T (MAIT) cells play an important role in innate host defence. MAIT cells appear to undergo exhaustion and are functionally weakened in chronic viral infections. However, their role in chronic hepatitis C virus (HCV) infection remains unclear. **MATERIALS AND METHODS:** We investigated the frequency of CD8(+) CD161(++) TCR Vα7.2(+) MAIT cells in a cross-sectional cohort of chronic HCV-infected patients (n = 25) and healthy controls (n = 25). Peripheral blood mononuclear cells were investigated for circulating MAIT cell frequency, liver-homing (CCR5 and CD103), biomarkers of immune exhaustion (PD-1, TIM-3 and CTLA-4), chronic immune activation (CD38 and HLA-DR), and immunosenescence (CD57) by flow cytometry. **RESULTS:** The frequency of MAIT cells was significantly decreased, and increased signs of immune exhaustion and chronic immune activation were clearly evident on MAIT cells of HCV-infected patients. Decrease of CCR5 on circulating MAIT cells is suggestive of their peripheral loss in chronic HCV-infected

patients. MAIT cells also showed significantly increased levels of HLA-DR, CD38, PD-1, TIM-3 and CTLA-4, besides CD57 in chronic HCV disease. **CONCLUSIONS:** Immune exhaustion and senescence of CD8(+) CD161(++) TCR Vα7.2(+) MAIT cells could contribute to diminished innate defence attributes likely facilitating viral persistence and HCV disease progression.

Antibody response to the hypervariable region-1 interferes with broadly neutralizing antibodies to hepatitis C virus. Keck ZY1, Girard-Blanc C2, Wang W1, et al. J Virol. 2016 Jan 6. pii: JVI.02458-15. [Epub ahead of print]
The hypervariable region-1 (HVR1) (amino acids (aa) 384-410) on the E2 glycoprotein of hepatitis C virus contributes to persistent infection by evolving escape mutations that attenuate binding of inhibitory antibodies and by blocking access of broadly neutralizing antibodies to their epitopes. A third proposed mechanism of immune antagonism is that poorly neutralizing antibodies binding to HVR1 interfere with binding of other superior neutralizing antibodies. Epitope mapping of human monoclonal antibodies (HMAbs) that bind to an adjacent, conserved domain on E2 encompassing aa 412-423 revealed two subsets, designated as HC33 HMAbs. While both subsets have contact residues within aa 412-423, alanine scanning mutagenesis suggested that one subset, which includes HC33.8, has an additional contact residue within HVR1. To test for interference of anti-HVR1 antibodies with binding of antibodies to aa 412-423 and other E2 determinants recognized by broadly neutralizing HMAbs, two murine MAbs against HVR1 (H77.16) and aa 412-423 (H77.39) were studied. As expected, H77.39 inhibited the binding of all HC33 HMAbs. Unexpectedly, H77.16 also inhibited the binding of both subsets of HC33 HMAbs. This inhibition also was observed against other broadly neutralizing HMAbs to epitopes outside of aa 412-423. Combination antibody neutralization studies by the median-effect analysis method with H77.16 and broadly reactive HMAbs revealed antagonism between these antibodies. Structural studies demonstrated conformational flexibility in this antigenic region, which supports the possibility of anti-HVR1 antibodies hindering the binding of broadly neutralizing MAbs. These findings support the hypothesis that anti-HVR1 antibodies can interfere with a protective humoral response against HCV infection. **IMPORTANCE:** The HVR1 contributes to persistent infection by evolving mutations that escape from neutralizing antibodies to HVR1 and by shielding broadly neutralizing antibodies from their epitopes. This study provides insight into a new immune antagonism mechanism by which the binding of antibodies to HVR1 blocks the binding and activity of broadly neutralizing antibodies to HCV. Immunization strategies that avoid the induction of HVR1 antibodies should increase the inhibitory activity of broadly neutralizing anti-HCV antibodies elicited by candidate vaccines.

Prolactin regulatory element binding protein is involved in hepatitis C virus replication compartment by interacting with NS4B. Kong L1, Fujimoto A1, Nakamura M1, et al. J Virol. 2016 Jan 6. pii: JVI.01540-15. [Epub ahead of print]
It has been proposed that hepatitis C virus (HCV) NS4B protein triggers the membranous HCV replication compartment, but the underlying molecular mechanism is not fully understood. Here, we screened for NS4B-associated membrane proteins by tandem affinity purification and proteome analysis and identified 202 host proteins. Subsequent small interfering RNA screening in replicon cells identified prolactin regulatory element binding (PREB) as a novel HCV host cofactor. The interaction between PREB and NS4B was confirmed by immunoprecipitation, immunofluorescence and proximity ligation assays. PREB colocalized with double-stranded

RNA and the newly synthesized HCV RNA labeled by bromouridine triphosphate in HCV replicon cells. Furthermore, PREB shifted to detergent-resistant membranes (DRM), where HCV replication complexes reside, in the presence of NS4B expression in Huh7 cells. However, a PREB mutant lacking the NS4B binding region (PREBd3) could not colocalize with double-stranded RNA and did not shift to the DRM in the presence of NS4B. These results indicate that PREB locates at the HCV replication complex by interacting with NS4B. PREB silencing inhibited the formation of membranous HCV replication compartment and increased the protease and nuclease sensitivity of HCV replicase proteins and RNA in DRM, respectively. Collectively, these data indicate that PREB promotes HCV RNA replication by participating in the formation of the membranous replication compartment and by maintaining its proper structure by interacting with NS4B. Furthermore, PREB was induced by HCV infection in vitro and in vivo. Our findings provide new insights into HCV host cofactors. **IMPORTANCE:** The hepatitis C virus (HCV) protein, NS4B, can induce alteration of the endoplasmic reticulum and formation of a 'membranous web' structure, which provides a platform for the HCV replication complex. The molecular mechanism by which NS4B induces membranous HCV replication compartment is not understood. We screened for NS4B-associated membrane proteins by tandem affinity purification and proteome analysis, followed by small interfering RNA screening. We identified prolactin regulatory element binding (PREB) as a novel HCV host cofactor. PREB is induced by HCV infection and recruited into the replication complex by interaction with NS4B. Recruited PREB promotes HCV RNA replication by participating in the formation of membranous HCV replication compartment. To our knowledge, this is the novel report to describe the effect of NS4B-binding protein on the formation of membranous HCV replication compartment. Our findings are expected to provide new insights into HCV host cofactors.

HIV/HCV COINFECTION

Evaluation of Drug-Drug Interactions Between Hepatitis C Antiviral Agents Ombitasvir, Paritaprevir/Ritonavir, and Dasabuvir and HIV-1 Protease Inhibitors. Khatri A1, Dutta S1, Wang H1, et al. Clin Infect Dis. 2016 Jan 5. pii: civ1213. [Epub ahead of print]
BACKGROUND: Guidelines for the treatment of HIV infection consistently recommend initiation of antiretroviral therapy in patients with hepatitis C virus (HCV)/HIV-1 coinfection. Therefore, potential drug interactions between antiretroviral drugs and HCV direct-acting antiviral agents (DAAs) must be carefully considered. The objective of this investigation was to evaluate the compatibility of a novel DAA combination (the 3D regimen) with commonly prescribed HIV-1 protease inhibitors (PIs). **METHODS:** Five phase 1, multiple-dose, open-label pharmacokinetic studies were performed in healthy volunteers (N=144). Participants in each study were randomly assigned 1:1 into cohorts assessing the effects of the steady-state 3D regimen on steady-state HIV-1 PIs or vice versa. The 3D regimen is comprised of ombitasvir 25 mg daily, paritaprevir/ritonavir 150/100 mg daily, and dasabuvir 250 or 400 mg twice daily. HIV-1 PIs assessed included atazanavir, darunavir, and lopinavir (administered with ritonavir). Safety, tolerability, and pharmacokinetic parameters were assessed to evaluate the compatibility of the drug regimens. **RESULTS:** Coadministration of the 3D regimen with the evaluated HIV-1 PIs was generally well tolerated in healthy volunteers. Morning administration of atazanavir 300 mg daily and darunavir regimens exhibited no clinically meaningful drug interactions with the 3D regimen. However, due to higher paritaprevir and/or ritonavir exposures, evening administration of atazanavir 300 mg plus ritonavir 100 mg or lopinavir/ritonavir 800/200 mg

with the 3D regimen is not recommended. **CONCLUSIONS:** The 3D regimen can be coadministered with morning atazanavir and darunavir regimens. However, evening atazanavir plus ritonavir and lopinavir/ritonavir regimens are not recommended in combination with the 3D regimen.

Cytokine Response Associated with Hepatitis C Virus Clearance in HIV Coinfected Patients Initiating Peg Interferon-α Based Therapy. Nguyen TT1, Niloofar R2, Rubbo PA2, et al. Mediterr J Hematol Infect Dis. 2016 Jan 1;8(1):e2016003. doi: 10.4084/MJHID.2016.003. eCollection 2016.
BACKGROUND: Treatment of hepatitis C virus (HCV) infection based on peginterferon-α (pegIFNα) and ribavirin induces important changes in cytokine release and T cell activation. **OBJECTIVE:** Immune response to pegIFNα-ribavirin therapy was explored in patients coinfected by HCV and HIV. **METHODS:** Concentrations of 25 cytokines and CD8(+) T cell activation were monitored in HCV/HIV coinfected patients classified as sustained virological responders (SVR, n=19) and non-responders (NR, n=11). **RESULTS:** High pretreatment concentrations of IP-10 (CXCL-10) and MCP-1 (CCL-2) were associated with a poor anti-HCV response. PegIFNα-ribavirin therapy increased CD8(+) T cell activation and induced significant changes in levels of eleven cytokines related to both Th1 and Th2 responses in SVR (IL-1β, IL-1RA, IL-4, IL-5, IL-6, IL-7, IL-12p40/70, IL-13, IP-10, eotaxin, MCP-1) but of only six cytokines in NR (IL-1β, IL-2, IL-5, IL-12p40/70, IL-13, eotaxin). The highest rise in MIP-1β and MCP-1 levels was observed four weeks after anti-HCV treatment initiation in SVR compared to NR (p=0.002 and p=0.03, respectively), whereas a decrease in IL-8 concentration was associated with treatment failure (p= 0.052). **CONCLUSIONS:** Higher and broader cytokine responses to pegIFNα-ribavirin therapy were observed in SVR patients compared to NR. Changes in IL-8, MIP-1β, and MCP-1 serum concentrations may be associated with efficacy of pegIFNα- and ribavirin-based therapies in patients coinfected by HCV and HIV.

We know that HIV-positive patients progress to cirrhosis faster than other patients. We also know that many HIV-positive patients were 'warehoused' and not treated for HCV because of treatment side-effects and other barriers. What might be effective messaging or educational approaches to re-engage these long-time HIV survivors who are out of care, or unaware of their looming liver disease?

Discordant response of CD4(+) T cells to antiretroviral therapy in HIV-infected patients coinfected with hepatitis C virus is accompanied by increased liver damage.
Shmagel NG1,2, Shmagel KV3,4, Saidakova EV1,5, Korolevskaya LB1,5, Chereshnev VA1,6,7. Dokl Biochem Biophys. 2015 Nov;465(1):358-60. doi: 10.1134/S1607672915060034. Epub 2016 Jan 5.
A study of HIV-infected patients coinfected with hepatitis C virus and receiving antiretroviral therapy (ART) but not treated with interferon was performed. Patients were divided into two groups-with standard and inefficient recovery of CD4(+) T cells. It was found that patients with discordant response of CD4(+) T cells to ART showed heavier destructive processes in the liver than the successfully recovered subjects. They had increased levels of ALT and AST. In these patients, the risk of development of liver cirrhosis is greater.

Impact of PNPLA3 variants on the liver histology of 168 patients with HIV infection and chronic hepatitis C. Sagnelli C1, Merli M2, Uberti-Foppa C2, et al. Clin Microbiol Infect. 2016 Jan 19. pii: S1198-743X(16)00007-0. doi: 10.1016/j.cmi.2015.11.025. [Epub ahead of print]
This study analyzed the impact of PNPLA3 variants on liver histology of 168 HIV/HCV coinfected patients who were naïve for HCV treatment. A pathologist unaware of the patients' condition graded liver fibrosis and necroinflammation (Ishak) and steatosis (Kleiner). Patients were tested for PNPLA3 variants and genotyped for the PNPLA3 rs738409 C to G variant underlying the I148M substitution. All were HBsAg-negative and stated no alcohol abuse. The mean age was 40.6(37.6-44.1), 72.6% were males, 42% showed HCV-genotype 3, 38.9% HCV-genotype 1 and 79.2% were receiving HAART. The 79 patients with the PNPLA3 p.148I/M or M/M variants more frequently showed severe steatosis (score 3-4) than the 89 with PNPLA3 p.148I/I, 43% vs. 24.7% (p=0.001), whereas no difference was observed in the degree of necroinflammation or fibrosis. Compared with 112 patients with lower scores, 56 with severe steatosis showed higher BMI (p=0.03), higher rate of HCV-genotype 3 (55.6% vs. 35.2%,p=0.01) and PNPLA3 p.148I/M or M/M (60.7% vs. 39.3%,p=0.01) and lower CD4+ cells/mm3 [514.00(390.5-673.0) vs. 500.00(399.0-627.0]; p=0.002). At multivariate analysis, BMI (p=0.01), HCV-genotype 3 (p=0.006), CD4+ cell count (p=0.005) and the PNPLA3 p.148I/M or M/M variants (p=0.01) were found to be independent predictors of severe liver steatosis. The PNPLA3 p.148 I/M or M/M variants and CD4+ cell count were the only independent predictors of severe steatosis in patients with HCV-genotype non-3. This is the first study to show that among HIV/HCV coinfected patients the PNPLA3 p.148I/M or M/M variant have substantially less impact on steatosis for those with HCV-genotype 3 than non-genotype 3.

HCV-HIV co-infected patients: no longer a 'special' population? Sulkowski MS1. Liver Int. 2016 Jan;36 Suppl 1:43-6. doi: 10.1111/liv.13021.
Prior to the advent of safe and highly effective hepatitis C virus (HCV) treatment, patients with human immunodeficiency virus (HIV)/HCV co-infection were referred to as a 'special' population. This definition was based on more rapid HCV disease progression in the presence of HIV co-infection, limited effectiveness of interferon-based HCV treatment and potential drug interactions between medications used to treat HIV and those to treat HCV infection. Although the availability of interferon-free, oral direct-acting antivirals (DAAs) has dramatically increased the effectiveness of HCV treatment in patients with HIV co-infection, this population still warrants special consideration. Specific issues for the treatment of patients with HIV/HCV co-infection in the era of oral DAAs include a high HCV disease burden with ongoing HCV infection and re-infection following successful treatment, frequent drug interactions that must be carefully evaluated and unanswered questions on the role of shorter HCV treatment durations.

Effect of HIV co-infection on adherence to a 12-week regimen of hepatitis C virus therapy with ledipasvir and sofosbuvir. Townsend K1, Petersen T, Gordon LA, et al. AIDS. 2016 Jan;30(2):261-6. doi: 10.1097/QAD.0000000000000903.
OBJECTIVE: As the treatment of hepatitis C virus (HCV) infection has evolved to directly acting antiviral agents, the impact of these directly acting antiviral-only regimens on improving adherence to HCV treatment in HIV/HCV coinfected populations has not been evaluated. The study compared adherence to ledipasvir/sofosbuvir (LDV/SOF) in HCV monoinfected and HIV/HCV coinfected individuals. **DESIGN:** Adherence was measured from participants in two phase 2 open-label studies (NCT01805882 and NCT01878799). **METHODS:** HCV treatment-

naive, genotype 1 study individuals [HCV monoinfected participants (N=20) and HIV/HCV coinfected participants, antiretroviral untreated (N = 13) or on combination antiretroviral therapy (N=37)] were treated with LDV (90mg) and SOF (400mg) administered as one tablet once daily for 12 weeks. Adherence was measured using three tools: medication event monitoring system cap, pill count, and patient report. **RESULTS:** Participants were predominately African American (83%) and male (73%), with a median age of 59 years. Participants had prompt HCV viral load decline and high adherence rates (97±0.5% by medication event monitoring system). Participant adherence decreased significantly from early (baseline week 4) as compared with late (weeks 8-12) in therapy in all three groups - HCV monoinfected (P=0.01), HIV/HCV antiretroviral untreated (P=0.02), and HIV/HCV antiretroviral treated participants (P=0.01). **CONCLUSION:** Adherence to LDV/SOF in this urban population was high and comparable between HCV monoinfected and HIV/HCV coinfected participants regardless of antiretroviral use.

Gut epithelial barrier dysfunction in human immunodeficiency virus-hepatitis C virus coinfected patients: Influence on innate and acquired immunity. Márquez M1, Fernández Gutiérrez Del Álamo C1, Girón-González JA1. World J Gastroenterol. 2016 Jan 28;22(4):1433-48. doi: 10.3748/wjg.v22.i4.1433.

Even in cases where viral replication has been controlled by antiretroviral therapy for long periods of time, human immunodeficiency virus (HIV)-infected patients have several non-acquired immunodeficiency syndrome (AIDS) related co-morbidities, including liver disease, cardiovascular disease and neurocognitive decline, which have a clear impact on survival. It has been considered that persistent innate and acquired immune activation contributes to the pathogenesis of these non-AIDS related diseases. Immune activation has been related with several conditions, remarkably with the bacterial translocation related with the intestinal barrier damage by the HIV or by hepatitis C virus (HCV)-related liver cirrhosis. Consequently, increased morbidity and mortality must be expected in HIV-HCV coinfected patients. Disrupted gut barrier lead to an increased passage of microbial products and to an activation of the mucosal immune system and secretion of inflammatory mediators, which in turn might increase barrier dysfunction. In the present review, the intestinal barrier structure, measures of intestinal barrier dysfunction and the modifications of them in HIV monoinfection and in HIV-HCV coinfection will be considered. Both pathogenesis and the consequences for the progression of liver disease secondary to gut microbial fragment leakage and immune activation will be assessed.

Association of CMV, HBV, or HCV Co-infection with Vaccine Response in Adults with Well-Controlled HIV Infection. Troy SB1,2, Rossheim AE1, Siik J1, Cunningham TD3, Kerry JA2. Hum Vaccin Immunother. 2016 Jan 11:0. [Epub ahead of print]

Even after CD4 count recovery on antiretroviral therapy, HIV infection is associated with decreased response to most vaccines compared to the general population. Chronic infections with viruses such as cytomegalovirus (CMV), hepatitis B virus (HBV), and hepatitis C virus (HCV), which are more prevalent in HIV-infected populations, have been linked to immune dysfunction and decreased vaccine response in the general population. However, whether co-infection with these other viruses contributes to the decreased vaccine response seen in adults with well-controlled HIV infection is unknown. We conducted a secondary analysis of data and serum from adults with well-controlled HIV infection from an inactivated polio vaccine trial (224

subjects) and a pneumococcal conjugate vaccine study (128 subjects). We evaluated the association of CMV, HBV, or HCV co-infection with post-vaccination antibody levels using both univariate and multivariate analyses, controlling for factors such as age, race, CD4 count, comorbidities, smoking status, and baseline antibody levels. Ninety-three percent, 7%, and 14% of subjects were co-infected with CMV, HBV, and HCV respectively. On both univariate and multivariate analysis, neither CMV nor HCV co-infection were significantly associated with post-vaccination antibody levels to either vaccine. HBV co-infection was significantly associated with post-vaccination antibody concentrations for pneumococcal serotype 7F on univariate analysis and 6A on multivariate analysis, but the association was with higher antibody concentrations. In conclusion, co-infection with CMV, HBV, or HCV does not appear to contribute to the decreased vaccine response seen in adults with well-controlled HIV infection.

Treating Hepatitis C in a Ryan White-Funded HIV Clinic: Has the Treatment Uptake Improved in the Interferon-Free Directly Active Antiviral Era? Cope R1, Glowa T2, Faulds S2, McMahon D2, Prasad R2. AIDS Patient Care STDS. 2016 Jan 8. [Epub ahead of print]

Now that highly efficacious, interferon-free (IFN-free), direct acting antivirals (DAA) for the treatment of hepatitis C (HCV) have closed the gap between treatment and cure, identifying barriers that prevent initiation of treatment is more crucial than ever. This is a retrospective study utilizing Electronic Medical Records and Prior Authorization Records to identify HCV treatment gaps, including predictors for intention-to-treat and treatment initiation in the first 15 months of a Ryan White funded human immunodeficiency virus (HIV)/HCV co-infection clinic. This study included 128 adults ≥18 years old with HIV and chronic HCV infection who had visited the treatment center at least once since January 2013. Provider intent-to-treat was used to differentiate patients actively considered for treatment based on documentation kept by a multidisciplinary HCV team. Members of this group who had gone on to initiate treatment were identified. Baseline characteristics were compared. Rates of active treatment consideration and treatment initiation were 30% and 14%, respectively. HCV treatment-naïve individuals were less likely to be considered for treatment [risk ratio (RR) 1.58, 95% confidence interval (CI) 1.07-2.32] and initiate therapy (RR 2.33, 95% CI 0.97-5.60). Advanced liver disease had no significant association. Black race (RR 1.96, 95% CI 0.90-4.25) and Medicaid insurance holders (RR 1.90, 95% CI 0.95-3.82) tended to be less likely to initiate therapy. The availability of IFN-free DAA regimens has yet to increase HCV treatment uptake in our HIV/HCV co-infected population. Barriers to HCV treatment initiation have shifted from medical contraindications to socioeconomic variables.

Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular carcinoma. Agüero F, Forner A, Manzardo C, et al. Hepatology. 2016 Feb;63(2):488-98. doi: 10.1002/hep.28321. Epub 2016 Jan 4.
The impact of human immunodeficiency virus (HIV) infection on patients undergoing liver transplantation (LT) for hepatocellular carcinoma (HCC) is uncertain. This study aimed to assess the outcome of a prospective Spanish nationwide cohort of HIV-infected patients undergoing LT for HCC (2002-2014). These patients were matched (age, gender, year of LT, center, and hepatitis C virus (HCV) or hepatitis B virus infection) with non-HIV-infected controls (1:3 ratio). Patients with incidental HCC were excluded. Seventy-four HIV-infected patients and 222 non-HIV-infected patients were included. All patients had cirrhosis, mostly due to HCV

infection (92%). HIV-infected patients were younger (47 versus 51 years) and had undetectable HCV RNA at LT (19% versus 9%) more frequently than non-HIV-infected patients. No significant differences were detected between HIV-infected and non-HIV-infected recipients in the radiological characteristics of HCC at enlisting or in the histopathological findings for HCC in the explanted liver. Survival at 1, 3, and 5 years for HIV-infected versus non-HIV-infected patients was 88% versus 90%, 78% versus 78%, and 67% versus 73% (P = 0.779), respectively. HCV infection (hazard ratio = 7.90, 95% confidence interval 1.07-56.82) and maximum nodule diameter >3 cm in the explanted liver (hazard ratio = 1.72, 95% confidence interval 1.02-2.89) were independently associated with mortality in the whole series. HCC recurred in 12 HIV-infected patients (16%) and 32 non-HIV-infected patients (14%), with a probability of 4% versus 5% at 1 year, 18% versus 12% at 3 years, and 20% versus 19% at 5 years (P = 0.904). Microscopic vascular invasion (hazard ratio = 3.40, 95% confidence interval 1.34-8.64) was the only factor independently associated with HCC recurrence.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Hepatitis C Virus Infection Screening Within Community Health Centers. Cook N, Turse EP, Garcia AS, Hardigan P, Amofah SA. J Am Osteopath Assoc. 2016 Jan 1;116(1):6-11. doi: 10.7556/jaoa.2016.001.

CONTEXT: Approximately 2.7 million people in the United States currently live with chronic hepatitis C virus (HCV) infection, and many are unaware that they have the disease. Community health centers (CHCs) serve as the primary care safety net for more than 22 million patients who are at risk for health inequities and represent an important frontline resource for early screening and treatment for HCV infection. **OBJECTIVE:** To understand HCV infection screening rates among CHC patients, and to quantify the screening gap by demographic characteristics. **METHODS:** The authors analyzed a deidentified dataset obtained through electronic health records from a large national network of CHCs. All adults at risk for HCV infection, according to the US Preventive Services Task Force (USPSTF) birth cohort screening guidelines for HCV infection, were considered eligible if they had a patient office visit between January 1, 2013, and December 31, 2013. Data were reviewed to determine the documentation of HCV infection screening from January 1, 2010, to December 31, 2013, and HCV infection screening rates were analyzed by age, race/ethnicity, and sex. **RESULTS:** Among 60,722 eligible patients, 5033 (8.3%) had an HCV infection screen in accordance with USPSTF birth cohort screening guidelines. Women were less likely to be screened than men in every race/ethnic group, including white Hispanic (9.3% in women vs 5.4% in men), black Hispanic (15.1% in women vs 9.0% in men), white non-Hispanic (13.6% in women vs 8.1% in men), black non-Hispanic (14.9% in women vs 8.9% in men), Caribbean Islander or Haitian (6.5% in women vs 3.7% in men), and other races/ethnicities (6.3% in women vs 3.6% in men). **CONCLUSION:** To the authors' knowledge, this is the first large-scale study among CHCs to assess the screening gap of the USPSTF birth cohort screening guidelines for HCV infection. This study suggests that CHCs should consider opportunities to improve HCV infection screening, thereby contributing to the reduction of health inequities resulting from untreated HCV infection.

Association with Spontaneous Hepatitis C Viral Clearance and Genetic Differentiation of IL28B/IFNL4 Haplotypes in Populations from Mexico. Gonzalez-Aldaco K1, Rebello Pinho JR2,3, Roman S1, et al. PLoS One. 2016 Jan 7;11(1):e0146258. doi: 10.1371/journal.pone.0146258. eCollection 2016.

AIM: To analyze the genetic heterogeneity of the Amerindian and admixed population (Mestizos) based on the IL28B (rs12979860, rs8099917) and IFNL4 (rs368234815) haplotypes, and their association with spontaneous clearance (SC) and liver damage in patients with hepatitis C infection from West Mexico. **METHODS:** A total of 711 subjects from West Mexico (181 Amerindians and 530 Mestizos) were studied for the prevalence of IL28B (rs12979860C/T, rs8099917G/T) and IFNL4 (rs368234815ΔG/TT) genotypes. A case-control study was performed in 234 treatment-naïve HCV Mestizos (149 chronic hepatitis C and 85 with SC) for the association of haplotypes with SC and liver damage. A real-time PCR assay was used for genotyping, and transitional elastography staged liver damage. **RESULTS:** Significant Fst-values indicated differentiation between the studied populations. The frequencies of the protective C, T, TT alleles were significantly lower in the Amerindians than in Mestizos ($p<0.05$). The r2 measure of linkage disequilibrium was significant for all variants and the T/G/ΔG risk haplotype predominated in Amerindians and secondly in Mestizos. The protective C/T/TT haplotype was associated with SC (OR = 0.46, 95% IC 0.22-0.95, p = 0.03) and less liver damage (OR = 0.32, 95% IC 0.10-0.97, p = 0.04) in chronic patients. The Structure software analysis demonstrated no significant differences in ancestry among SC and chronic patients. **CONCLUSIONS:** West Mexico´s population is genetically heterogeneous at the IL28B/IFNL4 polymorphisms. The T/G/ΔG high-risk haplotype predominated in Amerindians and the beneficial alternative haplotype in Mestizos. The C/T/TT haplotype was associated with SC and less liver damage in chronically infected Mestizo patients.

Racial diversity in mortality and morbidity in urban patients with hepatitis C. Stubbs A1, Naylor P1, Ravindran K1, et al J Viral Hepat. 2016 Jan 28. doi: 10.1111/jvh.12504. [Epub ahead of print]

Defining mortality for Caucasians and African American patients with chronic hepatitis C with respect to racial diversity is critical for counselling patients on therapy options. The objective of this study was to define racial diversity influence on mortality and morbidity of 3724 consecutive hepatitis C virus (HCV)-infected patients seen in an urban clinic between 1995 and 2008. Mortality, as of 2011, was defined using the SSA National Death Index and correlated with early visit medical information. The HCV chronically infected patient population consisted of 2879 African Americans (AA), 758 Caucasians and 87 other, and the majority were not treated for their infection prior to 2011. The average time to death from first visit was 5 years, the average age at death was 55 years, and despite racial diversity, AA were just as likely to be reported dead as Caucasians (23% AA vs 22% Caucasians). Cirrhosis and fibrosis (liver biopsy, AST Platelet Ratio Index or Fibrosis-4) at first visit as well as low albumin, diabetes, renal impairment and cardiac symptoms were associated with increased mortality. Treated patients who cleared the virus (sustained viral response (SVR); AA = 59; Caucasians = 40) had lower mortality than patients who were not treated (AA: 5% vs 27%; Caucasians 5% vs 26%). Hence, we find that race is not a factor in the early mortality of patients with chronic HCV infection and achieving a SVR reduced mortality. Unexpectedly, nonresponding AA also benefited by a lower mortality.

African American patients with kidney disease and low albumin were at highest risk and should be treated as soon as identified.

The screening of children born to HCV-positive mothers seems like an obvious and relatively easy population to test for HCV - no child should go undiagnosed or unscreened. Various systems play a role to ensure that screening occurs amongst at risk babies: the hospital system; OB/GYN or pediatric physician office. What might be best ways to educate HCV-positive mothers to ensure screening of their children, but also help them recognize seemingly unrelated symptoms of liver disease (immune system issues, skin problems, iron deficiencies, etc.) in their children?

Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C-Positive Women. Kuncio DE1, Newbern EC1, Johnson CC1, Viner KM1. Clin Infect Dis. 2016 Jan 20. pii: ciw026. [Epub ahead of print]

BACKGROUND: Vertical transmission of hepatitis C virus (HCV) is the most common route of pediatric HCV infection. Approximately 5% percent of children born to HCV-positive mothers develop chronic infection. Recommendations employ risk-based HCV testing of pregnant women, and screening children at a young age. This study assesses testing rates of children born to HCV-positive mothers in a major US city with a high burden of HCV infection. **METHODS:** HCV surveillance data reported to the Philadelphia Department of Public Health (PDPH) are housed in the Hepatitis Registry. Additional tests, including negative results, were retrospectively collected. HCV data were matched with 2011-2013 birth certificates of children ≥20 months to identify HCV-positive mothers and screened children. The observed perinatal HCV seropositivity rate was compared to the expected rate (5%). **RESULTS:** 8,119 females (12-54 years) were HCV-positive and in the Hepatitis Registry. Of these, 500 (5%) had delivered ≥1 child, accounting for 537 (1%) of the 55,623 children born in Philadelphia during the study period. Eighty-four (16%) of these children had HCV testing; four (1% of the total) were Confirmed cases. Twenty-four additional children are expected to have chronic HCV infection, but were not identified by 20 months of age. **CONCLUSION:** These findings illustrate that a significant number of women giving birth in Philadelphia are HCV-positive and that most of their at-risk children remain untested. To successfully identify all HCV-infected children and integrate them into HCV-specific care, practices for HCV screening of pregnant women and their children should be improved.

Predictors of Inpatient Mortality and Resource Utilization for the Elderly Patients With Chronic Hepatitis C (CH-C) in the United States.

Golabi P1, Otgonsuren M, Suen W, Koenig AB, Noor B, Younossi ZM. Medicine (Baltimore). 2016 Jan;95(3):e2482. doi: 10.1097/MD.0000000000002482.

New incidents of chronic hepatitis C (CH-C) have stabilized yet the full impact of CH-C is not realized. Assess inpatient mortality and resource utilization for CH-C patients hospitalized in the United States. Adult CH-C patients were identified from The National Inpatient Sample (NIS) 2005 to 2009 database using the International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes (070.51, 070.54, 070.70, 070.71, 070.41, and 070.44) also used to identify comorbidities.324,823 hospitalized CH-C patients were identified. Of these, 13.63% (N=44,288) were older than 65. The rate of hospitalization for the elderly cohort steadily increased over the study period with Medicare as the payer for the majority (86%). This cohort had higher inpatient charges, approximately a half day longer hospital stay ($P<0.001$) and more moderate or severe illness. During the index hospitalization, older CH-C patients were twice more likely to die than the younger age-group (5% versus 2%, $P<0.001$). In the adjusted model, older age (OR: 1.02

[95% CI, 1.02-1.03]), severity of illness (OR: 12.06 [95% CI, 10.68-13.62]), and number of diagnoses (OR: 1.10 [95% CI, 1.09-1.11]) were associated with higher in-hospital mortality; severity of illness and having private insurance were significantly associated with charge per hospital stay (P<0.001).The number of CH-C patients 65 and older increased due to the aging of the baby boomer population. Early treatment of CH-C patients with highly effective, well-tolerated, new anti-HCV regimens may prevent this significant societal burden.

We know there will never be a Ryan White system of care for HCV patients. Data also shows that despite USPSTF recommendations for screening, many systems are still not providing HCV screening to their patients. While there are many reasons for these two realities, we must work with existing systems to co-locate services and cross-train staff in order to increase the identification of HCV patients. What are some opportunities you can identify of co-locating or integrating HCV messages into diabetes care, renal clinics, or other related disease areas?

Impact of HCV Infection on Diabetes Patients for the Risk of End-Stage Renal Failure. Hwang JC1, Jiang MY, Lu YH, Weng SF. Medicine (Baltimore). 2016 Jan;95(3):e2431. doi: 10.1097/MD.0000000000002431.

Both diabetes mellitus (DM) and hepatitis C virus infection (HCVI) are associated with chronic kidney disease (CKD). The aim of this study was to evaluate whether HCVI increases the risk of end-stage renal disease (ESRD) in patients with DM. The National Health Insurance Research database of Taiwan was used to conduct this study. After excluding patients with a prior history of CKD, all patients with a first diagnosis of DM from January 1, 2000 to December 31, 2002 were enrolled. The patients who also had HCVI were defined as index cases (HCV group, n=9787). A comparison cohort at a 1:1 ratio of random incident patients with DM without HCVI matched by age, sex, age at the diagnosis of DM, duration between the diagnosis of DM and the index date, and various comorbidities through propensity score matching were recruited (non-HCV group, n=9787). The patients were followed until December 31, 2011.The cumulative incidence rate of developing ESRD was significantly higher in the HCV(+) group than in the non-HCV group (P=0.008). The incidence rate ratio (IRR) for the risk of ESRD was also significantly higher in the HCV(+) group (IRR: 1.44; 95% CI: 1.09-1.89) than in the non-HCV group, especially for those with a younger age (<50 years; IRR: 2.05; 95% CI: 1.22-3.45) and HCVI within 4 years after the diagnosis of DM (IRR: 1.85; 95% CI: 1.16-2.97). After adjusting for comorbidities in multivariate Cox proportional hazard regression analysis, HCVI (HR: 1.47; 95% CI: 1.11-1.93) was an independent factor for developing ESRD in the patients with DM. After starting dialysis for ESRD, the HCV(+) patients had a similar mortality rate to those without HCVI (P=0.84).HCVI increases the risk of developing ESRD in patients with DM, especially in younger patients and in those who develop HCVI sooner after a diagnosis of DM.

Increasing Prevalence of Cirrhosis among US Adults Aware or Unaware of their Chronic Hepatitis C Virus Infection. Udompap P1, Mannalithara A1, Heo N1, Kim D1, Ray Kim W2. J Hepatol. 2016 Jan 22. pii: S0168-8278(16)00014-3. doi: 10.1016/j.jhep.2016.01.009. [Epub ahead of print]

BACKGROUND AND AIMS: Cirrhosis from hepatitis C virus (HCV) infection is a major cause of end-stage liver disease and hepatocellular carcinoma worldwide. We determine the prevalence of cirrhosis among HCV-infected American adults including those unaware of their infection. **METHODS:** Using the National Health and Nutrition Examination Survey (NHANES) data, we identified participants aged⩾20 years with detectable serum HCV RNA. The prevalence of advanced fibrosis and cirrhosis was determined for Eras 1 (1988-94), 2 (1999-

2006) and 3 (2007-12) by using FIB-4 > 3.25 and APRI > 2.0, respectively. **RESULTS:** Out of 52,644 NHANES examinees, 49,429 were tested for HCV, of whom 725 met the inclusion criteria (positive HCV RNA with available data for FIB-4 and APRI). Based on APRI, 6.6% (95% confidence interval [CI]:2.2-11.0) of HCV-infected adults in Era 1, 7.6% (95%CI:3.4-11.8) in Era 2 and 17.0% (95%CI:8.0-26.0) in Era 3 had cirrhosis. In the multivariable regression analysis, this era effect was attributable to increasing age (odds ratio [OR]:1.04, 95%CI:1.02-1.07), diabetes (OR:2.33, 95%CI:1.01-5.40) and obesity (OR:2.96, 95%CI:1.15-7.57). Cirrhosis was as common among respondents who were unaware of their infection as those who were aware (both 11%). Results were identical when FIB-4 was used. **CONCLUSIONS:** Among HCV-infected American adults, the proportion with cirrhosis has increased rapidly. Cirrhosis prevalence remains high in individuals unaware of their HCV infection. These data highlight the urgency for HCV screening regardless of symptoms, systematic assessment for liver fibrosis in those with HCV infection and institution of antivirals to prevent advanced liver disease. **LAY STATEMENT:** Chronic hepatitis C virus (HCV) infection is a major cause of cirrhosis, creating a large public health burden. Based on the US National Health and Nutrition Examination Survey sample, we found the proportion of patients with cirrhosis among Americans with HCV infection increased from 6.6% to 17.0% over the past two decades. Patients who were unaware of their infection was just as likely to have cirrhosis as those who knew about their infection, which highlights the need for screening and treatment for HCV at the population level.

Prospective assessment of rapid diagnostic tests for the detection of antibodies to hepatitis C virus, a tool for improving access to care. Chevaliez S1, Poiteau L2, Rosa I3, et al. Clin Microbiol Infect. 2016 Jan 21. pii: S1198-743X(16)00025-2. doi: 10.1016/j.cmi.2016.01.009. [Epub ahead of print]
Large-scale hepatitis C screening is required to prevent further spread of the infection, improve access to care in the context of new HCV drug regimens without interferon alpha and subsequently reduce the risk of long-term complications of chronic liver disease. Rapid diagnostic tests (RDTs) represent an attractive alternative to enzyme immunoassay using blood from venipuncture. The aim of the present study was to prospectively assess the clinical performance of CE-marked RDTs detecting anti-HCV antibodies in fingerstick capillary whole blood and/or oral fluid. A total of 513 individuals, including 318 patients with chronic HCV infection, 25 patients with resolved HCV infection and 170 HCV-seronegative individuals, were prospectively enrolled. The specificity of RDTs with fingerstick whole blood varied from 98.8% to 100%. The clinical sensitivity was high for the OraQuick® and Toyo® tests (99.4% and 95.8%, respectively), but low for the Labmen® test (63.1%). The specificity and clinical sensitivity in crevicular fluid were both satisfactory for the OraQuick® test (100% and 97.6%, respectively). HCV antibody RDTs were easy and rapid to perform in the context of patient care. They were highly specific. Both the OraQuick® and Toyo® tests reached the expected level of performance for broad-scale use, with a performance advantage for the OraQuick® HCV test. RDTs appears as a promising new tool for broad-scale screening of HCV infection in high-to medium-risk populations. Thus, careful assessment of the performance of HCV RDTs must be recommended before they can be implemented in clinical practice.

Why do I treat my patients with mild hepatitis C? Calvaruso V1, Craxì A1. Liver Int. 2016 Jan;36 Suppl 1:7-12. doi: 10.1111/liv.13011.

The major advances achieved in the treatment of HCV by the development of new direct-acting antiviral agents (DAAs) allow treatment of almost the entire spectrum of patients with chornic infection. As a result of the exceedingly high cost of DAAs in many countries, IFN-free DAA regimens are mostly reserved to patients with advanced fibrosis or cirrhosis. Hence, treatment of patients with milder liver disease is often deferred. This could ultimately result in an increased burden of advanced liver disease and in increased long-term costs of management. Moreover, studies performed during the 'interferon era' and the early data on interferon-free regimens show that patients without severe fibrosis achieve higher rates of sustained virological response with less treatment-related adverse events. Unfortunately, there is no univocal way to predict the progression of liver fibrosis and therefore to identify the patients with early disease who would require urgent HCV treatment. Many studies have also demonstrated that treatment-induced HCV clearance reduces all-cause mortality regardless of the stage of liver fibrosis, pointing to an effect on extrahepatic manifestations of HCV infection. Last but not least, pharmacoeconomic studies show that DAA treatment of patients with mild HCV disease is cost-effective even at high prices of drugs, thus suggesting the opprtunity to treat regardless of the stage of liver disease.

Characterizing the Burden of Hepatitis C Infection Among Entrants to Pennsylvania State Prisons, 2004 to 2012. Mahowald MK1, Larney S2, Zaller ND3, et al. J Correct Health Care. 2016 Jan;22(1):41-5. doi: 10.1177/1078345815618384.
Although hepatitis C (HCV) infection is common among prisoners, relatively few undergo evaluation for treatment. This study reports the prevalence of chronic infection and the genotype distribution among an incarcerated population. HCV antibody testing was provided to adults entering Pennsylvania prisons; confirmatory and genotype testing were offered to those eligible for treatment. Antibody prevalence among 101,727 individuals was 18.1%. Among 7,633 individuals who underwent confirmatory testing, 69.3% had detectable RNA. Among 3,247 individuals who underwent genotype testing, genotype 1 was the most common (76.6%). The rate of chronic infection after HCV exposure is similar to that reported in the community, as is genotype distribution. Correctional facilities provide access to a population with a high disease burden, creating a public health opportunity for evaluation and treatment.

Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. Chahal HS1, Marseille EA2, Tice JA3, et al. JAMA Intern Med. 2016 Jan 1;176(1):65-73. doi: 10.1001/jamainternmed.2015.6011.
IMPORTANCE: Novel treatments for hepatitis C virus (HCV) infection are highly efficacious but costly. Thus, many insurers cover therapy only in advanced fibrosis stages. The added health benefits and costs of early treatment are unknown. **OBJECTIVE:** To assess the cost-effectiveness of (1) treating all patients with HCV vs only those with advanced fibrosis and (2) treating each stage of fibrosis. **DESIGN, SETTING, AND PARTICIPANTS:** This study used a decision-analytic model for the treatment of HCV genotype 1. The model used a lifetime horizon and societal perspective and was representative of all US patients with HCV genotype 1 who had not received previous treatment. Comparisons in the model included antiviral treatment of all fibrosis stages (METAVIR [Meta-analysis of Histological Data in Virial Hepatitis] stages F0 [no fibrosis] to F4 [cirrhosis]) vs treatment of stages F3 (numerous septa without cirrhosis) and F4 only and by specific fibrosis stage. Data were collected from March 1 to September 1,

2014, and analyzed from September 1, 2014, to June 30, 2015. **INTERVENTIONS:** Six HCV therapy options (particularly combined sofosbuvir and ledipasvir therapy) or no treatment. **MAIN OUTCOMES AND MEASURES:** Cost and health outcomes were measured using total medical costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs), calculated as the difference in costs between strategies divided by the difference in QALYs. **RESULTS:** We simulated 1000 individuals, but present the results normalized to a single HCV-infected person. In the base-case analysis, among patients receiving 8 or 12 weeks of sofosbuvir-ledipasvir treatment, treating all fibrosis stages compared with treating stages F3 and F4 adds 0.73 QALYs and $28 899, for an ICER of $39 475 per QALY gained. Treating at stage F2 (portal fibrosis with rare septa) costs $19 833 per QALY gained vs waiting until stage F3; treating at stage F1 (portal fibrosis without septa), $81 165 per QALY gained compared with waiting until stage F2; and treating at stage F0, $187 065 per QALY gained compared with waiting until stage F1. Results for other regimens show a similar pattern. At base-case drug prices, treating 50% of all eligible US patients with HCV genotype 1 would cost $53 billion. In sensitivity analyses, the ICER for treating all stages vs treating stages F3 and F4 was most sensitive to cohort age, drug costs, utility values in stages F1 and F2, and percentage of patients eligible for 8-week therapy. Except for patients aged 70 years, the ICER remains less than $100 000 per QALY gained. A 46% reduction in cost of sofosbuvir-ledipasvir therapy decreases the ICER for treating at all fibrosis stages by 48%. **CONCLUSIONS AND RELEVANCE:** In this simulated model, treating HCV infection at early stages of fibrosis appeared to improve health outcomes and to be cost-effective but incurred substantial aggregate costs. The findings may have implications for health care coverage policies and clinical decision making.

The association between chronic hepatitis C infection and cardiovascular risk.

Pateria P1, Jeffrey GP1,2, MacQuillan G1,2, et al. Intern Med J. 2016 Jan;46(1):63-70. doi: 10.1111/imj.12936.

BACKGROUND: Vascular disease is a common cause of death in patients with chronic hepatitis C (CHC) infection; however, the association between CHC and atherosclerosis is unclear. **AIMS:** To determine whether patients with CHC have increased subclinical vascular disease and whether genotype or antiviral treatment modifies this risk. **METHODS:** Fifty CHC patients and 22 age-matched and sex-matched healthy controls underwent clinical and biochemical assessment for vascular risk factors. In addition, vascular risk was assessed by measuring arterial stiffness (aortic augmentation index and carotid-femoral pulse wave velocity (PWV)), endothelial dysfunction (brachial artery flow-mediated dilatation (FMD) and dilatation post-glycerol trinitrate administration) and carotid intima-media thickness (CIMT). Assessment was repeated in subset of CHC patients (n = 12) undergoing antiviral treatment 18 months after initiation of treatment. **RESULTS:** Baseline vascular risk factors and measures of arterial stiffness, endothelial dysfunction and CIMT were not different between cases and controls ($P > 0.2$ for all). Genotype 1 CHC patients had greater endothelial dysfunction with lower FMD (8.2 ± 3.5% vs 10.9 ± 5.2%, $P = 0.03$) and higher right CIMT (0.6 ± 0.1 mm vs 0.5 ± 0.07 mm, $P = 0.04$) compared with non-genotype 1. Patients who achieved sustained virological response (7/12) showed significant improvement in insulin resistance (homeostasis model of assessment of insulin resistance 2.3 ± 1.2 vs 1.8 ± 0.8, $P = 0.02$) and arterial stiffness (PWV 7.4 ± 1.1 m/s vs 6.5 ± 0.6 m/s, $P = 0.04$). **CONCLUSIONS:** Subclinical vascular disease is not greater in CHC subjects compared with controls. However, among CHC subjects, genotype 1 infection is associated with greater endothelial dysfunction and increased carotid-intima medial thickness

compared with non-genotype 1 infection. Successful viral eradication may improve insulin resistance and arterial stiffness.

This article demonstrates noncompliance among nurses for the prevention of nosocomial transmission of HCV. What impact do you think it might have on adherence to Standard Precautions among nurses if they were offered rapid HCV screening and education, particularly for nurses who have been in practice for many years with past exposures?

Factors influencing nurse compliance with Standard Precautions. Powers D1, Armellino D2, Dolansky M3, Fitzpatrick J3. Am J Infect Control. 2016 Jan 1;44(1):4-7. doi: 10.1016/j.ajic.2015.10.001.

BACKGROUND: Exposure to blood and bodily fluids represents a significant occupational risk for nurses. The most effective means of preventing bloodborne pathogen transmission is through adherence to Standard Precautions (SP). Despite published guidelines on infection control and negative health consequences of noncompliance, significant issues remain around compliance with SP to protect nurses from bloodborne infectious diseases, including hepatitis B virus, hepatitis C virus (HCV), and HIV. **METHODS:** A descriptive correlational study was conducted that measured self-reported compliance with SP, knowledge of HCV, and perceived susceptibility and severity of HCV plus perceived benefits and barriers to SP use. Relationships between the variables were examined. Registered nurses (N = 231) working in ambulatory settings were surveyed. **RESULTS:** Fewer than one-fifth (17.4%) of respondents reported compliance with all 9 SP items. Mean score for correct responses to the HCV knowledge test was 81%. There was a significant relationship between susceptibility of HCV and compliance and between barriers to SP use and compliance. **CONCLUSIONS:** This study explored reasons why nurses fail to adopt behaviors that protect them and used the Health Belief Model for the theoretical framework. It concentrated on SP and HCV because more than 5 million people in the United States and 200 million worldwide are infected with HCV, making it 1 of the greatest public health threats faced in this century. Understanding reasons for noncompliance will help determine a strategy for improving behavior and programs that target the aspects that were less than satisfactory to improve overall compliance. It is critical to examine factors that influence compliance to encourage those that will lead to total compliance and eliminate those that prevent it.

LIVER CANCER

Percutaneous Treatment of Localized Infiltrative Hepatocellular Carcinoma Developing on Cirrhosis. Nault JC1,2,3, Nkontchou G4, Nahon P4,5,6, et al. Ann Surg Oncol. 2016 Jan 5. [Epub ahead of print]

BACKGROUND:

Infiltrating hepatocellular carcinoma (HCC) is characterized by a difficult diagnosis, dismal prognosis, and limited therapeutic options. We describe long-term results of percutaneous treatment of infiltrative HCC, i.e., multibipolar radiofrequency ablation (mbpRFA) and percutaneous intra-arterial ethanol injection (PIAEI). **METHODS:** All cirrhotic patients with localized (up to two segments) infiltrating HCC treated by mbpRFA or PIAEI between 2002 and 2012 were included. Survival was analyzed using the Kaplan-Meier method, log-rank test, and Cox univariate followed by multivariate analyses. **RESULTS:** Fifty-one patients were considered eligible for mbpRFA (n = 20) or PIAEI (n = 31). Cirrhosis etiologies were alcohol

(67 %), hepatitis C (33 %), hepatitis B (16 %), and/or NASH (16 %). HCC were multinodular in 31 % of cases, with a median main tumor size of 60 mm (range 30-200) and macrovascular invasion in 59 % of cases. The median serum level of alphafetoprotein was 125 ng/ml (range 2-215,000). Treatment-related adverse events occurred in 58 %, mainly postablation syndrome (31 %), and one death (2 %). Median overall survival was 18.3 months, with 63, 35, 20, and 12 % survival at 1, 2, 3, and 4 years, respectively. Baseline serum bilirubin >normal [hazard ratio (HR) 2.98; 95 % confidence interval (CI) 1.38-6.50; P = 0.0057] and tumor burden >70 mm (HR 1.02; 95 % CI 1.003-1.04; P = 0.0221) were associated with poorer overall survival. The radiological response using mRECIST criteria and an alphafetoprotein decrease 1 month post-procedure was associated with increased overall survival (P = 0.0002 and P = 0.024, respectively).
DISCUSSION: Despite its overall poor prognosis, localized infiltrating HCC can be safely treated using percutaneous approaches, with potential survival benefits for these difficult-to-treat patients.

Frequency of deaths in hepatitis C virus infected hepatocellular carcinoma patients and its relationship with raised serum alpha-fetoprotein levels. Shaikh FH1, Zeb S2, Chandio SA3, Munaf A2, Ghori MA2, Memon MS4, Burney AA5. J Pak Med Assoc. 2016 Jan;66(1):34-6.
OBJECTIVE: To determine the frequency of deaths in hepatitis C virus infected hepatocellular carcinoma patients, and its relationship with raised serum alpha-fetoprotein levels.
METHODS: The cross-sectional study was conducted at Isra University Hospital, Hyderabad, Pakistan, between March 2013 and April 2014, and comprised all patients diagnosed with hepatitis C virus and hepatocellular carcinoma over 30 years of age. Blood sample was drawn for the measurement of serum Alfa fetoprotein levels. Data was analysed using SPSS 16.
RESULTS: The mean age of the 165 patients was55.49±11.67 years. The mean tumour size was 5.63 ± 2.14cm. Of the total, 31(18.8%) patients had tumour size <3cm, 65(39.4%) 3-5cm and 69(41.8%) >5cm. The mean serum Alfa fetoprotein level was 7641.0±3665.32 IU/ml. Overall mortality rate was 70(41.9%). Tumour size >5cm was significantly associated with mortality (p=0.016). **CONCLUSIONS:** Serum Alfa fetoprotein levels were a useful tool for the detection of hepatocellular carcinoma in hepatitis C virus patients.

In a young, and therefore ever-changing and evolving disease like hepatitis C and liver cancer, we can expect research to contradict itself (notice the abstract above). This study suggests that other HCC biomarkers are needed, and monitoring of AFP, as of late, is seen as less reliable, although historically used. How can we combine what's learned through HCV research, what's learned from HCC patients, and other interrelated specialties (primary care, endocrinologists, etc.) to develop useful monitoring tools that increase patient morbidity and mortality?

Controversies regarding and perspectives on clinical utility of biomarkers in hepatocellular carcinoma. Song PP1, Xia JF1, Inagaki Y1, Hasegawa K1, Sakamoto Y1, Kokudo N1, Tang W1. World J Gastroenterol. 2016 Jan 7;22(1):262-74. doi: 10.3748/wjg.v22.i1.262.
The prevalence of hepatocellular carcinoma (HCC) worldwide parallels that of persistent infection with the hepatitis B virus (HBV) and/or hepatitis C virus (HCV). According to recommendations by the World Health Organization guidelines for HBV/HCV, alpha-fetoprotein (AFP) testing and abdominal ultrasound should be performed in routine surveillance of HCC every 6 mo for high-risk patients. These examinations have also been recommended worldwide by many other HCC guidelines over the past few decades. In recent years, however, the role of AFP in HCC surveillance and diagnosis has diminished due to advances in imaging modalities. AFP was excluded from the surveillance and/or diagnostic criteria in the HCC guidelines

published by the American Association for the Study of Liver Diseases in 2010, the European Association for the Study of the Liver in 2012, and the National Comprehensive Cancer Network in 2014. Other biomarkers, including the Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), des-γ-carboxyprothrombin, Dickkopf-1, midkine, and microRNA, are being studied in this regard. Furthermore, increasing attention has focused on the clinical utility of biomarkers as pre-treatment predictors for tumor recurrence and as post-treatment monitors. Serum and tissue-based biomarkers and genomics may aid in the diagnosis of HCC, determination of patient prognosis, and selection of appropriate treatment. However, further studies are needed to better characterize the accuracy and potential role of these approaches in clinical practice.

Transarterial Ethanol Ablation for Unresectable Hepatocellular Carcinoma: Analysis of Clinical and Tumor Outcomes. Yu SC1, Hui EP2, Tang P3, et al. J Vasc Interv Radiol. 2016 Jan 20. pii: S1051-0443(15)01105-7. doi: 10.1016/j.jvir.2015.11.032. [Epub ahead of print]
PURPOSE: To evaluate survival, tumor response, and treatment toxicity of transarterial ethanol ablation (TEA) in patients with unresectable hepatocellular carcinoma (HCC). **MATERIALS AND METHODS:** This prospective study involved 186 patients (146 men and 40 women; median age, 65 y [interquartile range, 57-72.3 y]). Of 186 patients, 146 (78.5%) were hepatitis B virus carriers, 18 (9.7%) were hepatitis C virus carriers, 82 (44.1%) had tumors ≥ 5 cm, and 43 (23.1%) had multifocal tumors. Overall survival (OS), complete response (CR) by European Association for the Study of the Liver criteria, time to progression (TTP), progression-free survival (PFS), and treatment toxicities were evaluated. Univariate and multivariate analyses for prognostic factors of OS were performed. **RESULTS:** Median OS was 25.7 months (95% confidence interval [CI], 20.9-30.5) and varied significantly between Child-Pugh A and B (28.7 mo vs 13.4 mo, P < .001), and Barcelona Clinic Liver Cancer A and B or C (37.1 mo vs 17.7 mo, P = .001). Prognostic factors for longer OS were solitary tumor, tumor size < 5 cm, > 1 treatments, and CR of all tumors at 6 months. TTP was 9.1 months (95% CI, 6.9-11.3). PFS was 8.4 months (95% CI, 7.1-9.7). CR occurred in 69.1% (159/230) of lesions and 48.9% (88/180) of patients at 6 months. Any one symptom of the postembolization syndrome of grade 2 severity occurred in < 22% (41/186) of patients. No treatment-related hepatitis or death occurred within 30 days. Transient respiratory decompensation occurred in three patients (1.6% [3/186]), and alcoholic intoxication occurred in one patient (0.5% [1/186]). **CONCLUSIONS:** TEA appears to be safe and effective for local control of HCC.

Diminished viral replication and compartmentalization of hepatitis C virus in hepatocellular carcinoma tissue. Harouaka D1, Engle RE1, Wollenberg K2, et al. Proc Natl Acad Sci U S A. 2016 Jan 19. pii: 201516879. [Epub ahead of print]
Analysis of hepatitis C virus (HCV) replication and quasispecies distribution within the tumor of patients with HCV-associated hepatocellular carcinoma (HCC) can provide insight into the role of HCV in hepatocarcinogenesis and, conversely, the effect of HCC on the HCV lifecycle. In a comprehensive study of serum and multiple liver specimens from patients with HCC who underwent liver transplantation, we found a sharp and significant decrease in HCV RNA in the tumor compared with surrounding nontumorous tissues, but found no differences in multiple areas of control non-HCC cirrhotic livers. Diminished HCV replication was not associated with changes in miR-122 expression. HCV genetic diversity was significantly higher in livers containing HCC compared with control non-HCC cirrhotic livers. Tracking of individual variants demonstrated changes in the viral population between tumorous and nontumorous areas, the

extent of which correlated with the decline in HCV RNA, suggesting HCV compartmentalization within the tumor. In contrast, compartmentalization was not observed between nontumorous areas and serum, or in controls between different areas of the cirrhotic liver or between liver and serum. Our findings indicate that HCV replication within the tumor is restricted and compartmentalized, suggesting segregation of specific viral variants in malignant hepatocytes.

Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database. Vilchez V1, Shah MB1, Daily MF1, et al. HPB (Oxford). 2016 Jan;18(1):29-34. doi: 10.1016/j.hpb.2015.10.001. Epub 2016 Jan 7.

BACKGROUND: Mixed hepatocellular and cholangiocarcinoma (HCC-CC) have been associated with a poor prognosis after liver transplantation (LT). We aimed to evaluate long-term outcomes in patients undergoing LT for HCC-CC versus patients with hepatocellular carcinoma (HCC) or cholangiocarcinoma (CC). **METHODS:** Retrospective analysis of the United Network for Organ Sharing (UNOS) database from 1994-2013. Overall survival (OS) in patients with HCC-CC, HCC, and CC, were compared. **RESULTS:** We identified 4049 patients transplanted for primary malignancy (94 HCC-CC; 3515 HCC; 440 CC). Mean age of patients with HCC-CC was 57 ± 10 years, and 77% were male. MELD score did not differ among the groups ($p = 0.637$). Hepatitis C virus was the most common secondary diagnosis within the HCC-CC (44%) and HCC (36%) cohorts, with primary sclerosing cholangitis in the CC (16%) cohort. OS rates at 1, 3 and 5 years for HCC-CC (82%, 47%, 40%) were similar to CC (79%, 58%, 47%), but significantly worse than HCC (86%, 72%, and 62% $p = 0.002$). **DISCUSSION:** Patients undergoing LT for HCC had significantly better survival compared to those transplanted for HCC-CC and CC. LT for mixed HCC-CC confers a survival rate similar to selected patients with CC. Efforts should be made to identify HCC-CC patients preoperatively.