



CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES
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COMPLEMENTARY AND ALTERNATIVE MEDICINE
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LIVER CANCER

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Clinical usefulness of new noninvasive serum biomarkers for the assessment of liver fibrosis and steatosis in children with chronic hepatitis C.](#)

Pokorska-Śpiewak M1, Kowalik-Mikołajewska B1, Aniszewska M1, Pluta M1, Marczyńska M1. Clin Exp Hepatol. 2017 Dec;3(4):198-202. doi: 10.5114/ceh.2017.71337. Epub 2017 Nov 10.

AIM OF THE STUDY: Recently, novel serum markers modified by the body mass index z-score (BMI z-score) were proposed as a reliable noninvasive alternative for the detection of significant fibrosis and steatosis in children with chronic hepatitis C (CHC). The aim of this study was to evaluate the clinical usefulness of these biomarkers. **MATERIAL AND ETHODS:** Thirty children aged 9.4 ± 3.7 years (14 males, 16 females) with CHC were included in this study. In all patients, histopathological evaluation of the liver fibrosis was performed using a 5-point METAVIR scoring system (≥ 2 points = significant fibrosis). Significant steatosis was diagnosed with $> 33\%$ of hepatocytes affected. The following noninvasive markers of liver disease were calculated: the modified aspartate transaminase (AST)-to-platelet ratio index (M-APRI: BMI z-score \times APRI), the modified Fibrosis-4 index (M-FIB-4: BMI z-score \times FIB-4), and a novel marker, B-AST (BMI z-score \times AST). The clinically useful cut-offs for each marker were selected as simple round numbers, indicating significant fibrosis and steatosis. **RESULTS:** Significant fibrosis was detected in 7/30 (23%) cases, and significant steatosis was observed in 4 (13%) patients. Comparison with the histopathological evaluation revealed that B-AST < 0 excluded significant fibrosis, and < 100 excluded all patients with significant steatosis. For the M-APRI, < 0 excluded significant fibrosis, and < 0.5 excluded significant steatosis. For the M-FIB-4, < 0 excluded significant fibrosis and < 0.2 excluded significant steatosis.

CONCLUSIONS: Negative values of all three markers that included the BMI z-score excluded all patients with both significant fibrosis and significant steatosis.

[Efficacy, safety and patient-reported outcomes of ledipasvir/sofosbuvir in NS3/4A protease inhibitor-experienced individuals with hepatitis C virus genotype 1 and HIV coinfection with and without cirrhosis \(ANRS HC31 SOFTRIH study\).](#)

Rosenthal E1, Fougerou-Leurent C2,3, Renault A3,4, et al. HIV Med. 2017 Dec 7. doi: 10.1111/hiv.12571. [Epub ahead of print]

OBJECTIVES: Studies evaluating the efficacy and safety of the fixed-dose combination ledipasvir (LDV)/sofosbuvir (SOF) in patients coinfecting with HIV-1 and hepatitis C virus (HCV) have mainly included treatment-naïve patients without cirrhosis. We aimed to evaluate the efficacy and safety of this combination in treatment-experienced patients with and without cirrhosis. **METHODS:** We conducted a multicentre, open-label, double-arm, nonrandomized

study in patients coinfecting with HIV-1 and HCV genotype 1 with and without cirrhosis, who had good viral suppression on their antiretroviral regimens. All patients were pretreated with a first-generation NS3/4A protease inhibitor (PI) plus pegylated interferon/ribavirin. Patients received a fixed-dose combination of LDV/SOF for 12 weeks, or for 24 weeks if cirrhosis was present. The primary endpoint was a sustained virological response (SVR) 12 weeks after the end of therapy. Secondary endpoints included safety, pharmacokinetics and patient-reported outcomes. **RESULTS:** Of the 68 patients enrolled, 39.7% had cirrhosis. Sixty-five patients [95.6%; 95% confidence interval (CI): 87.6-99.1%; $P < 0.0001$] achieved an SVR, with similar rates of SVR in those with and without cirrhosis. Tolerance was satisfactory, with mainly grade 1 or 2 adverse events. Among patient-reported outcomes, only fatigue significantly decreased at the end of treatment compared with baseline [odds ratio (OR): 0.36; 95% CI: 0.14-0.96; $P = 0.04$]. Mean tenofovir area under the plasma concentration-time curve (AUC) at week 4 was high, with mean \pm SD AUC variation between baseline and week 4 higher in cirrhotic than in noncirrhotic patients (3261.57 ± 1920.47 ng/mL vs. 1576.15 ± 911.97 ng/mL, respectively; $P = 0.03$). Mild proteinuria (54.4%), hypophosphataemia (50.0%), blood bicarbonate decrease (29.4%) and hypokalaemia (13.2%) were reported. The serum creatinine level was not modified. **CONCLUSIONS:** LDV/SOF provided a high SVR rate in PI-experienced subjects coinfecting with HCV genotype 1 and HIV-1, including patients with cirrhosis.
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[High Efficacy of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir in Hepatitis C Genotypes 4 and 1-infected Patients with Severe Chronic Kidney Disease.](#) Sanai FM1, Alghamdi AS2, Afghani AA3, et al. *Liver Int.* 2017 Dec 29. doi: 10.1111/liv.13674. [Epub ahead of print]

Limited data has shown high efficacy of co-formulated ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) in the treatment of hepatitis C virus (HCV) genotype (GT)-4, and combined with dasabuvir (DSV) in GT1 patients, with chronic kidney disease (CKD) stage 4-5 (<30 mL/min/1.73 m²). We assessed real-world safety and efficacy of OBV/PTV/r \pm DSV in GT1 and 4-infected patients. **METHODS:** In this observational cohort ($n=67$), we enrolled stage 4-5 CKD treatment-naïve or Peginterferon/RBV-experienced GT4-infected patients ($n=32$) treated for 12-24 weeks with OBV/PTV/r \pm RBV, and plus DSV in GT1 patients ($n=35$, including 3 with GT1/4 co-infection). RBV was dosed by physician discretion between 200 mg weekly - 200 mg daily. Primary endpoints were SVR12, calculated on intention-to-treat (ITT) basis, and occurrence of serious adverse events. **RESULTS:** The mean age of the cohort was 45.7 ± 12.7 years, 50.7% were female, 20.9% had cirrhosis, 35.8% were treatment-experienced and 97% were on hemodialysis. Three patients (F4) received 24 weeks treatment, 2 with GT4, and 1 with GT1a; and 19.4% were treated without RBV, including 9 GT1, and 4 GT4. Overall, 65 (97.1%) patients achieved SVR12, including 100% of those with a post treatment follow-up (modified ITT analysis). Of the 2 patients without SVR12, one died from sepsis-related complications and the other from a myocardial infarction 2 weeks after completing therapy. Grade 3-4 anemia occurred in 8.9%. **CONCLUSION:** A 12-week regimen of OBV/PTV/r \pm DSV with or without RBV is highly effective with a favourable safety profile amongst GT4 and GT1 patients with CKD stages 4-5. SVR12 rates were high regardless of patient characteristics. This article is protected by copyright. All rights reserved.

[HCV clearance by direct-acting antiviral treatments reverses insulin resistance in chronic hepatitis C patients.](#) Adinolfi LE1, Nevola R1,2, Guerrera B1,2, D'Alterio G1, Marrone A1, Giordano M1,2, Rinaldi J Gastroenterol Hepatol. 2017 Dec 11. doi: 10.1111/jgh.14067. [Epub ahead of print]

L1.

BACKGROUND AND AIM: Chronic hepatitis C (HCV), particularly genotype 1, is associated with insulin resistance (IR) and diabetes. We evaluated the impact of HCV clearance by all-oral direct-acting antiviral (DAAs) treatments on IR and glycemic control. **METHODS:** Included in this prospective case-control study were 133 consecutive HCV-genotype 1 patients with advanced liver fibrosis (F3-F4) without type 2 diabetes. Sixty-eight treated with DAAs and 65 untreated. Liver fibrosis was assessed by transient elastography. Pre-, end- and 3 months post-treatment withdrawal IR homeostasis was assessed by HOMA-IR, QUICKI and HOMA-B. **RESULTS:** At baseline, treated and untreated patients showed similar liver fibrosis levels, HOMA-IR was 4.90 ± 4.62 and 4.64 ± 5.62 , respectively. HOMA-IR correlated with HCV RNA levels. At the end of treatment, all patients cleared HCV RNA, regardless of liver fibrosis and BMI, a reduction in HOMA-IR at 2.42 ± 1.85 was showed ($p < 0.001$), in addition, increased insulin sensitivity, decreased insulin secretion, reduction of serum glucose and insulin levels were observed. Data were confirmed 3 months after treatment withdrawal in the 65 patients who cleared HCV. No variation occurred in untreated patients. Overall, 76.5% of SVR patients showed IR improvements, of which 41.2% normalized IR. Improvement of IR was strictly associated with HCV clearance, however, patients with the highest levels of fibrosis remain associated with some degree of IR. **CONCLUSIONS:** The data underline a role of HCV in development of IR and that viral eradication reverses IR and improves glycemic control and this could prevent IR-related clinical manifestations and complications.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Adiponectin levels and insulin resistance among patients with chronic hepatitis C.](#)

Carvalho RF1, Atta AM2, de Oliveira IS2, Santos TPS3, Santos JPA2, Schinoni MI4, de Sousa-Atta MLB5. Acta Trop. 2018 Feb;178:258-263. doi: 10.1016/j.actatropica.2017.12.004. Epub 2017 Dec 5.

Chronic hepatitis C virus (HCV) infection is associated with insulin resistance (IR), rapid disease progression, and decreased virological response to antiviral treatment. In addition, obesity is a risk factor for chronic hepatitis C evolution and is associated with IR. As adiponectin is an adipokine that is associated with obesity and IR, this study aimed to investigate serum levels of adiponectin among patients with HCV infection and IR. Thirty-three patients with untreated HCV infection underwent testing of serum adiponectin levels (capture ELISA) and were compared to 30 healthy subjects with similar body mass indexes (BMI). Data were also obtained for several homeostatic model assessment (HOMA) indexes: HOMA-IR, HOMA- β , and HOMA-adiponectin. Patients with HCV infection had higher adiponectin levels, which predominantly were observed among women. Hyperadiponectinemia was not associated with high BMI. Patients with HCV infection had higher HOMA-IR and HOMA- β values, although no difference was observed for HOMA-adiponectin. Patients with HCV infection and overweight/obese status had higher HOMA-IR values, although no association was observed for adiponectin levels. Hyperadiponectinemia and IR were not influenced by HCV load or liver fibrosis. The predictors of IR were BMI, glycemia, and serum levels of insulin and non-high-density lipoprotein

cholesterol, but not adiponectin levels. Thus, patients with chronic hepatitis C have significant metabolic alterations (hyperadiponectinemia and high HOMA-IR values) that are independent of HCV viremia and liver fibrosis. Among these patients, HOMA-IR but not HOMA-adiponectin was appropriate for diagnosing IR.

[New hepatitis C virus genotype 1 subtype naturally harbouring resistance-associated mutations to NS5A inhibitors.](#) Ordeig L1, Garcia-Cehic D1,2, Gregori J1,2,3, et al. *J Gen Virol.* 2018 Jan;99(1):97-102. doi: 10.1099/jgv.0.000996. Epub 2017 Dec 14.

Hepatitis C virus (HCV) is a highly divergent virus currently classified into seven major genotypes and 86 subtypes (ICTV, June 2017), which can have differing responses to therapy. Accurate genotyping/subtyping using high-resolution HCV subtyping enables confident subtype identification, identifies mixed infections and allows detection of new subtypes. During routine genotyping/subtyping, one sample from an Equatorial Guinea patient could not be classified into any of the subtypes. The complete genomic sequence was compared to reference sequences by phylogenetic and sliding window analysis. Resistance-associated substitutions (RASs) were assessed by deep sequencing. The unclassified HCV genome did not belong to any of the existing genotype 1 (G1) subtypes. Sliding window analysis along the complete genome ruled out recombination phenomena suggesting that it belongs to a new HCV G1 subtype. Two NS5A RASs (L31V+Y93H) were found to be naturally combined in the genome which could limit treatment possibilities in patients infected with this subtype.

[Probing the antigenicity of hepatitis C virus envelope glycoprotein complex by high-throughput mutagenesis.](#) Gopal R1, Jackson K1, Tzarum N2, et al. *PLoS Pathog.* 2017 Dec 18;13(12):e1006735. doi: 10.1371/journal.ppat.1006735. [Epub ahead of print]

The hepatitis C virus (HCV) envelope glycoproteins E1 and E2 form a non-covalently linked heterodimer on the viral surface that mediates viral entry. E1, E2 and the heterodimer complex E1E2 are candidate vaccine antigens, but are technically challenging to study because of difficulties in producing natively folded proteins by standard protein expression and purification methods. To better comprehend the antigenicity of these proteins, a library of alanine scanning mutants comprising the entirety of E1E2 (555 residues) was created for evaluating the role of each residue in the glycoproteins. The mutant library was probed, by a high-throughput flow cytometry-based assay, for binding with the co-receptor CD81, and a panel of 13 human and mouse monoclonal antibodies (mAbs) that target continuous and discontinuous epitopes of E1, E2, and the E1E2 complex. Together with the recently determined crystal structure of E2 core domain (E2c), we found that several residues in the E2 back layer region indirectly impact binding of CD81 and mAbs that target the conserved neutralizing face of E2. These findings highlight an unexpected role for the E2 back layer in interacting with the E2 front layer for its biological function. We also identified regions of E1 and E2 that likely located at or near the interface of the E1E2 complex, and determined that the E2 back layer also plays an important role in E1E2 complex formation. The conformation-dependent reactivity of CD81 and the antibody panel to the E1E2 mutant library provides a global view of the influence of each amino acid (aa) on E1E2 expression and folding. This information is valuable for guiding protein engineering efforts to enhance the antigenic properties and stability of E1E2 for vaccine antigen development and structural studies.

Complication Rates After Total Hip and Knee Arthroplasty in Patients With Hepatitis C Compared With Matched Control Patients.

Cancienne JM1, Kandahari AM, Casp A, Novicoff W, Browne JA, Cui Q, Werner BC. J Am Acad Orthop Surg. 2017 Dec;25(12):e275-e281. doi: 10.5435/JAAOS-D-16-00920.

BACKGROUND: A paucity of data exists regarding long-term outcomes among patients with hepatitis C who undergo total hip arthroplasty (THA) and total knee arthroplasty (TKA).

METHODS: We queried a database for patients with hepatitis C who underwent THA and TKA. We then identified their rates of several postoperative complications and compared them with the same rates among mutually exclusive matched control cohorts. **RESULTS:** Patients with hepatitis C who underwent THA and TKA had higher rates of infection, aseptic revision surgery, medical complications, and blood transfusion compared with matched control patients.

DISCUSSION: Our findings suggest that patients with hepatitis C who undergo THA and TKA are at increased risk of experiencing several postoperative complications, which could mean a substantial increase in the cost of care. **CONCLUSIONS:** Further research is needed to establish quantifiable associations between hepatitis C and postoperative complications among patients with the disease who undergo total joint arthroplasty.

Improvement of liver stiffness in patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response.

Tada T1, Kumada T1, Toyoda H1, Mizuno K1, Sone Y2, Kataoka S3, Hashinokuchi S3. J Gastroenterol Hepatol. 2017 Dec;32(12):1982-1988. doi: 10.1111/jgh.13788.

BACKGROUND AND AIM: There is insufficient research on whether direct-acting antiviral (DAA) therapy can improve liver fibrosis in patients with chronic hepatitis C virus (HCV). We evaluated sequential changes in liver stiffness using shear wave elastography in patients with HCV who received DAA therapy. **METHODS:** A total of 210 patients with HCV who received daclatasvir and asunaprevir therapy and achieved sustained virological response (SVR) were analyzed. Liver stiffness, as evaluated by shear wave elastography, and laboratory data were assessed before treatment (baseline), at end of treatment (EOT), and at 24 weeks after EOT (SVR24). **RESULTS:** Alanine aminotransferase levels (ALT) decreased over time, and there were significant differences between baseline and EOT and between EOT and SVR24. Although platelet counts did not significantly differ between baseline and EOT, they increased significantly from EOT to SVR24. The median (interquartile range) liver stiffness values at baseline, EOT, and SVR24 were 10.2 (7.7-14.7), 8.8 (7.1-12.1), and 7.6 (6.3-10.3) kPa, respectively ($P < 0.001$, baseline vs EOT; $P < 0.001$, EOT vs SVR24). Additionally, in patients with ALT ≤ 30 (indicating low necroinflammatory activity in the liver) and Fibrosis-4 index > 2.0 ($n = 75$), the liver stiffness values at baseline, EOT, and SVR24 were 9.6 (7.7-15.2), 9.2 (7.3-12.1), and 7.7 (6.3-10.1) kPa, respectively ($P < 0.001$, baseline vs EOT; $P < 0.001$, EOT vs SVR24). **CONCLUSION:** These results suggest that early improvement of liver stiffness starts during the administration of DAAs in patients who achieve SVR, and this effect is particularly pronounced in patients with progressive liver fibrosis.

The generation of a simian adenoviral vectored HCV vaccine encoding genetically conserved gene segments to target multiple HCV genotypes.

von Delft A1, Donnison TA1, Lourenço J2, et al. Vaccine. 2018 Jan 4;36(2):313-321. doi: 10.1016/j.vaccine.2017.10.079. Epub 2017 Dec 2.

BACKGROUND: Hepatitis C virus (HCV) genomic variability is a major challenge to the generation of a prophylactic vaccine. We have previously shown that HCV specific T-cell responses induced by a potent T-cell vaccine encoding a single strain subtype-1b immunogen target epitopes dominant in natural infection. However, corresponding viral regions are highly variable at a population level, with a reduction in T-cell reactivity to these variants. We therefore designed and manufactured second generation simian adenovirus vaccines encoding genomic segments, conserved between viral genotypes and assessed these for immunogenicity.

METHODS: We developed a computer algorithm to identify HCV genomic regions that were conserved between viral subtypes. Conserved segments below a pre-defined diversity threshold spanning the entire HCV genome were combined to create novel immunogens (1000-1500 amino-acids), covering variation in HCV subtypes 1a and 1b, genotypes 1 and 3, and genotypes 1-6 inclusive. Simian adenoviral vaccine vectors (ChAdOx) encoding HCV conserved immunogens were constructed. Immunogenicity was evaluated in C57BL6 mice using panels of genotype-specific peptide pools in ex-vivo IFN- γ ELISpot and intracellular cytokine assays.

RESULTS: ChAdOx1 conserved segment HCV vaccines primed high-magnitude, broad, cross-reactive T-cell responses; the mean magnitude of total HCV specific T-cell responses was 1174 SFU/106 splenocytes for ChAdOx1-GT1-6 in C57BL6 mice targeting multiple genomic regions, with mean responses of 935, 1474 and 1112 SFU/106 against genotype 1a, 1b and 3a peptide panels, respectively. Functional assays demonstrated IFN γ and TNF α production by vaccine-induced CD4 and CD8 T-cells. In silico analysis shows that conserved immunogens contain multiple epitopes, with many described in natural HCV infection, predicting immunogenicity in humans. **CONCLUSIONS:** Simian adenoviral vectored vaccines encoding genetic segments that are conserved between all major HCV genotypes contain multiple T-cell epitopes and are highly immunogenic in pre-clinical models. These studies pave the way for the assessment of multi-genotypic HCV T-cell vaccines in humans.

HIV/HCV COINFECTION

[Impact of Food Insecurity on Depressive Symptoms Among HIV-HCV Co-infected People.](#)

Aibibula W1, Cox J1,2, Hamelin AM1, et al. AIDS Behav. 2017 Dec;21(12):3464-3472. doi: 10.1007/s10461-017-1942-z.

Food insecurity (FI) is associated with depressive symptoms among HIV mono-infected people. Our objective was to examine to what extent this association holds among HIV-hepatitis C virus (HCV) co-infected people. We used data from a prospective cohort study of HIV-HCV co-infected people in Canada. FI was measured using the ten-item adult scale of Health Canada's Household Food Security Survey Module and was classified into three categories: food secure, moderate FI, and severe FI. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D-10) and was classified into absence or presence of depressive symptoms. FI, depressive symptoms, and other covariates were updated every 6 months. The association between FI and depressive symptoms was assessed using a stabilized inverse probability weighted marginal structural model. The study sample included 725 HIV-HCV co-infected people with 1973 person-visits over 3 years of follow up. At baseline, 23% of participants experienced moderate food insecurity, 34% experienced severe food insecurity and 52% had depressive symptoms. People experiencing moderate FI had 1.63 times (95% CI 1.44-1.86) the risk of having depressive symptoms and people experiencing severe FI had 2.01 times (95% CI 1.79-2.25) the risk of having depressive symptoms compared to people who were food

secure. FI is a risk factor for developing depressive symptoms among HIV-HCV co-infected people. Food supplementation, psychosocial support and counseling may improve patient health outcomes.

DNA methylation signatures of illicit drug injection and hepatitis C are associated with HIV frailty. Zhang X^{1,2}, Hu Y³, Justice AC^{2,4}, Li B⁵, Wang Z⁵, Zhao H⁵, Krystal JH^{1,2}, Xu K^{6,7}. *Nat Commun.* 2017 Dec 21;8(1):2243. doi: 10.1038/s41467-017-02326-1.

Intravenous illicit drug use (IDU) and hepatitis C infection (HCV) commonly co-occur among HIV-infected individuals. These co-occurring conditions may produce interacting epigenetic effects in white blood cells that influence immune function and health outcomes. Here, we report an epigenome-wide association analysis comparing IDU+/HCV+ and IDU-/HCV- in 386 HIV-infected individuals as a discovery sample and in 412 individuals as a replication sample. We observe 6 significant CpGs in the promoters of 4 genes, NLRC5, TRIM69, CX3CR1, and BCL9, in the discovery sample and in meta-analysis. We identify 19 differentially methylated regions on chromosome 6 harboring MHC gene clusters. Importantly, a panel of IDU+/HCV+-associated CpGs discriminated HIV frailty based upon a validated index with an area under the curve of 79.3% for high frailty and 82.3% for low frailty. These findings suggest that IDU and HCV involve epigenetic programming and that their associated methylation signatures discriminate HIV pathophysiologic frailty.

Injection Drug Use, Unemployment, and Severe Food Insecurity Among HIV-HCV Co-Infected Individuals: A Mediation Analysis. McLinden T¹, Moodie EEM¹, Hamelin AM¹, et al. *AIDS Behav.* 2017 Dec;21(12):3496-3505. doi: 10.1007/s10461-017-1850-2.

Severe food insecurity (FI), which indicates reduced food intake, is common among HIV-hepatitis C virus (HCV) co-infected individuals. Given the importance of unemployment as a proximal risk factor for FI, this mediation analysis examines a potential mechanism through which injection drug use (IDU) is associated with severe FI. We used biannual data from the Canadian Co-infection Cohort (N = 429 with 3 study visits, 2012-2015). IDU in the past 6 months (exposure) and current unemployment (mediator) were self-reported. Severe FI in the following 6 months (outcome) was measured using the Household Food Security Survey Module. An overall association and a controlled direct effect were estimated using marginal structural models. Among participants, 32% engaged in IDU, 78% were unemployed, and 29% experienced severe FI. After adjustment for confounding and addressing censoring through weighting, the overall association (through all potential pathways) between IDU and severe FI was: risk ratio (RR) = 1.69 (95% confidence interval [CI] = 1.15-2.48). The controlled direct effect (the association through all potential pathways except that of unemployment) was: RR = 1.65 (95% CI = 1.08-2.53). We found evidence of an overall association between IDU and severe FI and estimated a controlled direct effect that is suggestive of pathways from IDU to severe FI that are not mediated by unemployment. Specifically, an overall association and a controlled direct effect that are similar in magnitude suggests that the potential impact of IDU on unemployment is not the primary mechanism through which IDU is associated with severe FI. Therefore, while further research is required to understand the mechanisms linking IDU and severe FI, the strong overall association suggests that reductions in IDU may mitigate severe FI in this vulnerable subset of the HIV-positive population.

Boceprevir and Antiretroviral Pharmacokinetic Interactions in HIV/HCV Co-infected Persons: AIDS Clinical Trials Group Study A5309s.

Kiser JJ1, Lu D2, Rosenkranz SL2, Morse GD3, et al. *Drugs R D.* 2017 Dec;17(4):557-567. doi: 10.1007/s40268-017-0205-9.

OBJECTIVE: The objective of this study was to determine the magnitude of drug interactions between the hepatitis C virus (HCV) protease inhibitor boceprevir (BOC) and antiretroviral (ARV) agents in persons with HIV/HCV co-infection. **METHODS:** Participants taking two nucleos(t)ide analogs with either efavirenz, raltegravir, or ritonavir-boosted atazanavir, darunavir, or lopinavir underwent intensive pharmacokinetic (PK) sampling for ARV 2 weeks before (week 2) and 2 weeks after initiating BOC (week 6) and for BOC at week 6. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were used to compare ARV PK at weeks 2 and 6 and BOC PK at week 6 to historical data (HD) in healthy volunteers and HCV mono-infected patients. **RESULTS:** ARV PK was available for 55 participants. BOC reduced atazanavir and darunavir exposures by 30 and 42%, respectively. BOC increased raltegravir maximum concentration (C max) by 71%. BOC did not alter efavirenz PK. BOC PK was available for 53 participants. BOC exposures were similar in these HIV/HCV co-infected participants compared with HD in healthy volunteers, but BOC minimum concentrations (C min) were lower with all ARV agents (by 34-73%) compared with HD in HCV mono-infected patients. **CONCLUSIONS:** Effects of BOC on ARV PK in these HIV/HCV co-infected individuals were similar to prior studies in healthy volunteers. However, some differences in the effects of ARV on BOC PK were observed, indicating the magnitude of interactions may differ in HCV-infected individuals versus healthy volunteers. Findings highlight the need to conduct interaction studies with HCV therapies in the population likely to receive the combination.

Macrophage Activation and the Tumor Necrosis Factor Cascade in Hepatitis C Disease Progression Among HIV-Infected Women Participating in the Women's Interagency HIV Study.

French AL1, Martin JW, Evans CT, et al. *J Acquir Immune Defic Syndr.* 2017 Dec 1;76(4):438-444. doi: 10.1097/QAI.0000000000001524.

BACKGROUND: HIV/hepatitis C-coinfected persons experience more rapid liver disease progression than hepatitis C virus (HCV) mono-infected persons, even in the setting of potent antiretroviral therapy. **METHODS:** We sought to articulate the role of macrophage activation and inflammation in liver disease progression by measuring serial soluble markers in HIV/HCV-coinfected women. We compared markers measured during retrospectively defined periods of rapid liver disease progression to periods where little or no liver disease progression occurred. Liver disease progression was defined by liver biopsy, liver-related death or the serum markers AST-to-platelet ratio index and FIB-4. Soluble CD14, sCD163, lipopolysaccharide (LPS), tumor necrosis factor (TNF) receptor II, interleukin-6, and chemokine ligand 2 (CCL 2) were measured at 3 time points over 5 years. **RESULTS:** One hundred six time intervals were included in the analysis: including 31 from liver disease progressors and 75 from nonprogressors. LPS, sCD14, interleukin-6, and CCL2 levels did not differ in slope or quantity over time between rapid liver disease progressors and nonprogressors. TNFR2 and sCD163 were significantly higher in liver disease progressors at (P = 0.002 and <0.0001 respectively) and preceding (P = 0.01 and 0.003 respectively) the liver fibrosis outcome in unadjusted models, with similar values when adjusted for HIV RNA and CD4 count. **CONCLUSIONS:** In women with HIV/HCV coinfection, higher sCD163 levels, a marker of macrophage activation, and TNFR2 levels, implying activation of the TNF- α system, were associated with liver disease progression. Our results provide an

addition to the growing body of evidence regarding the relationship between macrophage activation, inflammation, and liver disease progression in HIV/HCV coinfection.

Direct-acting antiviral therapy enhances total CD4+ and CD8+ T-cells responses, but does not alter T-cells activation among HCV mono-infected, and HCV/HIV-1 co-infected patients.

Najafi Fard S1, Schietroma I2, Corano Scheri G2, et al. Clin Res Hepatol Gastroenterol. 2017 Dec 23. pii: S2210-7401(17)30262-0. doi: 10.1016/j.clinre.2017.11.006. [Epub ahead of print]

AIM: Chronic immune activation and poor T-cell immune response are strongly associated with disease progression and pathogenesis of both hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-1 infections. Little is known about the impact of anti-HCV Interferon (IFN)-free direct-acting antiviral (DAA) therapy on the systemic T-cells activation and patterns of peripheral T-cells producing pro-inflammatory cytokines. **PATIENTS AND METHODS:** Forty-five subjects including 18 HCV mono-infected, 17 HCV/HIV-1 co-infected patients under antiretroviral therapy (ART), and 10 healthy controls (HCs) were recruited. Blood samples were collected at baseline (T0) and 12 weeks after the end of DAA therapy (T1). Cell phenotypes (CD3, CD4, CD8), activation markers (CD38 and HLA-DR), and frequency of IFN- γ , interleukin (IL)-17, and IL-22 producing CD4+ and CD8+ T-cells were measured by flow cytometry. Plasma levels of related cytokines were also measured by enzyme-linked immunosorbent assay (ELISA). **RESULTS:** Both HCV, and HCV/HIV-1 patients before and after therapy, showed significant higher percentages of any T-cell subset expressing CD38 and/or HLA-DR compared to HCs. No differences were observed in T-cells activation at T1 compared to T0 in patient groups, and when HCV patients were compared to HCV/HIV-1 group ($P>0.05$). After therapy, the potential of total circulating T helper (Th) and T cytotoxic (Tc) cells producing IFN- γ , IL-17, and IL-22 were increased. Plasma level of IFN- γ at baseline was showed difference compared to HCs, and significantly reduced after therapy ($P<0.05$). **CONCLUSION:** Total T-cells immune response enhances after therapy, however, the state of immune activation may remain elevated for a longtime after the end of treatment and contribute to post-Sustained Virologic Response (SVR) consequences.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Assessing Racial Disparities in HCV Infection and Care Outcomes in a Southern Urban Population.

McGonigle K1, Carley T2, Hoff C2. J Racial Ethn Health Disparities. 2017 Dec 29. doi: 10.1007/s40615-017-0453-y. [Epub ahead of print]

OBJECTIVES: This study assessed racial disparities in access to healthcare services, hepatitis C virus (HCV) exposure, and retention in a treatment cascade in two indigent populations in an urban center in the Southern US. **PARTICIPANTS/METHODS:** Opt-in HCV antibody screening was offered at two large homeless centers and three residential substance abuse treatment centers (SATCs) in New Orleans, LA. Five hundred ninety-four participants experiencing homelessness and 342 residents of SATCs were assessed for previous access/perceived barriers to healthcare services and high-risk behaviors associated with HCV exposure. Participants were then screened using rapid HCV antibody testing and tracked through

a treatment cascade involving referral to a primary care provider (PCP), RNA confirmation, and specialist referral. **RESULTS:** In both the homeless and SATC populations, whites were more likely to report barriers to accessing healthcare and high-risk behaviors, especially prior intravenous drug use (IVDU). Interaction between age and race demonstrates a protective effect of white ethnicity at higher ages, at a level approaching statistical significance. Non-whites were equally likely to access follow-up care and treatment as whites. **CONCLUSIONS:** Despite many more risk factors reported by the white population, HCV antibody positivity was largely equal between the two racial groups. Known interactions between race and age in the African American population were demonstrated in these high-risk, urban populations. Whites were no more likely to achieve various levels of a treatment and care cascade. The results may demonstrate the impact of improved access to testing services and primary care, although access to treatment remains a significant barrier to eliminating racial disparities in HCV infection.

Development and Validation of Surveillance-Based Algorithms to Estimate Hepatitis C Treatment and Cure in New York City. Moore MS1, Bocour A, Jordan L, McGibbon E,

Varma JK, Winters A, Laraque F. J Public Health Manag Pract. 2017 Dec 7. doi: 10.1097/PHH.0000000000000688. [Epub ahead of print]

CONTEXT: Treatment options for chronic hepatitis C virus (HCV) have improved in recent years. The burden of HCV in New York City (NYC) is high. Measuring treatment and cure among NYC residents with HCV infection will allow the NYC Department of Health and Mental Hygiene (DOHMH) to appropriately plan interventions, allocate resources, and identify disparities to combat the hepatitis C epidemic in NYC. **OBJECTIVE:** To validate algorithms designed to estimate treatment and cure of HCV using RNA test results reported through routine surveillance. **DESIGN:** Investigation by NYC DOHMH to determine the true treatment and cure status of HCV-infected individuals using chart review and HCV test data. Treatment and cure status as determined by investigation are compared with the status determined by the algorithms. **SETTING:** New York City health care facilities. **PARTICIPANTS:** A total of 250 individuals with HCV reported to the New York City Department of Health and Mental Hygiene (NYC DOHMH) prior to March 2016 randomly selected from 15 health care facilities. **MAIN OUTCOME MEASURES:** The sensitivity and specificity of the algorithms. **RESULTS:** Of 235 individuals successfully investigated, 161 (69%) initiated treatment and 96 (41%) achieved cure since the beginning of 2014. The treatment algorithm had a sensitivity of 93.2% (95% confidence interval [CI], 89.2%-97.1%) and a specificity of 83.8% (95% CI, 75.3%-92.2%). The cure algorithm had a sensitivity of 93.8% (95% CI, 88.9%-98.6%) and a specificity of 89.4% (95% CI, 83.5%-95.4%). Applying the algorithms to 68 088 individuals with HCV reported to DOHMH between July 1, 2014, and December 31, 2016, 28 392 (41.7%) received treatment and 16 921 (24.9%) were cured. **CONCLUSIONS:** The algorithms developed by DOHMH are able to accurately identify HCV treatment and cure using only routinely reported surveillance data. Such algorithms can be used to measure treatment and cure jurisdiction-wide and will be vital for monitoring and addressing HCV. NYC DOHMH will apply these algorithms to surveillance data to monitor treatment and cure rates at city-wide and programmatic levels, and use the algorithms to measure progress towards defined treatment and cure targets for the city.

GHOST: global hepatitis outbreak and surveillance technology. Longmire AG1,2, Sims S1,3,2, Rytsareva I1, et al. BMC Genomics. 2017 Dec 6;18(Suppl 10):916. doi: 10.1186/s12864-017-4268-3.

BACKGROUND: Hepatitis C is a major public health problem in the United States and worldwide. Outbreaks of hepatitis C virus (HCV) infections associated with unsafe injection practices, drug diversion, and other exposures to blood are difficult to detect and investigate. Effective HCV outbreak investigation requires comprehensive surveillance and robust case investigation. We previously developed and validated a methodology for the rapid and cost-effective identification of HCV transmission clusters. Global Hepatitis Outbreak and Surveillance Technology (GHOST) is a cloud-based system enabling users, regardless of computational expertise, to analyze and visualize transmission clusters in an independent, accurate and reproducible way. **RESULTS:** We present and explore performance of several GHOST implemented algorithms using next-generation sequencing data experimentally obtained from hypervariable region 1 of genetically related and unrelated HCV strains. GHOST processes data from an entire MiSeq run in approximately 3 h. A panel of seven specimens was used for preparation of six repeats of MiSeq libraries. Testing sequence data from these libraries by GHOST showed a consistent transmission linkage detection, testifying to high reproducibility of the system. Lack of linkage among genetically unrelated HCV strains and constant detection of genetic linkage between HCV strains from known transmission pairs and from follow-up specimens at different levels of MiSeq-read sampling indicate high specificity and sensitivity of GHOST in accurate detection of HCV transmission. **CONCLUSIONS:** GHOST enables automatic extraction of timely and relevant public health information suitable for guiding effective intervention measures. It is designed as a virtual diagnostic system intended for use in molecular surveillance and outbreak investigations rather than in research. The system produces accurate and reproducible information on HCV transmission clusters for all users, irrespective of their level of bioinformatics expertise. Improvement in molecular detection capacity will contribute to increasing the rate of transmission detection, thus providing opportunity for rapid, accurate and effective response to outbreaks of hepatitis C. Although GHOST was originally developed for hepatitis C surveillance, its modular structure is readily applicable to other infectious diseases. Worldwide availability of GHOST for the detection of HCV transmissions will foster deeper involvement of public health researchers and practitioners in hepatitis C outbreak investigation.

Tennessee's In-State Vulnerability Assessment for a 'Rapid Dissemination of HIV or HCV Infection' Event Utilizing Data about the Opioid Epidemic. Rickles M1, Rebeiro PF2, Sizemore L1, Juarez P3, Mutter M1, Wester C1, McPheeters M1. Clin Infect Dis. 2017 Dec 7. doi: 10.1093/cid/cix1079. [Epub ahead of print]

BACKGROUND: Knowing which factors contribute to county-level vulnerability to an HIV/Hepatitis C (HCV) outbreak, and which counties are most vulnerable, guide public health and clinical interventions. We therefore examined the impact of locally available indicators related to the opioid epidemic on prior national models of HCV/HIV outbreak vulnerability. **METHODS:** Tennessee's 95 counties were the study sample. Predictors from 2012 and 2013 were used, mirroring prior methodology from the US Centers for Disease Control and Prevention (CDC). Acute HCV incidence was the proxy measure of county-level vulnerability. Seventy-eight predictors were identified as potentially predictive for HIV/HCV vulnerability. We used

multiple dimension reduction techniques to determine predictors for inclusion and Poisson regression to generate a composite index score ranking county level vulnerability for HIV/HCV. **RESULTS:** There was overlap of high-risk counties with the national analysis (25 of 41 counties). The distribution of vulnerability reinforces earlier research indicating that Eastern Tennessee is at particularly high risk, but also demonstrates that the entire state has high vulnerability. **CONCLUSIONS:** Prior research placed Tennessee among the top states for opioid prescribing, acute HCV infection, and greatest risk for an HIV/HCV outbreak. Given this confluence of risk, the Tennessee Department of Health expanded upon prior work to include more granular, local data, including on opiate prescribing. We also explored opioid prescribing patterns and nonfatal and fatal overdoses. The more complete statewide view of risk generated, not only in Eastern counties but also in the Western corridor, will enable local officials to monitor vulnerability and better target resources.

[Sensitivity and specificity of a new automated system for the detection of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus nucleic acid in blood and plasma donations.](#)

Galel SA1, Simon TL2, Williamson PC3, et al. Transfusion. 2017 Dec 17. doi: 10.1111/trf.14457. [Epub ahead of print]

BACKGROUND: Use of nucleic acid testing (NAT) in donor infectious disease screening improves transfusion safety. Advances in NAT technology include improvements in assay sensitivity and system automation, and real-time viral target discrimination in multiplex assays. This article describes the sensitivity and specificity of cobas MPX, a multiplex assay for detection of human immunodeficiency virus (HIV)-1 Group M, HIV-2 and HIV-1 Group O RNA, HCV RNA, and HBV DNA, for use on the cobas 6800/8800 Systems. **STUDY DESIGN AND METHODS:** The specificity of cobas MPX was evaluated in samples from donors of blood and source plasma in the United States. Analytic sensitivity was determined with reference standards. Infectious window periods (WPs) before NAT detectability were calculated for current donor screening assays. **RESULTS:** The specificity of cobas MPX was 99.946% (99.883%-99.980%) in 11,203 blood donor samples tested individually (IDT), 100% (99.994%-100%) in 63,012 donor samples tested in pools of 6, and 99.994% (99.988%-99.998%) in 108,306 source plasma donations tested in pools of 96. Seven HCV NAT-yield donations and one seronegative occult HBV infection were detected. Ninety-five percent and 50% detection limits in plasma (IU/mL) were 25.7 and 3.8 for HIV-1M, 7.0 and 1.3 for HCV, and 1.4 and 0.3 for HBV. The HBV WP was 1 to 4 days shorter than other donor screening assays by IDT. **CONCLUSION:** cobas MPX demonstrated high specificity in blood and source plasma donations tested individually and in pools. High sensitivity, in particular for HBV, shortens the WP and may enhance detection of occult HBV.

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[Insurance switching and mismatch between the costs and benefits of new technologies.](#)

Cutler D1, Ciarametaro M, Long G, Kirson N, Dubois R. Am J Manag Care. 2017 Dec;23(12):750-757.

OBJECTIVES: Many therapies have immediate costs but delayed benefits. Recent and anticipated transformative therapies may exacerbate these challenges. This study explored whether disconnects between short-term budget impacts and long-term costs and benefits, and among impacts on initial payers, downstream payers, and society, are expected for a range of

such therapies and whether they are likely consistent or variable, with implications for potential policy responses. **STUDY DESIGN:** Modeling. **METHODS:** We modeled the impacts of 5 hypothetical therapies affecting different patient types: curative gene therapy for a childhood disorder, highly effective hepatitis C virus therapy, disease-modifying Alzheimer disease therapy, and cardiovascular disease therapy for both rare genetic and higher-risk prior cardiovascular event populations. We constructed disease-specific models, modifying best-available Markov analysis estimates for standard-of-care state transition rates, utilities, and costs. We disaggregated total healthcare impacts into impacts on initial versus downstream payers, dividing payers into 3 types: commercial insurers, Medicaid, and Medicare. **RESULTS:** Although we found gaps between the impacts on initial and downstream payers in all examples, some substantial, the magnitude and reasons vary. **CONCLUSIONS:** As scientific advances generate transformative therapies with substantial structural disconnects between "who pays" and "who benefits," creative approaches may be needed by manufacturers, payers, and others to ensure appropriate access to cost-effective therapies, adequate economic incentives for future development, and sustainable payer economics. Mechanisms may amortize high up-front costs over time, provide for transfers among payers, or a combination. Our research suggests that approaches should be tailored to specific disease and therapy characteristics to be effective.

[The Effect of Interferon-Free Regimens on Health-Related Quality of Life in East Asian Patients with Chronic Hepatitis C.](#) Younossi ZM^{1,2}, Stepanova M³, Henry L³, et al. Liver Int. 2017 Dec 2. doi: 10.1111/liv.13650. [Epub ahead of print]

BACKGROUND/AIM: Interferon (IFN)-based regimens cause significant impairment of health-related quality of life (HRQL). HCV cure with IFN-free regimens improves HRQL. The effect of these regimens on HRQL in East Asian HCV patients is unclear due to lack of easy access. **AIM:** To assess HRQL in East Asian HCV patients treated with IFN-free regimen with sofosbuvir+ribavirin. **METHODS:** Patients completed Short Form-36 (SF-36) before, during and after treatment. **RESULTS:** 686 subjects were included [China: 56.7%, S. Korea: 18.8%, Taiwan: 12.7%, genotype 2: 40.8%, genotype 1: 29.6%, genotype 3: 18.4%, genotype 6: 11.2%; cirrhosis: 13.4%, treatment-naïve: 66.5%]. Patients either received pegylated-IFN, sofosbuvir, and ribavirin (IFN+SOF+RBV) for 12 weeks (n=155, genotypes 1 and 6) or SOF+RBV for 12-24 weeks (n=531, all genotypes). The SVR-12 rates was 95.5% and 96.0%; respectively (p=0.76). Baseline HRQL scores were similar between treatment groups (all p>0.05). By end of treatment, IFN-treated group experienced significant declines in most HRQL scores (on average, by up to -13.3 points on a 0-100 scale from the baseline level, p<0.02) while subjects on SOF/RBV had milder impairments (up to -5.4 points). Achieving SVR-12 was associated with HRQL improvement regardless of regimen (up to +2.9 points, p<0.05). The use of IFN-free treatment was a consistent independent predictor of higher HRQL scores during treatment (β : +2.1 to +10.7 points, p<0.02). **CONCLUSIONS:** East Asian HCV patients treated with an IFN-free regimen had better on-treatment HRQL scores. These data should inform policy makers about the comprehensive benefits of IFN-free regimens in East Asian patients with HCV. This article is protected by copyright. All rights reserved.

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[The emergency medicine evaluation and management of the patient with cirrhosis.](#) Long B¹, Koyfman A². Am J Emerg Med. 2017 Dec 23. pii: S0735-6757(17)31049-5. doi: 10.1016/j.ajem.2017.12.047. [Epub ahead of print]

BACKGROUND: Cirrhosis is a significant cause of death in the U.S. and has a variety of causes, most commonly Hepatitis C and alcohol. Liver fibrosis and nodule formation result in significant complications due to portal system hypertension. There are several deadly complications emergency physicians must consider. **OBJECTIVE OF THE REVIEW:** Provide an evidence-based update for the resuscitation of decompensating cirrhotic patients and an overview of cirrhosis complications. **DISCUSSION:** Cirrhosis is a common condition in the U.S. and leads to several deadly complications. The disease develops from liver fibrosis, elevating portal pressures and modifying patient hemodynamics. Cirrhosis results in significant anatomic and physiologic modifications involving the gastrointestinal, cardiopulmonary, neurologic, renal, immunologic, and hematologic systems. The disease can be divided into compensated and decompensated states, with decompensation associated with significant morbidity and mortality. Complications include variceal hemorrhage, ascites, increased risk of bacterial infection, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, umbilical hernia, and hepatic hydrothorax. Resuscitation including airway and circulation measures is paramount in these patients, and several new techniques are offered for the approach to intubation and resuscitation for patients with severe cirrhosis. **CONCLUSIONS:** Decompensating cirrhotics may require extensive resuscitation, and knowledge of the evaluation and management of complications associated with cirrhosis can improve care for patients with severe liver disease.

[Hepatitis C Testing Increased Among Baby Boomers Following The 2012 Change To CDC Testing Recommendations.](#) Barocas JA1, Wang J2, White LF3, Tasillo A4, Salomon JA5, Freedberg KA6, Linas BP7. Health Aff (Millwood). 2017 Dec;36(12):2142-2150. doi: 10.1377/hlthaff.2017.0684.

In 2012 the Centers for Disease Control and Prevention recommended routine testing for hepatitis C for people born in the period 1945-65. Until now, the recommendation's impact on hepatitis C screening rates in the United States has not been fully understood. We used an interrupted time series with comparison group design to analyze hepatitis C screening rates in the period 2010-14 among 2.8 million commercially insured adults in the MarketScan database. Hepatitis C screening rates increased yearly between 2010 and 2014, from 1.65 to 2.59 per 100 person-years. A 49 percent increase in screening rates among people born during 1945-65 followed the release of the recommendation, but no such increase was observed among adults born after 1965. The effect among the target population was sustained, and by twenty-four months after the recommendation's release, screening rates had increased 106 percent. We conclude that the hepatitis C testing policy change resulted in significantly increased testing among the target population and may have decreased the magnitude of the hepatitis C epidemic.

[Hepatitis C Virus Infection in the Older Patient.](#) Reid M1, Price JC1, Tien PC2. Infect Dis Clin North Am. 2017 Dec;31(4):827-838. doi: 10.1016/j.idc.2017.07.014.

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States and is of concern in older adults. HCV infection is associated with not only hepatic but also extrahepatic comorbidities common to the aging patient including diabetes, kidney and cardiovascular diseases, and neurocognitive impairment. The effect of direct-acting antiviral agents to treat HCV on these outcomes is limited. This article summarizes the literature regarding the epidemiology and natural history of HCV infection; the impact of age on clinical outcomes in

HCV-infected persons; and current knowledge regarding safety and efficacy of HCV treatment regimens in the older patient.

[**A Resident Initiative Improves Hepatitis C Screening Rates in Primary Care Clinics.**](#) Wong K, Abdelqader A, Camire L, Farshidpour M, Singh S, Abuwalla Z, Weisman D. J Grad Med Educ. 2017 Dec;9(6):768-770. doi: 10.4300/JGME-D-17-00199.1.

BACKGROUND: Electronic reminders for clinical patient counseling have proven to be an effective response to national recommendations to increase risk factor and birth cohort hepatitis C virus (HCV) screening. It is not known whether a resident-led educational intervention alone could increase screening rates where support for electronic intervention may be limited.

OBJECTIVE: We determined whether a resident-designed and resident-implemented educational intervention would significantly improve HCV screening rates in primary care clinics. **METHODS:** The baseline HCV screening rate was determined retrospectively in our resident community-based primary care clinics. We then implemented an educational intervention that included presenting during resident conference, posting signs in resident work areas, and providing educational pamphlets to patients. We collected screening rate data at 3 and 6 months postintervention. The screening rate was defined as patients screened in clinic divided by the number of patients eligible for screening. **RESULTS:** The screening rate increased significantly from preintervention (6%, 64 of 1023) to 3 months (35%, 363 of 1026) and 6 months (41%, 443 of 1070) and between 3 and 6 months ($P < .001$). The percentage of screened patients who pursued testing increased significantly between preintervention (62%, 16 of 26) and 6 months (81%, 105 of 130), and between 3 months (67%, 95 of 141) and 6 months ($P = .019$).

CONCLUSIONS: An educational intervention designed and implemented by residents significantly increased the screening and testing rates for HCV in community-based resident clinics.

[**Tree-based Claims Algorithm for Measuring Pretreatment Quality of Care in Medicare Disabled Hepatitis C Patients.**](#) Chirikov VV1, Shaya FT, Onukwugha E, Mullins CD, dosReis S, Howell CD. Med Care. 2017 Dec;55(12):e104-e112. doi: 10.1097/MLR.0000000000000405.

BACKGROUND: To help broaden the use of machine-learning approaches in health services research, we provide an easy-to-follow framework on the implementation of random forests and apply it to identify quality of care (QC) patterns correlated with treatment receipt among Medicare disabled patients with hepatitis C virus (HCV). **METHODS:** Using Medicare claims 2006-2009, we identified 1936 patients with 6 months continuous enrollment before HCV diagnosis. We ran a random forest on 14 pretreatment QC indicators, extracted the forest's representative tree, and aggregated its terminal nodes into 4 QC groups predictive of treatment. To explore determinants of differential QC receipt, we compared patient-level and county-level (linked AHRF data) characteristics across QC groups. **RESULTS:** The strongest predictors of treatment included "liver biopsy," "HCV genotype testing," "specialist visit," "HCV viremia confirmation," and "iron overload testing." High QC [$n=360$, proportion treated (pt)=33.3%] was defined for patients with at least 2 from the above-mentioned metrics. Good QC patients ($n=302$, pt=12.3%) had either "HCV genotype testing" or "specialist visit," whereas fair QC ($n=282$, pt=7.1%) only had "HCV viremia confirmation." Low QC patients ($n=992$, pt=2.5%) had none of the selected metrics. The algorithm accuracy of predicting treatment was 70% sensitivity and 78% specificity. HIV coinfection, drug abuse, and residence in counties with higher supply of hospitals with immunization and AIDS services correlated with lower QC. **CONCLUSIONS:**

Machine-learning techniques could be useful in exploring patterns of care. Among Medicare disabled HCV patients, the receipt of more QC indicators was associated with higher treatment rates. Future research is needed to assess determinants of differential QC receipt.

[The usefulness of Virtual Touch Quantification for staging liver fibrosis in patients with hepatitis C, and the factors affecting liver stiffness measurement failure compared with liver biopsy.](#) Tsukano N1, Miyase S1, Saeki T1, Mizobe K1, Iwashita H1, Arima N1, Fujiyama S1. *Hepatology*. 2017 Dec 11. doi: 10.1111/hepr.13041. [Epub ahead of print]

AIM: Assessing liver fibrosis in patients with hepatitis C is important to predict carcinogenesis. In this study, we evaluated the usefulness of virtual touch quantification (VTQ) for staging liver fibrosis, and investigated factors causing the discrepancy between the estimated fibrosis stage using VTQ and the pathological fibrosis stage. **METHODS:** Patients with hepatitis C (n=302) were assessed using VTQ and underwent pathological liver investigation within 1 week before and after VTQ. A receiver operator characteristic (ROC) curve was obtained for VTQ, fibrosis-4 (FIB-4) index, and aspartate aminotransferase-to-platelet ratio index (APRI), and each area under the ROC curve (AUROC) was compared to predict fibrosis stage. We used univariate and multivariate analyses to investigate the factors related to the discrepancy between the estimated fibrosis stage using VTQ and the pathological fibrosis stage. **RESULTS:** At any stage, VTQ was the most accurate for staging liver fibrosis. The VTQ cut-off values were 1.33 m/s (AUROC = 0.822) for \geq F2, 1.51 m/s (AUROC = 0.836) for \geq F3, and 1.92 m/s (AUROC = 0.890) for F4. Skin liver capsule distance (SCD) was the most relevant factor for the discrepancy between the estimated fibrosis stage using VTQ and the pathological fibrosis stage. The SCD cut-off value was 17.5 mm. **CONCLUSIONS:** VTQ is a non-invasive, simple method that is more accurate for staging liver fibrosis than FIB-4 index and APRI. However, when SCD is longer than 17.5 mm, there may be measurement failures.

HEPATOCELLULAR (LIVER) CANCER

[Liver resection of hepatocellular carcinoma in patients with portal hypertension and multiple tumors.](#)

Ohkubo T1, Midorikawa Y1, Nakayama H1, Moriguchi M1, Aramaki O1, Yamazaki S1, Higaki T1, Takayama T1. *Hepatology*. 2017 Dec 26. doi: 10.1111/hepr.13047. [Epub ahead of print]

AIM: Liver resection for hepatocellular carcinoma (HCC) has been recommended only for patients with a single tumor without portal hypertension. We aimed to validate this treatment strategy that is based on by the Barcelona Clinic Liver Cancer staging system. **METHODS:** Patients undergoing liver resection were divided into two groups: patients with single HCC without portal hypertension (Group 1) and those with at least one factors of portal hypertension and multiple tumors up to three lesions each \leq 3 cm (Group 2). We compared survivals and postoperative complications between the two groups. **RESULTS:** The median overall and recurrence-free survival periods of patients in Group 1 (N= 695) were 8.5 years (95% confidence interval [CI] 6.6-9.0) and 2.4 years (2.2-2.7), respectively, and were significantly longer compared with those of patients in Group 2 (N = 197) (5.6 years [95% CI, 4.8-6.7], P = 0.001, and 1.9 years [1.6-2.1], P < 0.001). On multivariate analysis, the independent factors for overall survival were hepatitis C virus infection (HR 1.29 [95% CI, 1.02-1.65], P = 0.032), multiple tumors (1.42 [1.01-1.98], P = 0.040), and vascular invasion (1.66 [1.31-2.10], P < 0.001). On the other hand, frequency of morbidities (23 [3.3%] patients vs 11 [5.5%] patients, P = 0.143) and

mortalities (3 [0.4%] patients vs 2 [1.0%] patients, $P = 0.305$) was not significantly different between the two groups. **CONCLUSIONS:** Patients with HCC with portal hypertension and/or multiple tumors could be the candidates for liver resection due to the safety of the procedure.

[The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ERCHIVES study.](#) Li DK^{1,2}, Ren Y³, Fierer DS⁴, et al. Hepatology. 2017 Dec 2. doi: 10.1002/hep.29707. [Epub ahead of print]

Recent studies have reported higher rates of hepatocellular carcinoma (HCC) in individuals treated with direct-acting antivirals (DAAs). However, making definitive conclusions has been challenging due to the heterogeneous populations and methodologies of these reports. We investigated whether DAA use is associated with higher rates of incident HCC compared to treatment with interferon-based regimens. We performed a retrospective population-based cohort study using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) database. In a cohort of 17,836 persons, SVR was achieved by 66.6% and 96.2% of the IFN and DAA groups, respectively. Among all treated persons, the risk of HCC was not higher in the DAA group compared to the IFN group (HR 1.07; [95% CI: 0.55, 2.08]). Among persons with cirrhosis who achieved SVR, neither the HCC incidence rate nor HCC-free survival were significantly different in the DAA group compared to the IFN group (21.2 vs. 22.8 per 1000 person years; $p=0.78$; and log-rank $p=0.17$, respectively). Untreated persons with cirrhosis had a significantly higher HCC incidence rate (45.3 per 1000 person years) compared to those treated with either IFN or DAAs ($p=0.03$). Both groups of treated persons had significantly lower probability of HCC development compared to untreated persons (log-rank $p=0.0004$).

CONCLUSIONS: DAA treatment is not associated with a higher risk of HCC in cirrhotics with chronic HCV infection in the short-term. Previously reported higher rates of HCC associated with DAA treatment may be explained by both the presence of relatively fewer baseline HCC risk factors in persons treated with IFN as well as selection bias, as DAA regimens were used to treat persons at higher risk for developing HCC. This article is protected by copyright. All rights reserved.

[Hepatitis C-related hepatocellular carcinoma: diagnostic and therapeutic management in HIV-patients.](#) D'Aleo F¹, Ceccarelli M, Venanzi Rullo E, et al. Eur Rev Med Pharmacol Sci. 2017 Dec;21(24):5859-5867. doi: 10.26355/eurrev_201712_14035.

The efficacy of the current HIV therapy has led to increased survival and prolongation of the average life expectancy of people living with HIV (PLWH), as well as the emergence of comorbidities and non-AIDS related cancer. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Current evidence suggests that HCC is an important cause of morbidity and mortality in HIV infected patients. In fact, HCC prevalence rate is indeed higher with respect to the general population average. In this paper, we review the diagnostic and therapeutic management of Hepatitis C-related hepatocellular carcinoma in HCV-HIV co-infected patients. Several therapeutic options are available depending on several factors as HCC stage, liver functions, comorbidities and they have been divided into three groups: potentially curative, proven effective but not curative, and unproven or ineffective therapy. In HIV-infected patients, surgical options are preferred compared to non-surgical therapies. Further studies, especially multicenter ones, are needed in order to define the most appropriate, evidence-based therapeutic approach to PLWH suffering from HCC. It also appears necessary to develop appropriate care guidelines for PLWH.

Hepatocellular Carcinoma Occurrence and Recurrence after Antiviral Treatment in HCV-Related Cirrhosis. Are Outcomes Different after Direct Antiviral Agents? A Review.

Spârchez Z1, Mocan T2. J Gastrointestin Liver Dis. 2017 Dec;26(4):403-410. doi: 10.15403/jgld.2014.1121.264.hcv.

Hepatitis C virus (HCV) infection is one of the major causes of hepatocellular carcinoma (HCC) worldwide. In the last decades, several studies have showed a lower rate of HCC occurrence or recurrence in patients with HCV-related cirrhosis after interferon-based antiviral therapies compared to untreated controls, even without reaching viral clearance. Unfortunately, interferon regimens could only yield viral clearance in approximately half of the patients. The recent development of new all-oral regimens with direct-acting antivirals (DAAs) has radically improved the cure rate to above 90%. In respect to these findings, many would have thought that interferon-free regimens would decrease the development and recurrence of HCC. Literature data have unexpectedly reported high rates of both the occurrence and recurrence of HCC after therapy with DAAs. However, it is probably too early to express some concerns. More recent data showed that both occurrence and recurrence of HCC are decreased by the DAAs. Interferon-free therapy is definitely not without limits. Together with the initial thoughts of an increased risk of HCC, these may lead to an unwanted restricted access to interferon-free regimens in specific subpopulations. This issue should be settled as soon as possible because millions of hepatitis C patients are and will be using DAAs in the present and future. Our purpose is to review the existing literature and to offer a more precise and rational interpretation of the existing data.

HCC Risk Scores: Useful or Not? Sherman M1. Semin Liver Dis. 2017 Nov;37(4):287-295. doi: 10.1055/s-0037-1607452. Epub 2017 Dec 22.

The advent and efficacy of surveillance for hepatocellular carcinoma (HCC) has necessitated the refinement of assessing who is at risk for this cancer. Initially, risk was assessed for all individuals with hepatitis B and all those with cirrhosis. However, the majority of these individuals do not develop HCC so that providing surveillance for all is a waste of resources. There are now many different scores that have been developed that allow better identification of who is at risk and who is not. Specific models have been developed for hepatitis B before and on treatment, for hepatitis C before and after treatment, and for cirrhosis in general. There are also models for assessing risk in the general population. Some models can only be applied to patients coming from the population in which the score was developed (e.g., hepatitis B). Others are more generalizable. Many lack external validation. With some exceptions, the models do not attempt to assess the score at which surveillance should start. Overall, the models provide some useful guidance as to who does not need to undergo surveillance, but the long-term performance and how changes in risk score correlate with changes in HCC risk has not been completely assessed.

lncRNA-HEIH in serum and exosomes as a potential biomarker in the HCV-related hepatocellular carcinoma. Zhang C1, Yang X2, Qi Q3, Gao Y4, Wei Q4, Han S3. Cancer Biomark. 2017 Dec 22. doi: 10.3233/CBM-170727. [Epub ahead of print]

BACKGROUND: Chronic hepatitis C (CHC) is a contagious liver disease that results from infection with the hepatitis C virus (HCV). The most serious consequence of CHC is HCV-

related hepatocellular carcinoma (HCC). **OBJECTIVE:** To illustrate the clinical significance of lncRNA HEIH expression in serum and exosomes in the development of HCV-related HCC. **METHODS:** Thirty-five CHC, twenty-two HCV-induced cirrhosis and ten HCV-related HCC patients in Huzhou Central Hospital from January 2016 to September 2016 were recruited in the present study. Basic patient information, clinical serological indicators, and clinical imaging data were investigated and analyzed. Serum samples were collected from patients after receiving informed consent. Exosomes were extracted from the serum, and electron microscopy was used to observe the ultrastructure of exosomes. Quantitative PCR was used to detect lncRNA HEIH gene expression in serum and exosomes. **RESULTS:** The changes in the ALT, GGT, HDL, INR, Alb and AFP levels in the patients with HCV-induced cirrhosis and HCV-related HCC were statistically significant. In patients with HCV-related HCC, lncRNA-HEIH expression in serum and exosomes was increased, but the ratio of lncRNA-HEIH expression in serum versus exosomes was decreased compared to patients with CHC.

[Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C without sustained response to combination therapy.](#) Chang KC1, Ye YH2, Wu CK2, Lin MT2, Tsai MC2, Tseng PL2, Hu TH2. J Formos Med Assoc. 2017 Dec 15. pii: S0929-6646(17)30393-5. doi: 10.1016/j.jfma.2017.11.008. [Epub ahead of print]

BACKGROUND/PURPOSE: Although antiviral therapy reduces development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC), HCC often develops in patients with non-sustained virologic response (non-SVR). We aimed to evaluate risk factors for HCC in HCV patients with non-SVR. **METHODS:** From March 2002 to December 2013, 800 patients with CHC who had received combined pegylated interferon (peg-IFN)/ribavirin (RBV) therapy without achieving SVR were enrolled. Main outcome measure was HCC development. Variables were cirrhosis, platelet count, α -fetoprotein (AFP) levels, aspartate aminotransferase (AST) to platelet ratio index (APRI), and IL28B polymorphism (CT + TT). **RESULTS:** One-hundred of 800 non-SVR patients developed HCC within a median 53.5-months follow-up. Cumulative incidence of HCC for all patients was 1.4%, 5.6% and 12.3%, respectively, at 1st, 3rd and 5th years of follow-up. In univariate analysis, patients who developed HCC tended to have LC ($p < 0.001$), lower platelet counts ($< 150 \times 10^9/l$, $p < 0.001$), higher AFP levels (≥ 20 ng/ml, $p < 0.001$), higher Fib-4 levels ($p < 0.001$), higher APRI levels ($p < 0.001$), IL 28B polymorphism (CT + TT) ($p < 0.001$) and higher incidence of diabetes mellitus (DM) ($p = 0.019$). Multivariate analysis in overall patients revealed that cirrhosis (HR: 2.94, 95% CI: 1.81-4.77, $p < 0.001$), IL28B rs12979860 (CT + TT) polymorphisms (HR: 3.22, 95% CI: 2.17-4.78, $p < 0.001$), and high APRI levels (≥ 2.57) (HR: 2.32, 95% CI: 1.47-3.67, $p < 0.001$) were independent risk factors for HCC. **CONCLUSIONS:** Liver cirrhosis, high APRI levels, and IL28B rs12979860 at baseline are independent risk factors for HCC development in patients without SVR after peg-IFN combination therapy.

[Interferon-free therapy of chronic hepatitis C with direct-acting antivirals does not change the short-term risk for de novo hepatocellular carcinoma in patients with liver cirrhosis.](#)

Mettke F1, Schlevogt B2, Deterding K1, et al. Aliment Pharmacol Ther. 2017 Dec 4. doi: 10.1111/apt.14427. [Epub ahead of print]

BACKGROUND: Hepatitis C virus (HCV) clearance with IFN-based therapies reduces the incidence of hepatocellular carcinoma (HCC). There has been some debate if IFN-free therapy

with direct-acting antivirals alters the risk for HCC. **AIM:** To investigate the HCC incidence in cirrhotic HCV patients who cleared HCV with direct-acting antivirals vs untreated controls. **METHODS:** We prospectively monitored 373 patients with chronic hepatitis C who received IFN-free therapies with direct-acting antiviral after January 2014. A retrospective control cohort of untreated cirrhotic patients was recruited out of 3715 HCV patients who were followed at our centre between 2007 and 2013, with similar HCC screening protocols. **RESULTS:** 158 direct-acting antiviral-treated and 184 control patients with liver cirrhosis were included in this analysis. The groups did not differ in gender and genotype distribution, severity of liver disease and prevalence of diabetes mellitus. Patients were followed up for a median of 440 (range 91-908) and 592 (range 90-1000) days. HCCs developed in 6 and 14 patients during follow-up, resulting in an incidence of 2.90 vs 4.48 HCCs per 100 person-years. In the direct-acting antiviral-treated group, there was no new case of HCC later than 450 days after treatment initiation. In multivariate analysis, higher MELD-Scores and AFP-levels were independently associated with HCC development. Transplant-free patient survival was similar in both groups. **CONCLUSIONS:** IFN-free direct-acting antiviral therapy of chronic hepatitis C does not alter the short-term risk for HCC in patients with liver cirrhosis. A reduced HCC incidence may become evident after more than 1.5 years of follow-up.

[Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection.](#) Dai CY1, Lin CY2, Tsai PC3, et al. J Chin Med Assoc. 2017 Dec 4. pii: S1726-4901(17)30298-8. doi: 10.1016/j.jcma.2017.06.018. [Epub ahead of print]

BACKGROUND: Health burdens of hepatocellular carcinoma (HCC) are emerging quickly in the world, including in Taiwan. Surgical resection has been recognized as the first-line treatment for early tumors. This study aimed to investigate the prognostic risk factors for mortality and recurrence rate in Taiwan, which has a high prevalence of chronic viral hepatitis. **METHODS:** A total of 397 HCC patients receiving tumor resection were consecutively examined in central Taiwan from 2008 to 2014. A hospital-based patient cohort was designed to collect serological markers to further assess liver function. We modified the Kaplan-Meier method according to the competing death risks for comparing recurrence and used multivariate Cox proportional hazard regression to adjust for significant risk factors. **RESULTS:** In addition to advanced fibrosis, tumor size ≥ 5 cm was significantly associated with higher mortality within the 5-year period when compared with < 5 cm (43.3% vs. 13.2%, $p < 0.0001$). Patients with tumor size ≥ 5 cm also easily progressed to early recurrence within two years when accounting for death as a competing risk (20.1% vs. 10.1%, $p = 0.01$). Higher AFP levels played a major role in further predicting higher mortality in those patients. We determined that there were a 4.5-fold and 2.2-fold higher mortalities in patients with size ≥ 5 cm/AFP ≥ 20 ng/mL and with size ≥ 5 cm/AFP < 20 ng/mL, respectively, when compared to patients with small tumors. **CONCLUSION:** Tumor size ≥ 5 cm might be a good predicting factor for death and early recurrence when considering death as a competing risk.