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

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Diabetes Mellitus is Associated With Higher Risk of Developing Decompensated Cirrhosis in Chronic Hepatitis C Patients.](#) Saeed MJ1, Olsen MA, Powderly WG, Presti RM. J Clin Gastroenterol. 2017 Jan;51(1):70-76.

GOALS: To investigate the association of diabetes with risk of decompensated cirrhosis in patients with chronic hepatitis C (CHC). **BACKGROUND:** Direct-acting antivirals are highly effective in treating CHC but very expensive. CHC patients at high risk of progression to symptomatic liver disease may benefit most from early treatment. **STUDY:** We conducted a retrospective cohort study using the 2006 to 2013 Truven Health Analytics MarketScan Commercial Claims and Encounters database including inpatient, outpatient, and pharmacy claims from private insurers. CHC and cirrhosis were identified using ICD-9-CM diagnosis codes; baseline diabetes was identified by diagnosis codes or antidiabetic medications. CHC patients were followed to identify decompensated cirrhosis. Multivariable Cox proportional hazards regression was used to model the risk of decompensated cirrhosis by baseline cirrhosis. **RESULTS:** There were 75,805 CHC patients with median 1.9 years follow-up. A total of 10,317 (13.6%) of the CHC population had diabetes. The rates of decompensated cirrhosis per 1000 person-years were: 185.5 for persons with baseline cirrhosis and diabetes, 119.8 for persons with cirrhosis and no diabetes, 35.3 for persons with no cirrhosis and diabetes, and 17.1 for persons with no cirrhosis and no diabetes. Diabetes was associated with increased risk of decompensated cirrhosis in persons with baseline cirrhosis (adjusted hazard ratio=1.4; 95% confidence interval, 1.3-1.6) and in persons without baseline cirrhosis (adjusted hazard ratio=1.9; 95% confidence interval, 1.7-2.1). **CONCLUSIONS:** In a privately insured US population with CHC, the adjusted risk of decompensated cirrhosis was higher in diabetic compared with nondiabetic patients. Diabetes status should be included in prioritization of antiviral treatment.

[Week 4-response predicts sustained virologic response to all-oral direct-acting antiviral-based therapy in cirrhotic patients with hepatitis C virus genotype 3 infection.](#) Pineda JA1, Morano-Amado LE2, Granados R3, et al. Clin Microbiol Infect. 2017 Jan 27. pii: S1198-743X(17)30005-8. doi: 10.1016/j.cmi.2016.12.034. [Epub ahead of print]

OBJECTIVE: The aim of this study was to determine the predictive capacity of response at treatment week (TW) 4 for the achievement of sustained virologic response 12 weeks after the scheduled end of therapy date (SVR12) to treatment against hepatitis C virus (HCV) genotype

(GT) 3-infection with all-oral direct-acting antiviral (DAA)-based regimens. **PATIENTS AND METHODS:** From a prospective multicohort study, HCV GT3-infected patients who completed a course of currently recommended DAA-based therapy at 33 Spanish hospitals and who had reached SVR12 evaluation timepoint were selected. TW4 HCV-RNA levels were categorized in target not detected (TND), below the lower limit of quantitation (LLOQTD) and \geq LLOQ. **RESULTS:** A total of 123 patients were included, 86 (70%) subjects received sofosbuvir/daclatasvir+/-ribavirin, 27 (22%) sofosbuvir/ledipasvir/ribavirin and 10 (8.1%) sofosbuvir/ribavirin, respectively. One-hundred and fourteen out of 123 (92.7%) patients presented SVR12 in an on-treatment approach, while 9/123 (7.3%) subjects relapsed, all of them had presented cirrhosis at baseline. In those who achieved TND, LLOQTD and \geq LLOQ, SVR12 was observed in 81/83 [98%; 95% confidence interval (CI): 91.5%-99.7%], 24/28 (85.7%; 95%CI: 67.3%-96%) and 9/12 (75%; 95%CI: 42.8%-94.5%), respectively; p (linear association)=0.001. Corresponding numbers for subjects with cirrhosis were: 52/54 (96.3%; 95%CI: 87.3%-95.5%), 14/18 (77.8%; 95%CI: 52.4%-93.6%) and 7/10 (70%; 95%CI: 34.8%-93.3%); p=0.004. **CONCLUSIONS:** TW4-response indicates the probability to achieve SVR12 to currently used DAA-based therapy in HCV genotype 3-infected individuals with cirrhosis. This finding may be useful to tailor treatment strategy in this setting.

[Efficacy of a 12-Week Simeprevir Plus Peginterferon/Ribavirin \(PR\) Regimen in Treatment-Naïve Patients with Hepatitis C Virus \(HCV\) Genotype 4 \(GT4\) Infection and Mild-To-Moderate Fibrosis Displaying Early On-Treatment Virologic Response.](#) Asselah T1, Moreno C2, Sarrazin C3, et al. PLoS One. 2017 Jan 5;12(1):e0168713. doi: 10.1371/journal.pone.0168713. eCollection 2017.

BACKGROUND: HCV GT4 accounts for up to 20% of HCV infections worldwide. Simeprevir, given for 12 weeks as part of a 24- or 48-week combination regimen with PR is approved for the treatment of chronic HCV GT4 infection. Primary study objectives were assessment of efficacy and safety of simeprevir plus PR in treatment-naïve patients with HCV GT4 treated for 12 weeks. Primary efficacy outcome was sustained virologic response 12 weeks post-treatment (SVR12). Additional objectives included investigation of potential associations of rapid virologic response and baseline factors with SVR12. **METHODS:** This multicentre, open-label, single-arm study (NCT01846832) evaluated efficacy and safety of simeprevir plus PR in 67 patients with HCV GT4 infection. Patients were treatment-naïve, aged 18-70 years with METAVIR F0-F2 fibrosis. Patients with early virologic response (HCV RNA <25 IU/mL [detectable/undetectable in IL28B CC patients or undetectable in IL28B CT/TT patients] at Week 2 and undetectable at Weeks 4 and 8) were eligible to stop all treatment at the end of Week 12, otherwise PR therapy was continued to Week 24. **RESULTS:** Of 67 patients treated, 34 (51%) qualified for 12-week treatment including all but one patient with IL28B CC genotype (14/15). All patients in the 12-week group had undetectable HCV RNA at end of treatment, and 97% (33/34) achieved SVR12. No new safety signals with simeprevir plus PR were identified. The proportion of patients experiencing Grade 3-4 adverse events was lower in the 12-week group than in the 24-week group. **CONCLUSIONS:** Our findings on simeprevir plus PR therapy shortened to 12 weeks in patients with HCV GT4 infection with favourable baseline characteristics and displaying early on-treatment virologic response are encouraging. No new safety signals were associated with simeprevir plus PR in this study.

[New resistance-associated substitutions and failure of dual oral therapy with daclatasvir and asunaprevir.](#) Mawatari S1, Oda K2, Tabu K2, et al. J Gastroenterol. 2017 Jan 11. doi: 10.1007/s00535-016-1303-0. [Epub ahead of print]

BACKGROUND: Daclatasvir (DCV) and asunaprevir (ASV) combination therapy has been primarily used in patients without NS5A L31 or Y93 resistance-associated substitutions (RASs) before treatment. We examined the characteristics of patients without these baseline RASs who did not achieve hepatitis C virus eradication with DCV and ASV combination therapy and identified new baseline NS5A RASs that are closely associated with failure of combination therapy. **METHODS:** Three hundred thirty-five patients with hepatitis C virus genotype 1 infection with no NS5A L31, NS5A Y93, and NS3 D168 RASs before DCV and ASV combination therapy and no history of protease inhibitor therapy were enrolled. All RASs were evaluated by direct sequencing. **RESULTS:** Sustained virologic response at 12 weeks (SVR12) was achieved in 297 patients (89%). Patients with NS5A Q24, L28, and/or R30 RASs or concomitant NS5A F37 and Q54 RASs had a significantly lower SVR12 rate than patients without these RASs (70% vs 92%, $p < 0.001$ and 79% vs 92%, $p = 0.002$ respectively). Multivariate analysis showed that NS5A Q24, L28, and/or R30 RASs and concomitant NS5A F37 and Q54 RASs were significantly associated with virologic failure. The SVR12 rate in patients without NS5A Q24, L28, and/or R30 RASs and concomitant NS5A F37 and Q54 RASs was 96.2% (202/210). **CONCLUSIONS:** In patients without NS5A L31 or Y93 RASs, the presence of NS5A Q24, L28, and/or R30 RASs and concomitant NS5A F37 and Q54 RASs at the baseline was associated with failure of DCV and ASV combination therapy. The coexistence of baseline RASs other than NS5A L31 and Y93 may affect the therapeutic effectiveness of DCV and ASV combination therapy.

[Simeprevir and daclatasvir for 12 or 24 weeks in treatment-naïve patients with HCV genotype 1b and advanced liver disease.](#) Hézode C1, Almasio PL2, Bourgeois S3, et al. Liver Int. 2017 Jan 30. doi: 10.1111/liv.13376. [Epub ahead of print]

BACKGROUND & AIMS: We investigated the efficacy and safety of simeprevir (SMV) plus daclatasvir (DCV) in treatment-naïve patients with chronic, genotype (GT) 1b hepatitis C virus (HCV) infection and advanced liver disease, excluding patients with pre-defined NS5A resistance-associated substitutions (RAS) **METHODS:** This phase II, open-label, single-arm, multicentre study included patients aged ≥ 18 years with advanced fibrosis or compensated cirrhosis (METAVIR F3/4). Patients with NS5A-Y93H or L31M/V RAS at screening were excluded. SMV (150 mg) + DCV (60 mg) once daily was administered for 12 or 24 weeks; treatment could be extended to 24 weeks prior to or at the Week 12 visit. Primary efficacy endpoint was sustained virologic response 12 weeks after end of treatment (SVR12) **RESULTS:** A total of 106 patients were treated; 27% patients were aged > 65 years, 39% had cirrhosis, 53% had eGFR 30-89 mL/min, 14% had diabetes, and 38% had arterial hypertension. Overall, 42/106 received 12 weeks of treatment and 64/106 received 24 weeks of treatment. Ninety-seven (92%) patients achieved SVR12. Reasons for failure were viral breakthrough (VBT) ($n=7$) at Weeks 4 to 16, early treatment discontinuation ($n=1$) and viral relapse ($n=1$). Seventy-four (70%) patients had ≥ 1 adverse event (AE) during treatment, including six (6%) patients with ≥ 1 SAE. Three (3%) patients discontinued treatment due to AEs **CONCLUSIONS:** SMV+DCV demonstrated strong antiviral activity and was well-tolerated in patients with HCV GT1b infection, advanced liver disease and a high prevalence of comorbidities. However, VBT occurred in seven patients, making this regimen unsatisfactory. This article is protected by copyright. All rights reserved.

[Glecaprevir and Pibrentasvir for 12 Weeks for HCV Genotype 1 Infection and Prior Direct-acting Antiviral Treatment.](#) Poordad F1, Felizarta F2, Asatryan A3, et al. *Hepatology*. 2017 Jan 27. doi: 10.1002/hep.29081. [Epub ahead of print]

Although direct-acting antiviral (DAA) therapies for chronic hepatitis C virus (HCV) infection have demonstrated high rates of sustained virologic response, virologic failure may still occur, potentially leading to the emergence of viral resistance, which can decrease the effectiveness of subsequent treatment. Treatment options for patients who failed previous DAA-containing regimens, particularly those with NS5A inhibitors, are limited, and remain an area of unmet medical need. This phase 2, open-label study (MAGELLAN-1) evaluated the efficacy and safety of glecaprevir (GLE) + pibrentasvir (PIB) ± ribavirin (RBV) in HCV genotype 1-infected patients with prior virologic failure to HCV DAA-containing therapy. A total of 50 non-cirrhotic patients were randomized to three arms: 200 mg GLE + 80 mg PIB (Arm A), 300 mg GLE + 120 mg PIB with 800 mg once-daily RBV (Arm B), or 300 mg GLE + 120 mg PIB without RBV (Arm C). By intent-to-treat analysis, sustained virologic response at post-treatment week 12 (SVR12) was achieved in 100% (6/6, 95% CI 61 - 100), 95% (21/22, 95% CI 78 - 99), and 86% (19/22, 95% CI 67 - 95) of patients in Arms A, B, and C, respectively. Virologic failure occurred in no patients in Arm A, and 1 patient each in Arms B and C (two patients lost to follow-up in Arm C). The majority of adverse events were mild in severity; no serious adverse events related to study drug and no relevant laboratory abnormalities in alanine aminotransferase, total bilirubin, or hemoglobin, were observed.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Hepatitis C Virus Induces MDSCs-Like Monocytes through TLR2/PI3K/AKT/STAT3 Signaling.](#) Zhai N1, Li H1, Song H1, Yang Y1, Cui A1, Li T1, Niu J2, Crispe IN1,3, Su L1,4, Tu Z1,2. *PLoS One*. 2017 Jan 23;12(1):e0170516. doi: 10.1371/journal.pone.0170516. eCollection 2017.

BACKGROUND AND AIMS: Recent studies reveal the accumulation of myeloid derived suppressor cells (MDSCs) in human peripheral blood mononuclear cells (PBMCs) following HCV infection, which may facilitate and maintain HCV persistent infection. The mechanisms by which HCV induces MDSCs are poorly understood. In the present study, we investigated the mechanisms by which HCV induces MDSCs that lead to suppression of T cell proliferation and expansion of CD4⁺Foxp3⁺ regulatory T cells. **METHODS:** Purified monocytes from healthy donors were cultured with HCV core protein (HCVc) or cell culture-derived HCV virions (HCVcc), and characterized the phenotype and function of these monocytes by flow cytometry, quantitative PCR, ELISA and western blot assays. In addition, peripheral blood from healthy donors and chronic HCV infected patients was collected, and MDSCs and CD4⁺CD25⁺CD127⁻ regulatory T cells were analyzed by flow cytometry. **RESULTS:** Both HCVc and HCVcc induced expression of IDO1, PD-L1 and IL-10, and significantly down-regulated HLA-DR expression in human monocytes. HCVc-treated monocytes triggered CD4⁺Foxp3⁺ Tregs expansion, and inhibited autologous CD4⁺ T cell activation in an IDO1-dependent fashion. Our results showed that HCV virions or HCV core proteins induced MDSC-like suppressive monocytes via the TLR2/PI3K/AKT/STAT3 signaling pathway. Monocytes derived from patients with chronic HCV infection displayed MDSCs characteristics. Moreover, the percentages of CD14⁺ MDSCs and CD4⁺CD25⁺CD127⁻ Tregs in chronic HCV infected patients were significantly higher than healthy individuals, and the frequency of MDSCs

correlated with CD4+CD25+CD127- Tregs. **CONCLUSIONS:** HCV induced MDSC-like suppressive monocytes through TLR2/PI3K/AKT/STAT3 signaling pathway to induce CD4+Foxp3+ regulatory T cells and inhibit autologous CD4+ T cell activation. It will be of interest to test whether antagonizing suppressive functions of MDSCs could enhance immune responses and virus control in chronic HCV infection.

Functional Polymorphism in the Interleukin 6 (IL6) Gene with Respect to Depression Induced in the Course of Interferon- α and Ribavirin Treatment in Chronic Hepatitis

Patients. Frydecka D1, Pawłowski T2, Pawlak D3, Małyszczak K2,4. Arch Immunol Ther Exp (Warsz). 2017 Jan 12. doi: 10.1007/s00005-016-0441-7. [Epub ahead of print]

Interleukin (IL)-6 is a multifactorial cytokine known to be increased in patients with chronic hepatitis C (CHC) and to be predictive of depression incidence. The aim of the study was to explore the association between IL6 gene C-174G polymorphism and depressive symptom severity in the longitudinal study design following the course of pegylated interferon/ribavirin treatment in CHC patients. In our study, we included 62 CHC subjects. They were assessed using present state examination, Beck Depression Inventory (BDI) and Montgomery Åsberg Depression Rating Scale (MADRS) at weeks 0, 3, 5, 9, 13, 24 and 24 weeks after the end of treatment. The risk of depression was associated with higher baseline MADRS score and BDI score. Interestingly, when stratified by IL6 C-174G polymorphism, higher baseline depressive symptom severity measured by MADRS and BDI predicted higher risk of depression in the course of antiviral treatment only in high IL-6 producers-G allele carriers (patients with GG and CG genotypes) ($p = 0.004$, $p = 0.00008$, respectively). There is interaction between severity of baseline depressive symptoms at the beginning of antiviral therapy and IL6 gene C-174G polymorphism leading to increased risk for the development of depressive episode in CHC patients in the course of antiviral treatment.

HIV/HCV COINFECTION

Mx1, OAS1 and OAS2 polymorphisms are associated with the severity of liver disease in HIV/HCV-coinfected patients: A cross-sectional study. García-Álvarez M1, Berenguer J2,3, Jiménez-Sousa MA1, et al. Sci Rep. 2017 Jan 31;7:41516. doi: 10.1038/srep41516.

The mechanisms involved in the chronic hepatitis C progression are incompletely understood. The aim was to analyze the association between 2'5'oligoadenylate synthetase 1,2 and 3 (OAS1-3) and myxovirus resistance proteins 1 (Mx1) polymorphisms and severity of liver disease in human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfecting patients. We performed a cross-sectional study in 219 patients that underwent a liver biopsy. DNA genotyping for Mx1 (rs469390), OAS1 (rs2285934), OAS2 (rs1293762) and OAS3 (rs2010604) was performed by using GoldenGate assay. The outcome variables on liver biopsy were: (i) significant fibrosis ($F \geq 2$); (ii) moderate activity grade ($A \geq 2$). Additive model of inheritance for genetic association test was used. The likelihood of having significant fibrosis ($F \geq 2$) was lower in patients carrying OAS2 rs1293762 A allele [adjusted odds ratio (aOR) = 0.51; $p = 0.040$]. Besides, the likelihood of having moderate activity grade ($A \geq 2$) was higher in patients carrying Mx1 rs464397 C allele (aOR = 1.63; $p = 0.028$) and Mx1 rs469390 G allele (aOR = 1.97; $p = 0.005$), while it was lower in patients carrying OAS1 rs2285934 A allele (aOR = 0.64; $p = 0.039$) and OAS2 rs1293762 A allele (aOR = 0.41; $p = 0.009$). In conclusion, Mx1 and

OAS1-2 polymorphisms were associated with the severity of liver disease in HIV/HCV-coinfected patients, suggesting a significant role in the progression of hepatic fibrosis.

[Association of serum albumin and aspartate transaminase with 5-year all-cause mortality in HIV/hepatitis C virus coinfection and HIV mono-infection.](#) Scherzer R1, Heysmsfield SB, Rimland D, et al. AIDS. 2017 Jan 2;31(1):71-79.

OBJECTIVE: Liver disease markers have been associated with mortality in HIV-infected individuals in the modern era of effective antiretroviral therapy. Our objective was to determine which markers are most predictive of mortality in HIV-mono-infected and HIV/hepatitis C virus (HCV)-coinfected persons. **RESEARCH DESIGN AND METHODS:** We measured serum albumin, total protein, calculated globulin, aspartate transaminase (AST), and alanine transaminase in 193 HIV/HCV-coinfected and 720 HIV-mono-infected persons in the study of Fat Redistribution and Metabolic Change in HIV Infection. We evaluated associations of each marker with 5-year, all-cause mortality, adjusting for cardiovascular, HIV-related factors, inflammation, renal disease, muscle, and adiposity. **RESULTS:** After 5 years of follow-up, overall mortality was 21% in HIV/HCV-coinfected and 12% in HIV-mono-infected participants. After multivariable adjustment, lower albumin and higher AST were independently associated with increased mortality. Lower albumin was associated with 49% increased odds of mortality overall [per 0.5 g/dl decrease, 95% confidence interval (CI): 1.2-1.9]; the association was stronger in HIV/HCV-coinfected [odds ratio (OR)=2.1, 95% CI: 1.4-3.2] vs. HIV-mono-infected (OR=1.3, 95% CI: 1.0-1.7; HCV-by-albumin interaction: P=0.038). Higher AST was associated with 41% increased odds of mortality (per AST doubling; 95% CI: 1.1-1.8); associations were much stronger among HIV/HCV-coinfected (OR=2.5, 95% CI: 1.5-4.1) than HIV-mono-infected (OR=1.1, 95% CI: 0.8-1.5; HCV-by-AST interaction: P=0.0042). **CONCLUSION:** Lower serum albumin and higher AST appear to be important mortality risk factors in HIV/HCV-coinfection, but much less so in HIV-mono-infected individuals. The association of low albumin with mortality may reflect its role as a negative acute phase response protein. AST levels do not appear to be useful in predicting mortality in HIV-mono-infection and should be considered primarily in the context of HCV-coinfection.

[Eradication of HCV and non-liver-related non-AIDS-related events in HIV/HCV coinfection.](#) Berenguer J1,2, Rodríguez-Castellano E3, Carrero A1,2, et al. Hepatology. 2017 Jan 21. doi: 10.1002/hep.29071. [Epub ahead of print]

We assessed non-liver-related non-AIDS-related (NLR-NAR) events and mortality in a cohort of HIV/HCV-coinfected patients treated with interferon and ribavirin between 2000 and 2008. The censoring date was May 31, 2014. Cox regression analysis was performed to assess the adjusted hazard rate (HR) of overall death in responders and non-responders. Fine and Gray regression analysis was conducted to determine the adjusted sub-hazard rate (sHR) of NLR deaths and NLR-NAR events considering death as the competing risk. The NLR-NAR events analyzed included diabetes mellitus, chronic renal failure, cardiovascular events, NLR-NAR cancer, bone events, and non-AIDS-related infections. The variables for adjustment were age, sex, prior AIDS, HIV-transmission category, nadir CD4+ T-cell count, antiretroviral therapy, HIV-RNA, liver fibrosis, HCV genotype, and exposure to specific anti-HIV drugs. Of the 1,625 patients included, 592 (36%) had a sustained viral response (SVR). After a median five-year follow-up, SVR was found to be associated with a significant decrease in the hazard of diabetes mellitus (sHR 0.57 [95% CI, 0.35 - 0.93] P= .024) and decline in the hazard of chronic renal failure close

to the threshold of significance (sHR 0.43 [95% CI, 0.17 - 1.09], P=.075). **CONCLUSION:** Our data suggest that eradication of HCV in coinfecting patients is associated not only with a reduction in the frequency of death, HIV progression, and liver-related events, but also with a reduced hazard of diabetes mellitus and possibly of chronic renal failure. These findings argue for the prescription of HCV therapy in coinfecting patients regardless of fibrosis stage. This article is protected by copyright. All rights reserved.

Endosomal toll-like receptor gene polymorphisms and susceptibility to HIV and HCV co-infection - Differential influence in individuals with distinct ethnic background.

Valverde-Villegas JM1, Dos Santos BP2, de Medeiros RM1, Mattevi VS3, Lazzaretti RK4, Sprinz E4, Kuhmmer R4, Chies JA5. Hum Immunol. 2017 Feb;78(2):221-226. doi: 10.1016/j.humimm.2017.01.001. Epub 2017 Jan 4.

The genetic background of human populations can influence the susceptibility and outcome of infection diseases. Toll-like receptors (TLRs) have been previously associated with susceptibility to human immunodeficiency virus (HIV) infection, disease progression and hepatitis C, virus (HCV) co-infection in different populations, although mostly in Europeans. In this study, we investigated the genetic role of endosomal TLRs on susceptibility to HIV infection and HCV co-infection through the analysis of TLR7 rs179008, TLR8 rs3764880, TLR9 rs5743836 and TLR9 rs352140 polymorphisms in 789 Brazilian individuals (374 HIV+ and 415 HIV-), taking into account their ethnic background. Amongst the 357 HIV+ individuals with available data concerning HCV infection, 98 were positive. In European descendants, the TLR9 rs5743836 C carriers displayed a higher susceptibility to HIV infection [dominant, Odds Ratio (OR)=1.53; 95% CI: 1.05-2.23; P=0.027]. In African descendants, TLR9 rs5743836 CT genotype was associated with protection to HIV infection (codominant, OR=0.51; 95% CI: 0.30-0.87; P=0.013). Also, the TLR9 rs352140 AA variant genotype was associated with susceptibility to HIV+/HCV+ co-infection in African descendants (recessive, OR=2.92; 95% CI: 1.22-6.98, P=0.016). These results are discussed in the context of the different ethnic background of the studied individuals highlighting the influence of this genetic/ethnic background on the susceptibility to HIV infection and HIV/HCV co-infection in Brazilian individuals.

APRI and FIB4 as effective markers for monitoring esophageal varices in HIV/HCV co-infected patients due to contaminated blood products for hemophilia.

Natsuda KI, Takatsuki M1, Tanaka T1, et al. Hepatol Res. 2017 Jan 28. doi: 10.1111/hepr.12866. [Epub ahead of print]

AIM: We examined the feasibility of the aspartate transaminase (AST)-platelet ratio index (APRI) and FIB4, which are well-established markers for liver fibrosis, as indicators for monitoring esophageal varices in patients who were co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) due to contaminated blood products for hemophilia in Japan. **PATIENTS AND METHODS:** Forty-three HIV/HCV co-infected patients were enrolled. All were hemophilic men (median age 41, range 29-66 yrs). We analyzed the correlations between fibrosis indices (APRI, FIB4) and various liver function tests, fibrosis markers, liver stiffness measured by acoustic radiation force impulse (ARFI) elastography, and the findings of gastrointestinal endoscopy. **RESULTS:** APRI and FIB4 were well correlated with several of the factors related to liver fibrosis and the existence of esophageal varices in the patients. The cut-off values for detecting esophageal varices estimated as the area under the receiver operating characteristic curve were 0.85 for APRI and 1.85 for FIB4. **CONCLUSION:** In patients co-infected with HIV/HCV due to contaminated blood products for hemophilia, APRI

and FIB4 are effective for monitoring esophageal varices, even among patients who are apparently doing well with good liver function as Child-Pugh grade A.

Hepatitis Delta and HIV Infection. Soriano V1, Sherman KE, Barreiro P. AIDS. 2017 Jan 24. doi: 10.1097/QAD.0000000000001424. [Epub ahead of print]

Viral liver diseases are frequent co-morbidities and major contributors to death in HIV-positive individuals on antiretroviral therapy. Whereas cure of hepatitis C and control of hepatitis B with antivirals avert liver disease progression in most HIV-coinfected patients, the lack of satisfactory treatment for hepatitis delta virus (HDV) infection remains a major threat for developing cirrhosis and liver cancer in this population. In the European Union and North America, sexual contact has replaced injection drug use as major transmission route for HDV in HIV-positive persons. Peginterferon alpha is the only approved HDV therapy; however, sustained HDV-RNA clearance is achieved by less than 25%. The recent discovery of NTCP as key HBV and HDV cell entry receptor has opened the door to a new therapeutic era. Indeed, promising results have been released using Myrcludex-B, a NTCP inhibitor. More encouraging are data with new classes of HDV blockers, such as prenylation inhibitors (i.e., Lonafarnib) and nucleic acid polymers. At this time, sustained suppression of HDV replication is the primary goal of HDV therapy, since it is associated with normalization of liver enzymes and histological improvement. Of note, the use of specific antivirals for HDV must be given along with anti-HBV agents, to prevent HBV rebounds following removal of viral interference. The lack of persistent forms of HDV-RNA could provide a unique opportunity for curing hepatitis delta, even without eliminating HBV cccDNA. Ultimately, suppression of HDV replication along with HBsAg clearance once drugs are off would be the best reflect of hepatitis delta cure.

Depression in HIV and HCV co-infected patients: a systematic review and meta-analysis.

Fialho R1,2, Pereira M3, Rusted J1, Whale R2,4. Psychol Health Med. 2017 Jan 19:1-16. doi: 10.1080/13548506.2017.1280177. [Epub ahead of print]

The aim of this study was to carry out a systematic review and meta-analysis of the differences in the prevalence of depression and presence of depressive symptoms between HIV/HCV co-infection, HIV mono-infection, and hepatitis C virus (HCV) mono-infection. A systematic electronic search of bibliographic databases was performed to locate articles published from the earliest available online until December 2014. Outcomes of depression were based on clinical interviews and validated self-reported measures of depression/depressive symptoms. Of the 188 records initially screened, 29 articles were included in the descriptive systematic review and six were included in the meta-analysis. The meta-analytic results indicated that, as measured by self-reported measures of depression, HIV/HCV co-infected patients were significantly more likely to report depressive symptoms than either HIV (SMD = .24, 95% CI: .03-.46, p = .02) or HCV mono-infected (SMD = .55, 95% CI: .17-.94, p = .005) patients. The variability of the results of the reviewed studies, largely dependent on the samples' characteristics and the methods of assessment of depression, suggests that a clear interpretation of how depression outcomes are affected by the presence of HIV/HCV co-infection is still needed. Failing to diagnose depression or to early screen depressive symptoms may have a significant impact on patients' overall functioning and compromise treatments' outcomes.

[Assessment of Abilities of Gastroenterology Fellows to Provide Information to Patients With Liver Disease.](#)

Chaudhary N1, Lucero C2, Villanueva G2, Poles M2, Gillespie C3, Zabar S3, Weinschel E2. Clin Gastroenterol Hepatol. 2017 Jan 19. pii: S1542-3565(17)30054-X. doi: 10.1016/j.cgh.2016.12.037. [Epub ahead of print]

PURPOSE: Patient education is critical in ensuring patient compliance and good health outcomes. Fellows must be able to effectively communicate with their patients, delivering enough information for the patient to understand their medical problem and maximize patient compliance. We created an objective structured clinical examination (OSCE) with four liver disease cases to assess fellows' knowledge and ability to inform standardized patients about their clinical condition. **METHODS:** We developed four cases highlighting different aspects of liver disease and created a four station OSCE: hepatitis B, acute hepatitis C, new diagnosis of cirrhosis, and an end-stage cirrhotic non transplant candidate. The standardized patient (SP) with hepatitis B was minimizing the fact that she could not read English. The acute hepatitis C SP was a nursing student who is afraid that having hepatitis C might jeopardize her career. The SP with the new diagnosis of alcoholic cirrhosis needed to stop drinking, and the end-stage liver disease patient had to grapple with his advanced directives. Twelve fellows from four GI training programs participated. Our focus was to assess the fellows' knowledge about liver diseases and the ACGME competencies of health literacy, shared decision making, advanced directives and goals of care. The goal for the fellows was to communicate effectively with the SPs, and acknowledge that each patient had an emotionally charged issue to overcome. The SPs used a checklist to rate fellow's performance. Faculty and the SPs observed the cases and provided feedback. The fellows were surveyed on their performance regarding the case. **RESULTS:** The majority of fellows were able to successfully summarize findings and discuss a plan with the patient in the new diagnosis of cirrhosis (76.92%) and hepatitis C case (100%), but were less successful in the hepatitis B (30.77%) and end-of-life case (41.67%). Overall, a small percentage of fellows reflected that they did a good job (22-33%), except at the end-of-life case (67%). The fellows' greatest challenge was trying to cover a lot of information in a single outpatient visit. **CONCLUSION:** Caring for patients with liver diseases can be complex and time consuming. The patients and fellows' observations were discordant in several areas: for example. the fellows believed they excelled in the end-of-life case, but the SP thought only a small percentage of fellows were able to successfully summarize and discuss the plan. This discrepancy and others highlight important areas of focus in training programs. OSCEs are important to help the fellows facilitate striking the right balance of information delivery and empathy, and this will lead to better patient education, compliance, rapport, and satisfaction.

[Eight- or 12-Week Treatment of Hepatitis C with Ledipasvir/Sofosbuvir: Real-World Experience in a Large Integrated Health System.](#)

Lai JB1,2, Witt MA1, Pauly MP2, Ready J2, Allerton M1, Seo S2, Witt DJ3. Drugs. 2017 Jan 11. doi: 10.1007/s40265-016-0684-y. [Epub ahead of print]

BACKGROUND: Second-generation direct-acting antiviral agents are integral to treatment of hepatitis C (HCV) infection. Eight-week courses of ledipasvir/sofosbuvir (LDV/SOF) have been

supported in some studies, but data are limited on efficacy in real-world use. Controversy exists regarding applicability of clinical trials to real-world effectiveness. We report virologic responses of patients with HCV genotype 1 infection receiving LDV/SOF for 8 or 12 weeks in a large integrated healthcare system. **METHODS:** All patients receiving LDV/SOF, without ribavirin, were identified from pharmacy records, and outcomes are reported. Only treatment-naïve patients without evidence of cirrhosis and hepatitis C viral load less than 6 million IU/ml were candidates for 8-week therapy. Treatment was at clinician discretion, but delivered by a multidisciplinary team and reviewed for appropriateness and adherence to these criteria by one of the authors, all experienced in hepatitis C treatment. Sustained viral response at 12 weeks (SVR 12) was contrasted between those receiving 8 and those receiving 12 weeks of treatment. **RESULTS:** Completed prescriptions for LDV/SOF, without ribavirin, as of 30 September 2015 were identified in 1021 patients. Five patients discontinued therapy due to medical reasons and 35 had incomplete follow-up viral load data, thus there were 981 evaluable patients: 377 treated for 8 weeks and 604 treated for 12 weeks. SVR 12 was virtually identical at 93.6 and 93.5%, respectively. Baseline characteristics differed between the two groups, as only treatment-naïve, non-cirrhotic, non-HIV-infected patients were eligible for an 8-week course of therapy. **CONCLUSIONS:** Eight-week courses of LDV/SOF are comparable to 12-week courses in real-world use among selected patients supported by a multidisciplinary team.

[Engagement in the Hepatitis C Care Cascade Among Homeless Veterans, 2015.](#) Noska AJ1, Belperio PS2, Loomis TP2, O'Toole TP1, Backus LI2. Public Health Rep. 2017 Jan 1:33354916689610. doi: 10.1177/0033354916689610. [Epub ahead of print]

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The Veterans Health Administration (VHA) is the largest provider of hepatitis C virus (HCV) care nationally and provides health care to >200,000 homeless veterans each year. We used the VHA's Corporate Data Warehouse and HCV Clinical Case Registry to evaluate engagement in the HCV care cascade among homeless and non-homeless veterans in VHA care in 2015. We estimated that, among 242,740 homeless veterans in care and 5,424,712 non-homeless veterans in care, 144,964 (13.4%) and 188,156 (3.5%), respectively, had chronic HCV infection. Compared with non-homeless veterans, homeless veterans were more likely to be diagnosed with chronic HCV infection and linked to HCV care but less likely to have received antiviral therapy despite comparable sustained virologic response rates. Homelessness should not necessarily preclude HCV treatment eligibility with available all-oral antiviral regimens.

[The impact of antiviral therapy for hepatitis C on the quality of life: a perspective.](#)

Dusheiko G1. Liver Int. 2017 Jan;37 Suppl 1:7-12. doi: 10.1111/liv.13292.

Instruments to assess the impact of hepatitis C virus infection on health and measurements of reported outcomes in patients (health-related quality of life [HRQOL]) are not frequently used to assign priority for treatment. Several systematic reviews have been performed that provide a comprehensive analysis to help understand patient reported outcomes (PROs) with direct acting antiviral treatment. Clinical trials with direct acting antivirals (DAAs) provide an important opportunity to assess PROs without interferon or ribavirin. Significant improvement in quality of life parameters have been noted with DAA therapy. The results show improvement in HRQOL indices when interferon-free and particularly interferon and ribavirin-free treatments are

compared to interferon and ribavirin treatment. Improvements in HRQOL indices are an encouraging aspect of the cure of chronic hepatitis C. It is unclear whether these measurable HRQOL improvements can be translated into a net benefit improvement in work productivity and a social dimension that is significant enough to convince payers of the added value of early and more widespread treatment.

[Against the Odds: Syringe Exchange Policy Implementation in Indiana.](#) Meyerson BE1, Lawrence CA2, Miller L2, Gillespie A3, Raymond D4, Kelley K5, Shannon DJ2. AIDS Behav. 2017 Jan 20. doi: 10.1007/s10461-017-1688-7. [Epub ahead of print]

Indiana recently passed legislation allowing local governments to establish syringe exchanges. While the effectiveness of syringe exchange programming is established, there is a dearth of studies about associated policy adoption and implementation. This study documents the experiences of 24 Indiana counties engaged in the process of establishing syringe exchange programming under new state law. A mixed method, qualitative, exploratory case study was conducted from May 2015 to April 2016. We observed rapid and widespread policy adoption interest, and yet counties reported significant policy ambiguity, epidemiologic and resource capacity issues. The emergence of health commons involving information and tangible resource sharing networks allowed institutional rearrangement in the midst of resource scarcity; however, such rearrangement appeared to be a central threat to policy adoption and implementation given state structural barriers. The emerging commons could be a critical policy success factor, as it would achieve efficiencies not possible in the current resource environment, and can help achieve institutional rearrangement for the improvement of population health. Several recommendations for improvement are offered.

[Point-of-care testing \(POCT\) in molecular diagnostics: Performance evaluation of GeneXpert HCV RNA test in diagnosing and monitoring of HCV infection.](#) Gupta E1, Agarwala P2, Kumar G2, Maiwall R2, Sarin SK2. J Clin Virol. 2017 Jan 29;88:46-51. doi: 10.1016/j.jcv.2017.01.006. [Epub ahead of print]

BACKGROUND: Molecular testing at the point-of-care may turn out to be game changer for HCV diagnosis and treatment monitoring, through increased sensitivity, reduced turnaround time, and ease of performance. One such assay GeneXpert® has recently been released.

OBJECTIVES: Comparative analysis between performances of GeneXpert® and Abbott HCV-RNA was done. **STUDY DESIGN:** 174 HCV infected patients were recruited and, one time plasma samples from 154 patients and repeated samples from 20 patients, obtained at specific treatment time-points (0, 4, 12 and 24) weeks were serially re-tested on Xpert®. **RESULTS:** Genotype 3 was the commonest, seen in 80 (66%) of the cases, genotype 1 in 34 (28.3%), genotype 4 in 4 (3.3%) and genotypes 2 and 5 in 1 (0.8%) each. Median HCV RNA load was 4.69 log₁₀ (range: 0-6.98log₁₀) IU/ml. Overall a very good correlation was seen between the two assays (R²=0.985), concordance of the results between the assays was seen in 138 samples (89.6%). High and low positive standards were tested ten times on Xpert® to evaluate the precision and the coefficient of variation was 0.01 for HPC and 0.07 for the LPC. Monitoring of patients on two different regimes of treatment, pegylated interferon plus ribavirin and sofosbuvir plus ribavirin was done by both the systems at baseline, 4, 12 and 24 weeks. Perfect correlation between the assays in the course of therapy at different treatment time- point in genotypes 3 and 1 was seen. **CONCLUSION:** The study demonstrates excellent performance of the Xpert® HCV assay in viral load assessment and in treatment course monitoring consistency.

[Characterization and Management of Patients with Heroin versus Non-Heroin Opioid Overdoses: Experience at an Academic Medical Center.](#) Morizio KM1, Baum RA2, Dugan A3, Marin JE3, Bailey AM2. *Pharmacotherapy*. 2017 Jan 18. doi: 10.1002/phar.1902. [Epub ahead of print]

STUDY OBJECTIVES: To characterize the differences between patients who had heroin and non-heroin opioid overdoses and to determine whether there were any significant differences in their management with regard to the naloxone use. **DESIGN:** Retrospective cohort study. **SETTING:** Large, academic medical center. **PATIENTS:** A total of 923 patients admitted to the medical center who were identified for overdose by heroin or other opiate-related narcotics between January 2010 and September 2015; 480 patients experienced a non-heroin opioid overdose event, and 443 patients experienced a heroin overdose event. **MEASUREMENTS AND MAIN RESULTS:** Patients presenting with heroin overdose tended to be younger and male, with higher rates of hepatitis C virus infection compared with those presenting with non-heroin opioid overdose ($p<0.05$). Patients in the heroin group were also more likely to have a previous overdose event, history of injection drug use, and history of prescription opioid abuse compared with the non-heroin group ($p<0.05$). Those presenting with heroin overdose were more likely to receive naloxone in the pre-hospital setting ($p<0.05$) but were less likely to receive naloxone once admitted ($p<0.05$). Patients with non-heroin opioid overdoses required more continuous infusions of naloxone ($p<0.05$) and admission to the intensive care unit ($p<0.05$). Of all 923 patients, 178 (19.3%) had a repeat admission for any reason, and 70 (7.6%) were readmitted over the course of the study period for another overdose event with the same drug. The proportion of patients presenting with a heroin overdose steadily increased from 2010 to 2015 and the number of patients presenting to the emergency department with non-heroin opioid overdoses steadily decreased. As rates of heroin overdose increased each year, the incidence of HCV infection increased dramatically. **CONCLUSION:** This study indicates that the incidence of heroin overdoses has significantly increased over the last several years, and the rates of hepatitis C virus infection 4-fold since the start of the study period. Patients admitted for non-heroin opioid overdose were more likely to be admitted to the hospital and intensive care unit compared with those admitted for heroin overdose. The rise in overdose events only further illustrates that there is a gap in our understanding of the cycle of addiction, drug abuse, and overdose events.

[Pegylated interferon \$\alpha\$ /ribavirin therapy enhances bone mineral density in children with chronic genotype 4 HCV infection.](#) Megahed A1, Salem N2, Fathy A3,4, Barakat T1, Alsayed MA1, Mabood SA5, Zalata KR6,7, Abdalla AF1. *World J Pediatr*. 2017 Jan 27. doi: 10.1007/s12519-017-0013-x. [Epub ahead of print]

BACKGROUND: The impact of chronic hepatitis C (CHC) on bone mineral density (BMD) has been well studied in adults with a relative paucity of data in children, especially concerning effect of treatment with pegylated interferon (PEG-IFN) plus ribavirin (RV). In the current work, we assessed prospectively changes in BMD in children with CHC before, during, and after treatment. **METHODS:** Forty-six consecutive children with noncirrhotic genotype 4 CHC were subjected to dual-energy X-ray absorptiometry at baseline, 24 weeks, 48 weeks of therapy and 24 weeks after treatment. BMD, bone mineral content (BMC), and Z score of lumbar spine (L2-L4) were reported. Tanner pubertal stage, viral load, liver function tests, serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and liver histopathology were assessed in all

included children. **RESULTS:** Thirty (65.2%) patients had normal BMD, 10 (21.7%) were at risk for low BMD, and 6 (13.1%) had low BMD for chronological age. Patients with low BMD were significantly older ($P=0.001$), with higher frequency of delayed puberty than other groups ($P=0.002$). Baseline densitometric parameters (BMD & BMC) were significantly positively correlated with patients' age, weight, height, body mass index and hemoglobin level; while they were insignificantly correlated with basal viral load, histopathology activity index and fibrosis score. Densitometric parameters improved significantly on PEG-IFN plus RV treatment, this improvement was found to be sustainable 24 weeks after therapy. **CONCLUSIONS:** Low BMD is detectable in a proportion of CHC children. Antiviral therapy leads to a sustainable increase in BMD.

[Persistent neuropsychiatric impairment in HCV patients despite clearance of the virus?!](#)

Dirks M1, Pflugrad H1, Haag K1, et al. J Viral Hepat. 2017 Jan 24. doi: 10.1111/jvh.12674.

[Epub ahead of print]

BACKGROUND: One of the most disabling symptoms of hepatitis C virus (HCV)-infection is chronic fatigue. While this is accepted for HCV-polymerase chain reaction (PCR)-positive patients a relationship between HCV-infection and chronic fatigue is questioned after successful virus eradication. **AIMS:** As fatigue is a subjective criterion we aimed to evaluate in addition mood alterations and cognitive function in HCV-exposed patients with only mild liver disease and to assess a) possible interrelationships between these factors and health related quality of life, and b) the impact of viremia and former interferon treatment. **METHODS:** 159 anti-HCV-positive individuals without advanced liver disease answered health related quality of life (HRQoL), fatigue and depression questionnaires and underwent a battery of attention and memory tests. Accompanying diseases which could distort the results of the study such as HIV-co-infection or drug addiction were exclusion criteria. The patients were subdivided into four groups according to their viremia-status and interferon treatment history. Patients' data were evaluated with respect to norms given in the respective test manuals and in addition compared to those of 33 age-matched healthy controls. **RESULTS:** Eighty-five percent of the patients had chronic fatigue, 50-60% mild depression or anxiety, 45% memory deficits and 30% attention deficits, irrespective of their HCV-viremia-status or treatment history. HRQoL correlated negatively with chronic fatigue ($p<0.001$), while cognitive deficits - especially memory function were independent from fatigue and depression. **CONCLUSIONS:** HCV-infection may cause long-standing cerebral dysfunction that significantly impairs HRQoL and may even persist after clearance of the virus. This article is protected by copyright. All rights reserved.

[Antiviral therapies for managing viral hepatitis in lymphoma patients.](#)

Merli M1,2, Rattotti S1, Gotti M3, Arcaini L3. Expert Opin Pharmacother. 2017 Jan 31. doi:

10.1080/14656566.2017.1288718. [Epub ahead of print]

INTRODUCTION: In patients with lymphoma the detection of positive hepatitis B or C viruses (HBV and HCV) serology involves crucial therapeutic consequences. In HBV-infected patients the serological profile of active (HBsAg-positive) or resolved (HBsAg-negative/anti-HBcAb-positive) infection is associated to differential risk of viral reactivation during rituximab-based therapy and require appropriate strategies of monitoring and of antiviral prophylaxis. In HCV-associated NHL patients consolidated data demonstrated that interferon (IFN)-based antiviral therapy (AT) is able to induce lymphoma regression strictly related to viral eradication, while preliminary data of the new direct-acting antivirals (DAAs) are very promising. Areas Covered:

This review summarizes current evidences about HBV reactivation risk in patients undergoing rituximab-based treatments and appropriate options of antiviral prophylaxis with lamivudine, entecavir or tenofovir, as well as pre-emptive strategy in HBsAg-negative/HBcAb-positive patients. Moreover previous experiences with IFN-based AT as well as recent studies with DAAs in HCV-associated indolent lymphomas or diffuse large B-cell lymphoma (DLBCL) are reviewed. Expert Opinion: Entecavir or tenofovir prophylaxis is recommended for HBsAg-positive patients, while universal prophylaxis with lamivudine may be preferred in HBsAg-negative/anti-HBc-positive patients. In asymptomatic patients with HCV-associated indolent lymphoma DAA-based AT should be used as first-line option, while in DLBCL its deliver after immunochemotherapy-induced complete remission is suggested.

Cirrhosis and liver transplantation in patients co-infected with HIV and hepatitis B or C: an observational cohort study. Warren-Gash C1,2, Childs K3, Thornton A4, et al. *Infection*. 2017 Jan 4. doi: 10.1007/s15010-016-0976-x. [Epub ahead of print]

This study assessed the likelihood of referral for liver transplantation assessment in a prospective cohort of patients co-infected with HIV and hepatitis B or C with complications of cirrhosis. There were 141 co-infected patients from 11 UK centres with at least one complication of cirrhosis recorded (either decompensation or hepatocellular carcinoma) out of 772 identified with cirrhosis and/or HCC. Only 23 of these 141 (16.3%) were referred for liver transplantation assessment, even though referral is recommended for co-infected patients after the first decompensation episode.

Using database linkages to monitor the continuum of care for hepatitis C virus among syringe exchange clients: Experience from a pilot intervention. Hochstatter KR1, Hull SJ2, Stockman LJ3, et al. *Int J Drug Policy*. 2017 Jan 23;42:22-25. doi: 10.1016/j.drugpo.2016.12.006. [Epub ahead of print]

BACKGROUND: Because many people who inject drugs (PWID) are at high risk of hepatitis C virus (HCV) and have poor access to medical care, many HCV-infected PWID remain undiagnosed and unaccounted for in surveillance systems. Syringe exchange programs (SEPs) are an under-utilized resource for collecting information missing from surveillance systems. Partnerships with public health agencies represent a potentially innovative approach to studying the HCV epidemic for PWID. The goal of this study was to characterize the HCV care continuum for a cohort of PWID using database linkages. **METHODS:** Data needed to describe the HCV care continuum for 235 PWID were collected from surveillance data provided by the Wisconsin Division of Public Health, a computerized survey administered by SEP staff, and a follow-up interview delivered by academic research staff. When possible, we attempted to confirm each individual's position in the HCV care continuum with at least 2 of the 3 data sources. **RESULTS:** Participants ranged in age from 18-63 years, 60% self-identified as non-Hispanic white, and 77% were male. Overall, we determined that 208 (89%) of the 235 participants had ever been tested for HCV and 72 (31%) had ever tested positive. Of those 72, 46 (64%) had been linked to care, 14 (19%) received pre-treatment evaluation, and 4 (6%) reported initiating treatment. Confirmation by at least 2 data sources ranged from 14-57% of cases for each stage of HCV care. **CONCLUSION:** Available data sources show a large degree of variability when used to characterize the HCV care continuum. New strategies to enhance the quality and completeness of these data sources could substantially improve ongoing efforts to monitor the HCV care continuum among PWID.

[Hepatitis C virus infection and the risk of cancer among elderly US adults: A registry-based case-control study.](#) Mahale P^{1,2}, Torres HA³, Kramer JR⁴, Hwang LY², Li R⁵, Brown EL², Engels EA¹. *Cancer*. 2017 Jan 24. doi: 10.1002/cncr.30559. [Epub ahead of print]

BACKGROUND: Hepatitis C virus (HCV) infection causes hepatocellular carcinoma (HCC) and subtypes of non-Hodgkin lymphoma (NHL). Associations with other cancers are not established. The authors systematically assessed associations between HCV infection and cancers in the US elderly population. **METHODS:** This was a registry-based case-control study using Surveillance, Epidemiology, and End Results (SEER)-Medicare data in US adults aged ≥ 66 years. Cases ($n = 1,623,538$) were patients who had first cancers identified in SEER registries (1993-2011). Controls ($n = 200,000$) were randomly selected, cancer-free individuals who were frequency-matched to cases on age, sex, race, and calendar year. Associations with HCV (documented by Medicare claims) were determined using logistic regression.

RESULTS: HCV prevalence was higher in cases than in controls (0.7% vs 0.5%). HCV was positively associated with cancers of the liver (adjusted odds ratio [aOR] = 31.5; 95% confidence interval [CI], 29.0-34.3), intrahepatic bile duct (aOR, 3.40; 95% CI, 2.52-4.58), extrahepatic bile duct (aOR, 1.90; 95% CI, 1.41-2.57), pancreas (aOR, 1.23; 95% CI, 1.09-1.40), and anus (aOR, 1.97; 95% CI, 1.42-2.73); nonmelanoma nonepithelial skin cancer (aOR, 1.53; 95% CI, 1.15-2.04); myelodysplastic syndrome (aOR, 1.56; 95% CI, 1.33-1.83); and diffuse large B-cell lymphoma (aOR, 1.57; 95% CI, 1.34-1.84). Specific skin cancers associated with HCV were Merkel cell carcinoma (aOR, 1.92; 95% CI, 1.30-2.85) and appendageal skin cancers (aOR, 2.02; 95% CI, 1.29-3.16). Inverse associations were observed with uterine cancer (aOR, 0.64; 95% CI, 0.51-0.80) and prostate cancer (aOR, 0.73; 95% CI, 0.66-0.82). Associations were maintained in sensitivity analyses conducted among individuals without documented alcohol abuse, cirrhosis, or hepatitis B or human immunodeficiency virus infections and after adjustment for socioeconomic status. Associations of HCV with other cancers were not observed.

CONCLUSIONS: HCV is associated with increased risk of cancers other than HCC in the US elderly population, notably bile duct cancers and diffuse large B-cell lymphoma. These results support a possible etiologic role for HCV in an expanded group of cancers. *Cancer* 2017. © 2017 American Cancer Society.

[Check Hep C: A Community-Based Approach to Hepatitis C Diagnosis and Linkage to Care in High-Risk Populations.](#) Ford MM¹, Johnson N, Rude E, Laraque F, Varma JK, Hagan H. *J Public Health Manag Pract*. 2017 Jan 30. doi: 10.1097/PHH.0000000000000519. [Epub ahead of print]

CONTEXT: In New York City (NYC), an estimated 146,500 people, or 2.4% of the adult population, have chronic hepatitis C virus (HCV) infection and half may be unaware of their infection. Despite a 2014 state law requiring health care providers to screen for HCV infection in primary care settings, many high-risk HCV-positive persons are not, and a large proportion of those screened do not receive RNA testing to confirm infection, or antiviral therapies.

OBJECTIVE: The NYC Department of Health's Check Hep C program was designed to increase hepatitis C diagnosis and improve linkage to care at community-based organizations.

DESIGN: Coordinated, evidence-based practices were implemented at 12 sites, including HCV antibody testing, immediate blood draw for RNA testing, and patient navigation to clinical services. **RESULTS:** From May 2012 through April 2013, a total of 4751 individuals were tested for HCV infection and 880 (19%) were antibody-positive. Of antibody-positive

participants, 678 (77%) had an RNA test, and of those, 512 (76%) had current infection. Of all participants, 1901 were born between 1945 and 1965, and of those, 201 (11%) were RNA-positive. Ever having injected drugs was the strongest risk factor for HCV infection (40% vs 3%; adjusted odds ratio [AOR] = 19.1), followed by a history of incarceration (18% vs 4%; AOR = 2.2). Of the participants with current infection, 85% attended at least 1 follow-up hepatitis C medical appointment. Fourteen patients initiated hepatitis C treatment at a Check Hep C site and 6 initiators achieved cure. **CONCLUSION:** The community-based model successfully identified persons with HCV infection and linked a large proportion to care. The small number of patients initiating hepatitis C treatment in the program identified the need for patient navigation in high-risk populations. Results can be used to inform screening and linkage-to-care strategies and to support the execution of hepatitis C screening recommendations.

Primary Care Perspectives on Hepatitis C Virus Screening, Diagnosis and Linking Patients to Appropriate Care. Lebovics E1, Torres R2, Porter LK3. Am J Med. 2017 Feb;130(2):S1-S2. doi: 10.1016/j.amjmed.2017.01.001. Epub 2017 Jan 11.

Enormous progress has been made in recent years toward effectively treating and curing patients with chronic hepatitis C (CHC). However, at least half of the possible 7 million individuals infected with hepatitis C virus (HCV) in the US remain undiagnosed. The formidable task of increasing the number of patients diagnosed, and subsequently linked to appropriate care has fallen to primary care clinicians, who are mandated by some US States to offer screening to individuals born between 1945 and 1965 (the Baby Boomer Generation). This peer-reviewed video roundtable discussion

http://hepcresource.amjmed.com/Content/jplayer/video_roundtable.html#video0 addresses the challenges encountered by primary care clinicians faced with the increasing societal need to screen for HCV, make appropriate diagnoses, and subsequently link infected patients to appropriate care. Discussion in this roundtable initially focuses on the offering of HCV screening to patients in primary care settings. Roundtable participants discuss the need for primary care clinicians to ask appropriate risk factor-based questions of their patients, especially if the ongoing HCV epidemic is to be curtailed. The participants note, however, that the majority of patients currently infected with HCV in the US are Baby Boomers, and USPTF guidelines require this population to be tested for HCV regardless of any past risk-taking behaviors. So while asking the right questions is important, the failure of a Baby Boomer to recall risk-taking behavior does not preclude HCV screening. In fact, clinicians should proactively screen all persons in this birth cohort, and be more sensitive and open to screening requests from these individuals. Roundtable participants also discuss how HCV screening results should be communicated to patients, and how physicians can keep patients engaged and not lost to follow-up after an initial positive HCV antibody test. Patients screened and found to be HCV antibody positive require a follow-up HCV RNA test, and every effort must be made to overcome the challenge of losing patients between these two steps. Good communication between the physician, the physician's office staff, and the patient is necessary. In addition, point-of-care tests and PCR reflex testing can alleviate the need for HCV antibody positive patients to arrange subsequent office visits to undergo confirmatory HCV RNA testing. Physician and patient perspectives are presented throughout this roundtable discussion to obtain a complete picture of the management barriers encountered prior to initiation of therapy. Physician perspectives are provided by Edward Lebovics, the Upham Professor of Gastroenterology and Director of the Sarah C. Upham Division of Gastroenterology and Hepatobiliary Diseases at New York Medical

College and Westchester Medical Center in Valhalla, New York, and Richard Torres, Chief Medical Officer at Optimus Health Care and an Associate Professor of Medicine at Yale School of Medicine. Torres has been a primary care provider for 29 years, working at the largest federally qualified community health center in Southwestern CT, which provides over 240,000 patient visits annually primarily to populations that are underserved and suffering from healthcare disparities. Patient perspectives in this roundtable are provided by Lucinda K. Porter, RN, who is the author of two books for hepatitis C patients, and is a former hepatology nurse and hepatitis C patient. She has been advocating for others since 1997, and writes for the HCV Advocate. Lucinda is a contributing editor of HEP magazine, and she blogs at www.LucindaPorterRN.com. The overall goal of this video roundtable discussion is to demonstrate that when provided with appropriate clinical knowledge, and aided by supportive collaborations with appropriate specialists, primary care clinicians should be able to effectively screen, diagnose, and link patients with hepatitis C to appropriate care. While patients need to be educated on the possible outcomes of a positive HCV antibody test, the significance of a positive HCV RNA test, and how to prevent further transmission, they should also be assured that currently available therapies have dramatically increased the chances of being cured. Appropriate education and the availability of excellent treatment options will hopefully quell fears and increase the morale of patients as they navigate the process of HCV screening and diagnosis.

HEPATOCELLULAR (LIVER) CANCER

[Independent of Cirrhosis, Hepatocellular Carcinoma risk is increased with Diabetes and Metabolic Syndrome: A retrospective cohort study.](#) Kasmari A1, Welch A2, Liu G3, Leslie D3, McGarrity T2, Riley T2. *Am J Med.* 2017 Jan 18. pii: S0002-9343(17)30034-7. doi: 10.1016/j.amjmed.2016.12.029. [Epub ahead of print]

BACKGROUND: Hepatocellular carcinoma is the most common primary liver malignancy, commonly a sequelae of hepatitis C infection, but can complicate cirrhosis of any cause. Whether metabolic syndrome and its components, type II diabetes (), hypertension, and hyperlipidemia increase the risk of hepatocellular carcinoma independent of cirrhosis is unknown. **METHODS:** Retrospective cohort study was conducted using the MarketScan® insurance claims database from 2008-2012. Individuals with hepatocellular carcinoma aged 19-64 and age and gender matched controls were included. Multivariate analysis of hepatocellular carcinoma risk factors was performed. **RESULTS:** Hepatitis C (OR 2.102) was the largest risk factor for hepatocellular carcinoma. Other independent risk factors were type II diabetes (OR 1.353) and hypertension (OR 1.229). Hyperlipidemia was protective against hepatocellular carcinoma (OR 0.885). The largest risk increase occurred with hypertension with type II diabetes and hepatitis C (OR 4.580); though hypertension and type II diabetes without hepatitis C still incurred additional risk (OR 3.399). Type II diabetes and hyperlipidemia had a similar risk if hepatitis C was present (OR 2.319) or not (OR 2.395). Metformin (OR 0.706) and cholesterol medications (OR 0.645) were protective in diabetics. Insulin (OR 1.640) increased the risk of hepatocellular carcinoma compared to the general type II diabetes population. **CONCLUSION:** In the absence of cirrhosis, type II diabetes and hypertension were independent risk factors for hepatocellular carcinoma. Hyperlipidemia and medical management of type II diabetes with metformin and cholesterol medication appeared to reduce the incidence of hepatocellular carcinoma. In contrast, insulin was associated with a higher risk of hepatocellular carcinoma.

Clinical characteristics and prognosis of non-B, non-C hepatocellular carcinoma: The impact of patient sex on disease-free survival.

Hashimoto M1, Tashiro H2, Kobayashi T1, Kuroda S1, Hamaoka M1, Ohdan H1.

BACKGROUND: The number of patients with hepatocellular carcinoma (HCC) negative for both hepatitis B virus surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb) has increased recently. The purpose of the present study was to investigate the clinical characteristics and prognoses of non-B non-C HCC (NBNC-HCC) patients. **MATERIALS AND METHODS:** From January 2000 to December 2013, 154 patients with NBNC-HCC and 560 patients with HBsAg or HCVAb positive (BC)-HCC who underwent curative resection were analyzed retrospectively. The clinical features of NBNC-HCC and BC-HCC were compared, and the prognoses of NBNC-HCC patients were analyzed. **RESULTS:** In comparison to patients with BC-HCC, patients with NBNC-HCC had better liver function but higher pathological tumor stages. The disease-free survival (DFS) duration was significantly higher in patients with NBNC-HCC than it was in those with BC-HCC. In patients with NBNC-HCC, aspartate aminotransferase ≥ 40 IU/L, albumin level < 3.5 g/dL, and multiple tumors were independent risk factors of overall survival; and male sex and multiple tumors were independent risk factors of DFS. **CONCLUSION:** Patients with NBNC-HCC had significantly longer DFS durations than those with BC-HCC. The patient sex had an impact on the postsurgical outcomes of patients with NBNC-HCC in DFS.

Impact of Viral Etiology on Postoperative De Novo Recurrence After Hepatectomy for Hepatocellular Carcinoma in Cirrhotic Patients.

Sasaki K1, Shindoh J2, Nishioka Y3, Margonis GA1, Sugawara T3, Andreatos N1, Hashimoto M3, Pawlik TM4. J Gastrointest Surg. 2017 Jan 3. doi: 10.1007/s11605-016-3344-3. [Epub ahead of print]

BACKGROUND AND AIM: Liver cirrhosis (LC) and hepatocellular carcinoma (HCC) are associated with viral hepatitis, especially hepatitis B virus (HBV) and hepatitis C virus (HCV). Whether differences exist in postoperative de novo carcinogenesis from established cirrhosis according to viral etiology remains unclear. **METHODS:** Data from 313 LC patients with viral hepatitis (HBV-LC, n = 108 and HCV-LC, n = 205) who underwent curative-intent hepatectomy for HCC were retrospectively collected. Clinicopathological characteristics, cumulative recurrence, chronological change of recurrence rate, and predictors of recurrence were analyzed. **RESULTS:** Baseline patient characteristics were different among patients with HBV versus HCV as HCC-LC patients had a lower albumin, higher alanine transaminase, and higher incidence of tumor multicentricity (all $P < 0.050$). The 1-, 3-, and 5-year cumulative recurrence was 16.7, 38.6, and 53.7% in HBV-LC versus 20.8, 52.2, and 71.6% in HCV-LC ($P = 0.002$) patients, respectively. The postoperative annual recurrence rates of HCV-LC were consistently higher than that of HBV-LC patients. After matching on clinicopathologic characteristics, while recurrence was comparable in the early time period, HCV-LC patients had a 2-5% higher incidence of recurrence compared with HBV-LC patients after 20 months post-resection. On multivariable analysis, HCV infection was an independent predictor of recurrence (HR 1.55; 95% CI 1.13-2.13). **CONCLUSION:** HCV-related LC was associated with a higher postoperative de novo carcinogenesis than HBV-related LC. Establishment of different treatment algorithms as well as follow-up surveillance protocols stratified by viral etiology may be warranted.

[The impact of direct antiviral agents on the development and recurrence of hepatocellular carcinoma.](#) Reig M1, Boix L1, Bruix J1. *Liver Int.* 2017 Jan;37 Suppl 1:136-139. doi: 10.1111/liv.13321.

Direct antiviral agents mark a major progress for the treatment of chronic hepatitis C virus infection. The rate of cure is higher than 90% in most populations and the safety profile is good. However, like any treatment, there are potential unexpected adverse events. Several reports have indicated that antiviral therapy may be associated with the reactivation of hepatitis B virus or the emergence of herpes virus in a time-related manner. Recently, several studies have described a potential unexpected incidence of hepatocellular carcinoma in treated patients, both in those without a prior history of cancer and those who have been successfully treated and were disease-free for different periods of time. Furthermore, the emergence of cancer is also characterized by a more aggressive and faster progression to advanced stages, making treatment impossible. Thus, a careful risk-benefit analysis must be made when considering antiviral treatment with the new agents in patients with hepatitis C virus.

[Immunosuppression strategies in liver transplantation patient; patients with hepatocellular carcinoma.](#) Giakoustidis AE1, Giakoustidis DE2. *Immunotherapy.* 2017 Jan;9(2):197-206. doi: 10.2217/imt-2016-0110.

Hepatocellular carcinoma (HCC) consists the main primary malignant tumor of the liver. There is an underlining liver cirrhosis mainly attributed to chronic hepatitis B virus or hepatitis C virus, alcoholic liver disease, nonalcoholic steatohepatitis and other pathologic conditions. Liver transplantation consists a radical management, treating both cancer and cirrhosis. By introducing the Milan Criteria for liver transplantation in HCC patients there was a 5-year survival escalation. Even though there is a careful selection of patients with HCC for transplantation, recurrent disease is still high. The role of immunosuppression therapy is of paramount importance, in order to avoid acute and chronic graft rejection while protecting the patient from tumor recurrence. In recent years newer immunosuppressive agents such as the mTOR inhibitors are proposed, having dual properties, as both immunosuppressive and antitumors agents.

[Assessment of hepatocellular carcinoma risk based on peg-interferon plus ribavirin treatment experience in this new era of highly effective oral antiviral drugs.](#) Lee SH1, Jin YJ, Shin JY, Lee JW. *Medicine (Baltimore).* 2017 Jan;96(1):e5321. doi: 10.1097/MD.0000000000005321.

In this new era of highly effective oral antiviral drugs for chronic hepatitis C virus (HCV), indications for antiviral treatment may be extendable. This study undertaken to identify suitable candidates for peg-interferon plus ribavirin (PEG-IFN/RBV) treatment by evaluating hepatocellular carcinoma (HCC) risk in patients with chronic HCV treated or not with PEG-IFN/RBV. This large-scale retrospective study was conducted on 1176 patients with chronic HCV without a history of HCC (treatment group [n=489] and no-treatment group [n=687]). In the treatment group, patients treated with PEG-IFN/RBV were dichotomized based on the achievement of sustained virologic response (SVR) into SVR (+) and SVR (-) groups. Median follow-up for all study subjects was 31 months (range 6-144 months). Three-year cumulative HCC development rates in the SVR (+) (1.1%) and SVR (-) (8.6%) subgroups were significantly lower than in the no-treatment group (13.5%) (P<0.01 and P<0.01, respectively). In all study subjects, presence of cirrhosis (hazard ratio [HR], 9.92, P<0.01), age (HR 1.03, P<0.01), SVR (-) (HR 7.02, P<0.01), and no-treatment (HR 6.76, P<0.01) were found to be independent risk

factors of HCC development. In the treatment group, age, the presence of cirrhosis, and SVR (-) were predictors of HCC development. In the no-treatment group, age, male, and the presence of cirrhosis were independent predictors for HCC development. HCC risk increased in patients with chronic HCV with older age, cirrhosis, SVR (-) after PEG-IFN/RBV treatment, and no PEG-IFN/RBV treatment. Active antiviral therapy based on highly effective oral drugs needs to be considered in these patients.

[A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma.](#) Cabibbo G1, Petta S1, Barbàra M1, et al. *Liver Int.* 2017 Jan 6. doi: 10.1111/liv.13357. [Epub ahead of print]

BACKGROUND & AIMS: Determining risk for recurrence or survival after curative resection or ablation in patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) is important for stratifying patients according to expected outcomes in future studies of adjuvant therapy in the era of direct-acting antivirals (DAAs). The aims of this meta-analysis were to estimate the recurrence and survival probabilities of HCV-related early HCC following complete response after potentially curative treatment and to identify predictors of recurrence and survival. **METHODS:** Studies reporting time-dependent outcomes (HCC recurrence or death) after potentially curative treatment of HCV-related early HCC were identified in MEDLINE through May 2016. Data on patient populations and outcomes were extracted from each study by three independent observers and combined using a distribution-free summary survival curve. Primary outcomes were actuarial probabilities of recurrence and survival. **RESULTS:** Eleven studies met the inclusion criteria. Pooled estimates of actuarial recurrence rates were 7.4% at 6 months and 47.0% at 2 years. Pooled estimates of actuarial survival rates were 79.8% at 3 years and 58.6% at 5 years. Heterogeneity among studies was highly significant for all outcomes. By univariate meta-regression analyses, lower serum albumin, randomized controlled trial study design and follow-up were independently associated with higher recurrence risk, whereas tumour size and alpha-fetoprotein levels were associated with higher mortality. **CONCLUSIONS:** This meta-analysis showed that recurrence risk and survival are extremely variable in patients with successfully treated HCV-related HCC, providing a useful benchmark for indirect comparisons of the benefits of DAAs and for a correct design of randomized controlled trials in the adjuvant setting.

[Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced Hepatocellular Cancer: A Meta-Analysis of Randomized Phase III Trials.](#) Jackson R1, Psarelli EE1, Berhane S1, Khan H1, Johnson P1. *J Clin Oncol.* 2017 Jan 3;JCO2016695197. [Epub ahead of print]

PURPOSE: Following the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, sorafenib has become the standard of care for patients with advanced unresectable hepatocellular carcinoma, but the relation between survival advantage and disease etiology remains unclear. To address this, we undertook an individual patient data meta-analysis of three large prospective randomized trials in which sorafenib was the control arm.

METHODS: Of a total of 3,256 patients, 1,643 (50%) who received sorafenib were available. The primary end point was overall survival (OS). A Bayesian hierarchical approach for individual patient data meta-analyses was applied using a piecewise exponential model. Results are presented in terms of hazard ratios comparing sorafenib with alternative therapies according to hepatitis C virus (HCV) or hepatitis B virus (HBV) status. **RESULTS:** Hazard ratios show

improved OS for sorafenib in patients who are both HBV negative and HCV positive (log [hazard ratio], -0.27; 95% CI, -0.46 to -0.06). Median unadjusted survival is 12.6 (11.15 to 13.8) months for sorafenib and 10.2 (8.88 to 12.2) months for "other" treatments in this subgroup. There was no evidence of improvement in OS for any other patient subgroups defined by HBV and HCV. Results were consistent across all trials with heterogeneity assessed using Cochran's Q statistic. **CONCLUSION:** There is consistent evidence that the effect of sorafenib on OS is dependent on patients' hepatitis status. There is an improved OS for patients negative for HBV and positive for HCV when treated with sorafenib. There was no evidence of any improvement in OS attributable to sorafenib for patients positive for HBV and negative for HCV.

[Proteomics approaches for early detection and targeted therapy of hepatocellular carcinoma.](#) Khare T1, Khare S1, Ibdah JA1. World J Gastrointest Oncol. 2017 Jan 15;9(1):1-3. doi: 10.4251/wjgo.v9.i1.1.

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer related mortality worldwide. HCC incidences have increased worldwide though more prevalent in Asia and Africa. Hepatitis B virus and hepatitis C virus infections are mostly responsible of increased number of HCC cases. Biomarkers can help early detection and improve treatment regimen in patients as advanced stage is chemo-refractive with limited treatment options. Potential of proteomics in finding new biomarkers for early detection has been explored more recently. Future developments in this area rely on how efficiently we manage vast amount of data generated by these techniques and speed up the clinical trials to improve patient care.