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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Real-world outcomes of ledipasvir/sofosbuvir in treatment-naive patients with hepatitis C. Younossi ZM, Park H, Gordon SC, et al. Am J Manag Care. 2016 May;22(6 Spec No.):SP205-11.

OBJECTIVES: Studies of hepatitis C virus (HCV) regimens have documented substantially reduced effectiveness in sustained virologic response (SVR) in the context of real-world clinical practice compared with clinical trials. Real-world and clinical trial SVR and cost-per-SVR data have not been reported for the all-oral, peginterferon-free and ribavirin (RBV)-free ledipasvir/sofosbuvir (LDV/SOF) regimen. Our objective was to compare the rates of SVR achievement and cost per SVR between pooled data from clinical studies of LDV/SOF and from real-world clinical practice. **METHODS:** Data were derived from the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET), a real-world, multicenter, prospective, observational study; and from the TRIO Network, a retrospective database of HCV-treated patients. The 1-year cost per SVR was calculated as the total cost of an SVR ([cost of treatment regimen, adverse events, and monitoring costs] per SVR) during the first year of treatment. **RESULTS:** After 12 weeks, the SVR rates obtained in real-world studies ranged from 94% to 98%, comparing favorably with the SVRs achieved in the ION-1 and ION-3 trials (94% and 95%-99% with 8 and 12 weeks of RBV-free therapy, respectively). A single SVR, on average, cost $84,989 among patients enrolled in the ION-3 trial, with higher costs ($101,204) among patients with compensated cirrhosis compared with noncirrhotic patients ($81,668). In the pooled TARGET/TRIO population, the average cost of an SVR was $84,770, with costs of $101,380 and $81,368 in patients with compensated cirrhosis and patients without cirrhosis, respectively. **CONCLUSIONS:** Unlike the results obtained with prior HCV regimens, this study suggests that similar SVR rates are achieved with LDV/SOF in clinical trial-based studies and real-world studies. Further, achieving an SVR in real-world clinical practice was not associated with excess costs.

Correlation between vitamin D levels and apoptosis in geriatric patients infected with hepatitis C virus genotype 4. Gabr SA1, Alghadir AH2, Allam AA3, et al. Clin Interv Aging. 2016 May 4;11:523-33. doi: 10.2147/CIA.S104599. eCollection 2016.

BACKGROUND: Vitamin D levels play a pivotal role in most biological processes and differ according to age. A deficiency of vitamin D in chronic hepatitis C (CHC) patients has been

shown to be linked with the severity of liver fibrosis, but little is known about the mechanism of this association. **OBJECTIVE:** In this study, we evaluate the potential interrelation between vitamin D levels, oxidative stress, and apoptosis, based on liver fibrosis in geriatric patients infected with hepatitis C virus (HCV) genotype 4. **SUBJECTS AND METHODS:** A total of 120 adult individuals aged 30-68 years were recruited in this study. Of these, 20 healthy subjects (15 men and five women) with a mean age of 48.3±6.1 years were selected as controls, and 100 patients with a mean age of 47.8±4.9 years with chronic HCV (CHC) who had undergone liver biopsy (80 men and 20 women) were included in this study. Based on liver radiographic (computed tomography, magnetic resonance imaging) and histological Metavir system analyses, the CHC patients were classified into three groups: asymptomatic CHC carriers (n=30), fibrosis (n=25), and cirrhosis (n=45). HCV RNA, HCV genotypes, inflammatory cytokines AFP and TNFα, 25-hydroxyvitamin D (25[OH]D) levels, apoptotic markers single-stranded DNA (ssDNA) and soluble Fas (sFas), and oxidative stress markers nitric oxide (NO) and total antioxidant capacity (TAC) were estimated by using molecular, immunoassay, and colorimetric techniques. **RESULTS:** Approximately 30% of the study population (n=30) were diagnosed as asymptomatic CHC carriers, and 70% of the study population (n=70) had severe fibrosis; these were classified into fibrosis and cirrhosis. There was a significant reduction in 25(OH)D levels and TAC activity, along with an increase in levels of NO, AFP, TNFα, ssDNA, and sFas in fibrosis and cirrhosis subjects compared with those of asymptomatic CHC carriers and health controls. The deficiency in 25(OH)D levels correlated positively with sFas, ssDNA, AFP, TNFα, NO, and TAC, and negatively with age, sex, liver function, body mass index, homeostatic model assessment - insulin resistance, HCV RNA, and viral load. Significant intercorrelation was reported between serum 25(OH)D concentrations and apoptotic and oxidative markers, which suggested progression of liver pathogenesis and fibrogenesis via oxidative and apoptotic mechanisms. **CONCLUSION:** The data showed that vitamin D status was significantly correlated with pathogenesis and fibrogenesis of the liver in geriatric patients infected with HCV genotype 4. The deficiency in 25(OH)D levels was shown to have a pivotal role in the pathogenesis of liver via apoptotic, oxidative stress, and inflammatory mechanistic pathways. The data point to adequate vitamin D levels being recommended for a good response to treatment strategies, especially in older CHC patients.

Many veterans do not receive their healthcare from the VA and therefore may have more limited opportunities to receive treatment. What are some other viable methods to engage veteran communities NOT engaged in healthcare services? What other types of collateral materials may need developing to reach this important population?

Efficacy of Sofosbuvir Plus Ribavirin in Veterans With Hepatitis C Virus Genotype 2 Infection, Compensated Cirrhosis, and Multiple Comorbidities. Ho SB1, Monto A2, Peyton A3, et al. Clin Gastroenterol Hepatol. 2016 May 26. pii: S1542-3565(16)30213-0. doi: 10.1016/j.cgh.2016.05.024. [Epub ahead of print]

BACKGROUND & AIMS: We conducted a Phase 4, open-label study with limited exclusion criteria to evaluate the safety and efficacy of sofosbuvir and ribavirin in veterans with hepatitis C virus (HCV) genotype 2 infection and compensated cirrhosis. This population is often excluded from clinical studies.**METHODS:** We performed a prospective study of treatment-naïve (n = 47) and treatment-experienced (n = 19) patients with chronic HCV genotype 2 infection and compensated cirrhosis at 15 Department of Veterans Affairs sites. All subjects were given sofosbuvir (400 mg, once daily) plus ribavirin (1000-1200 mg/day) in divided doses for 12

weeks. Patients with major psychiatric diseases or alcohol or substance use disorders were not excluded. The primary endpoint was sustained virologic response 12 weeks after therapy (SVR12). **RESULTS:** Fifty-two patients achieved an SVR12 (79%; 95% CI, 67%-88%); 16 of these patients were treatment experienced (84%; 95% CI, 60%-97%) and 36 were treatment naïve (77%; 95% CI, 62%-88%). All patients had at least 1 comorbidity. Thirty-five percent had depression, 24% had post-traumatic stress disorder, and 30% had anxiety disorder. In addition, 29% had current substance use. Of the 7 patients (11%) who discontinued the study treatment prematurely, 3 did so due to adverse events. The most common adverse events were fatigue, anemia, nausea, and headache. Serious adverse events occurred in 8 patients. Only 2 of the serious adverse events (anemia and nausea) were considered to be related to study treatment. **CONCLUSION:** In a phase 4 study, 12 weeks treatment with sofosbuvir and ribavirin led to a SVR12 in almost 80% of veterans with HCV genotype 2 infection, compensated cirrhosis, and multiple comorbidities, regardless of their treatment history.

Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. Mandorfer M1, Kozbial K2, Schwabl P1, et al. J Hepatol. 2016 May 27. pii: S0168-8278(16)30238-0. doi: 10.1016/j.jhep.2016.05.027. [Epub ahead of print]
Freissmuth C2, Schwarzer R1, Stern R2, Chromy D1, Stättermayer AF2, Reiberger T1, **BACKGROUND & AIMS:** We aimed to investigate the impact of sustained virologic response (SVR) to interferon (IFN)-free therapies on portal hypertension in patients with paired hepatic venous pressure gradient (HVPG) measurements. **METHODS:** One hundred and four patients with portal hypertension (HVPG⩾6mmHg) who underwent HVPG and liver stiffness measurement before IFN-free therapy (baseline [BL]) were retrospectively studied. Among 100 patients who achieved SVR, 60 patients underwent HVPG and transient elastography (TE) after antiviral therapy (follow-up [FU]). **RESULTS:** SVR to IFN-free therapies significantly decreased HVPG across all BL-HVPG strata: 6-9mmHg (BL:7.37±0.28vs.FU:5.11±0.38mmHg;-2.26±0.42mmHg;P<0.001), 10-15mmHg (BL:12.2±0.4vs.FU:8.91±0.62mmHg;-3.29±0.59mmHg;P<0.001) and ⩾16mmHg (BL:19.4±0.73vs.FU:17.1±1.21mmHg;-2.3±0.89mmHg;P=0.018). In the subgroup of patients with BL-HVPG of 6-9mmHg, HVPG normalized (<6mmHg) in 63%(12/19) of patients, while no patient progressed to ⩾10mmHg. Among patients with BL-HVPG⩾10mmHg, a clinically relevant HVPG-decrease ⩾10% was observed in 63%(26/41); 24%(10/41) had a FU-HVPG<10mmHg. Patients with Child-Pugh stage B were less likely to have a HVPG-decrease (HR:0.103;95%CI:0.02-0.514;P=0.006), when compared to Child-Pugh A patients. In the subgroup of patients with BL CSPH, the relative change in liver stiffness (per%;HR:0.972;95%CI:0.945-0.999;P=0.044) was a predictor of a HVPG-decrease ⩾10%. The area under the receiver operating characteristic curve for the diagnosis of FU CSPH by FU liver stiffness was 0.931(95%CI:0.865-0.997). **CONCLUSIONS:** SVR to IFN-free therapies might ameliorate portal hypertension across all BL HVPG strata. However, changes in HVPG seemed to be more heterogeneous among patients with BL-HVPG of ⩾16mmHg and a HVPG-decrease was less likely in patients with more advanced liver dysfunction. TE might be useful for the non-invasive evaluation of portal hypertension after SVR.

Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-naïve or Previously Treated Patients with HCV Genotype 1 or 3

Infections. Gane EJ1, Schwabe C2, Hyland RH3, et al. Gastroenterology. 2016 May 27. pii: S0016-5085(16)34513-9. doi: 10.1053/j.gastro.2016.05.021. [Epub ahead of print]
BACKGROUND & AIMS: We performed a phase 2 trial of the efficacy and safety of 4, 6, and 8 weeks of sofosbuvir, given in combination with the NS5A inhibitor velpatasvir and the NS3/4A protease inhibitor GS-9857, in patients with hepatitis C virus (HCV) infection.
METHODS: We enrolled 161 treatment-naïve or previously treated patients infected with HCV genotypes 1 or 3 with or without compensated cirrhosis at 2 centers in New Zealand, from September 2014 through March 2015. All patients received sofosbuvir (400 mg) and velpatasvir (100 mg) plus GS-9857 (100 mg) once daily. The primary efficacy endpoint was sustained virologic response at 12 weeks after therapy (SVR12). The duration of therapy was determined by baseline patient characteristics: 4 or 6 weeks for treatment-naïve patients without cirrhosis, 6 weeks for treatment-naïve patients with cirrhosis, and 6 or 8 weeks for treatment-experienced patients with or without cirrhosis. **RESULTS:** Four weeks of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in 4/15 (27%) treatment-naïve patients with HCV genotype 1 without cirrhosis. Six weeks of this combination produced a SVR12 in 14/15 (93%) treatment-naïve patients with HCV genotype 1 without cirrhosis, in 13/15 (87%) treatment-naïve genotype 1 patients with cirrhosis, in 15/18 (83%) treatment-naïve patients with HCV genotype 3 with cirrhosis, and in 20/30 (67%) patients with HCV genotype 1 who had failed an all-oral regimen of 2 or more direct-acting antiviral agents (DAAs). Eight weeks of the drug combination produced an SVR12 in 17/17 (100%) patients with HCV genotype 1, in 19/19 (100%) patients with HCV genotype 3 and cirrhosis who had failed peg-interferon plus ribavirin, in 25/28 (89%) patients with HCV genotype 1 who had failed protease inhibitor-based triple therapy, and in 4/4 (100%) patients with HCV genotype 3 who had failed an all-oral regimen of 2 or more DAAs. The most common reported adverse events were headache, nausea, and fatigue.
CONCLUSIONS: Eight weeks of treatment with the combination of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in most treatment-naïve or previously treated patients with HCV genotype 1 or 3 infections, including those with compensated cirrhosis.

Effectiveness and safety of daclatasvir plus asunaprevir for HCV genotype 1b patients aged 75 and over with or without cirrhosis. Ogawa E1, Furusyo N1, Yamashita N2, et al. Hepatol Res. 2016 May 3. doi: 10.1111/hepr.12738. [Epub ahead of print]
AIM: The aim of this study was to evaluate the efficacy and safety of 24-week daclatasvir (NS5A inhibitor) plus asunaprevir (NS3/4A protease inhibitor) treatment for elderly patients with HCV genotype 1b infection. **METHODS:** This prospective, multicenter study consisted of 321 Japanese HCV genotype 1b patients who were interferon-ineligible/intolerant or non-responders to interferon-based regimens, including 103 (32.1%) aged ≥ 75 and 127 (39.6%) with cirrhosis. Sustained virological response (SVR) at 24 weeks after the end of treatment and adverse effects were analyzed according to age. **RESULTS:** The overall SVR rate was 90.3%. 94.5% (69/73), 88.3% (128/145), and 90.3% (93/103) of the patients aged < 65, 65-74, and ≥ 75, respectively, achieved SVR. For the entire cohort, pre-existent NS5A resistance-associated variants (RAVs) and prior simeprevir failure were independently associated with treatment failure. According to the analysis of the patients without these unfavorable pretreatment factors, 90.8% (89/98) aged ≥ 75 achieved SVR, although this was significantly lower than for those aged < 65 (98.5%, 66/67) (P < 0.05). The frequency of adverse effects was comparable for the < 75 and ≥ 75 age groups, the most common being an elevated alanine aminotransferase level (>150 U/L, 8.7%), however, no decompensating events were seen. **CONCLUSIONS:**

Daclatasvir plus asunaprevir for HCV genotype 1b was well tolerated and effective for patients without pre-existent NS5A RAVs or simeprevir failure, irrespective of fibrosis status. However, it was less effective for very old patients aged ≥ 75 than for those aged < 65.

Resistance Analyses of Japanese Hepatitis C-Infected Patients Receiving Sofosbuvir or Ledipasvir/Sofosbuvir Containing Regimens in Phase 3 Studies. Mizokami M1, Dvory-Sobol H2, Izumi N3, et al. J Viral Hepat. 2016 May 15. doi: 10.1111/jvh.12549. [Epub ahead of print] High rates of sustained virologic response (SVR) has been achieved in Japanese patients with chronic hepatitis C virus (HCV) genotype (GT)1 and GT2 infection treated with ledipasvir/sofosbuvir (LDV/SOF) ±ribavirin (RBV) and SOF+RBV, respectively. We evaluated the effect of baseline HCV NS5A and NS5B resistance-associated variants (RAVs) on treatment outcome and characterized variants at virologic failure. Baseline deep sequencing for NS5A and NS5B genes was performed for all GT1 patients. Deep sequencing of NS5A (GT1 only) and NS5B (GT1 and GT2) was performed for patients who failed treatment or discontinued early with detectable HCV RNA (i.e., >25 IU/mL). In patients with HCV GT1 infection, 22.3% (GT1a: 2/11; GT1b: 74/330) had ≥1 baseline NS5A RAV. The most frequent NS5A RAVs in GT1b were Y93H (17.9%, 59/330) and L31M (2.4%, 8/330). Despite the presence of NS5A RAVs at baseline, 100% and 97% of patients achieved SVR12, compared with 100% and 99% for those with no NS5A RAVs with LDV/SOF and LDV/SOF+RBV, respectively. All patients with NS5B RAVs at baseline achieved SVR12. Of the 153 patients with GT2 infection (GT2a 60.1%, GT2b 39.9%), 3.3% (5/153) experienced viral relapse. No S282T or other NS5B RAVs were detected at baseline or relapse; no change in susceptibility to SOF or RBV was observed at relapse. In conclusion, LDV/SOF and SOF+RBV demonstrate a high barrier to resistance in Japanese patients with HCV GT1 and GT2 infection. The presence of baseline NS5A RAVs did not impact treatment outcome in GT1 Japanese patients treated with LDV/SOF for 12 weeks.

Boceprevir Plus Peginterferon Alfa-2a/Ribavirin in Treatment-Naïve Hepatitis C Virus Genotype 1 Patients: International Phase IIIb/IV TriCo Trial. Ferenci P1, Caruntu FA2, Lengyel G3, Messinger D4, Bakalos G5, Flisiak R6. Infect Dis Ther. 2016 May 26. [Epub ahead of print]
INTRODUCTION: Boceprevir was not previously studied with peginterferon alfa-2a/ribavirin in phase III trials in treatment-naïve chronic hepatitis C patients. The international phase IIIb/IV TriCo study was, therefore, designed to evaluate boceprevir in combination with peginterferon alfa-2a/ribavirin in treatment-naïve genotype 1 patients. **METHODS:** A total of 165 treatment-naïve genotype 1 patients were assigned to boceprevir plus peginterferon alfa-2a/ribavirin therapy according to the label. All patients received a 4-week lead-in with peginterferon alfa-2a/ribavirin, after which boceprevir (2400 mg/day) was introduced. The total duration of treatment ranged from 28 to 48 weeks depending on the virological response at Weeks 4, 8, and 24, and on fibrosis status. The primary efficacy outcome was sustained virological response (SVR) [undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) 12 weeks after actual end of treatment, SVR12]. **RESULTS:** The overall SVR12 rate was 81% (133/165, 95% confidence interval 74-86%). After 8 weeks of treatment, 61% of patients had undetectable HCV RNA, and 78 patients (47%) had an early response (undetectable HCV RNA at Weeks 8 and 24) and were eligible to stop all therapy at Week 28. Among early responders the SVR12 rate was 95% (74/78), and among patients with cirrhosis assigned to 48 weeks' treatment, the SVR12 rate was 67% (14/21). The overall relapse rate was 7% (10/143), and was 4% (3/77) among early

responders. The most common adverse events were anemia (41%), neutropenia (32%), and dysgeusia (31%). **CONCLUSION:** High SVR12 rates can be achieved with boceprevir plus peginterferon alfa-2a/ribavirin in treatment-naïve HCV genotype 1 patients, including patients with well-compensated cirrhosis. Treatment is well tolerated when label restrictions are taken into account.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Autoimmunity and lymphoproliferation markers in naïve HCV-RNA positive patients without clinical evidences of autoimmune/lymphoproliferative disorders. Gulli F1, Basile U1, Gragnani L2, et al. Dig Liver Dis. 2016 May 24. pii: S1590-8658(16)30430-3. doi: 10.1016/j.dld.2016.05.013. [Epub ahead of print]
BACKGROUND: HCV can lead to both chronic liver disease and B-cell lymphoproliferative disorders. A strong association exists between HCV and mixed cryoglobulinaemia (MC). **METHODS:** Anti-nuclear antibodies (ANA), rheumatoid factor Ig-G (RF-IgG), free light chain κ and λ (FLC-κ, FLC-λ) levels and κ/λ ratio were evaluated in 50/420 subjects unexpectedly resulted anti-HCV positive after routine screenings for non-hepathological procedures. **RESULTS:** Three/fifty patients had HCV-RNA undetectable in the serum and were excluded from the analysis. Thirty-nine/fifty patients had laboratory evidence of circulating cryoglobulins without liver disease and MC-related symptoms. Among them, 17 resulted ANA-positive. The mean cryocrit was higher in ANA-positive patients, while no other demographic/clinical differences were observed between the groups. Significantly higher levels of RF-IgG were observed in ANA-positive vs ANA-negative patients. κ and λ FLC were higher in ANA-positive patients. A ROC analysis, based on ANA-positivity vs ANA-negativity, confirmed a high sensitivity and specificity of RF-IgG test. **CONCLUSIONS:** Published data concerning MC come mostly from symptomatic vasculitis. We analyzed HCV-patients without MC symptoms, founding cryoglobulins in the majority of them. The increased levels of FR-IgG and FLC in CGs-ANA-positive patients, suggest these test could be used to identify a state of silent autoimmune and/or lymphoproliferative condition before the transition to a frank disease in naïve HCV-patients without symptoms of extrahepatic manifestations.

The role of human parvovirus B19 and hepatitis C virus in the development of thyroid disorders. Fallahi P1, Ferrari SM1, Vita R2, Benvenga S2,3,4, Antonelli A5. Rev Endocr Metab Disord. 2016 May 25. [Epub ahead of print]
The presence of viruses in the thyroid has been shown, but whether they are implicated in thyroid diseases or are only spectators is under investigation. The most important candidate viruses for autoimmune thyroid disorders (AITD) are hepatitis C virus (HCV) and human parvovirus B19 (or Erythrovirus B19 or EVB19). Retrospective and prospective case-control studies conducted on pathology slides showed (by PCR, in situ hybridization or immunohistochemistry) EVB19 was present in thyroid tissues of patients with autoimmune thyroiditis (AT), Graves' disease and thyroid cancer. Though AITD can be associated with acute EVB19 infection, it is not clear whether EVB19 could have a pathogenetic role in autoimmune thyroid diseases pathophysiology. Many studies have shown that frequently, patients with HCV chronic infection (CHC) show elevated serum anti-thyroperoxidase (TPOAb) and/or anti-thyroglobulin autoantibodies levels, ultrasonographic signs of chronic AT, and subclinical hypothyroidism. In patients with HCV-associated mixed cryoglobulinemia (MC + HCV), AITD

were more prevalent with respect to controls, and also vs HCV patients without cryoglobulinemia. Papillary thyroid cancer was more prevalent in MC + HCV or CHC patients than in controls, especially in patients with AT. Recently it has been shown an elevated incidence of new cases of AT and thyroid dysfunction in MC patients. These results suggest an attentive monitoring of thyroid function and nodules in HCV patients with risk factors (female gender, a borderline high initial thyrotropin, TPOAb positivity, a hypoechoic and small thyroid) for the development of thyroid disorders.

Primer ID ultra-deep sequencing reveals dynamics of drug resistance-associated variants in breakthrough hepatitis C viruses: relevance to treatment outcome and resistance screening. Barnard R1, Chopra A, James I, et al. Antivir Ther. 2016 May 24. doi: 10.3851/IMP3056. [Epub ahead of print]

BACKGROUND: Use of direct-acting antiviral drugs (DAAs) that target the Hepatitis C virus may be hampered by the rapid selection of viral strains that harbour drug resistance-associated variants (RAVs). These RAVs are often associated with a fitness cost and tend to occur on low frequency strains within treatment naïve subjects. To address the clinical relevance of low frequency RAVs in the setting of DAAs, this study utilised a Primer ID ultra-deep sequencing approach to mitigate PCR errors and bias to accurately quantify viral sequences in subjects that failed DAA treatment. **METHODS:** Subjects were enrolled in the follow-up study P05063 of previous treatment with boceprevir and all had detectable RAVs at virological failure (VF) based on Sanger-based population sequencing. Twelve subjects had three time-points available: baseline, VF, and follow-up (median 830.5 days). Viral RNA was amplified using unique primer identifiers (primer IDs) and sequenced using 454 ultra-deep sequencing. **RESULTS:** The sequencing strategy used in this study improved the detection of clinically relevant low frequency strains bearing RAVs compared to population sequencing and showed that these strains can persist for up to two years post-treatment failure. Strains carrying multiple RAVs were common in breakthrough viruses. Putative compensatory mutations were identified. **CONCLUSIONS:** The Primer ID ultra-deep sequencing approach identifies RAVs that can reduce drug sensitivity at levels below the detection threshold for population sequencing. The approach also removes PCR errors and biases, suggesting this sequencing strategy should become the standard approach by which to perform temporal quasispecies studies and resistance screening.

Vaccination is a vital public health intervention that averts future complications, and in a case like HCV could save countless lives and billions of dollars. In a perfect world, where an HCV vaccine exists and affordable treatments are accessible, what might be some potential ripple effects on the behavior of high risk communities who would otherwise be at risk for HCV acquisition or transmission? Would there still be such vigilance around clean needles and works? Or is there room for a lackadaisical approach knowing a cure or immunity are available?

The Potential Impact of a Hepatitis C Vaccine for People Who Inject Drugs: Is a Vaccine Needed in the Age of Direct-Acting Antivirals? Stone J1, Martin NK2,1, Hickman M1, et al. PLoS One. 2016 May 25;11(5):e0156213. doi: 10.1371/journal.pone.0156213. eCollection 2016.

BACKGROUND AND AIMS: The advent of highly effective hepatitis C (HCV) treatments has questioned the need for a vaccine to control HCV amongst people who inject drugs (PWID). However, high treatment costs and ongoing reinfection risk suggest it could still play a role. We compared the impact of HCV vaccination amongst PWID against providing HCV treatment.

METHODS: Dynamic HCV vaccination and treatment models among PWID were used to determine the vaccination and treatment rates required to reduce chronic HCV prevalence or incidence in the UK over 20 or 40 years. Projections considered a low (50% protection for 5 years), moderate (70% protection for 10 years) or high (90% protection for 20 years) efficacy vaccine. Sensitivities to various parameters were examined. **RESULTS:** To halve chronic HCV prevalence over 40 years, the low, moderate and high efficacy vaccines required annual vaccination rates (coverage after 20 years) of 162 (72%), 77 (56%) and 44 (38%) per 1000 PWID, respectively. These vaccination rates were 16, 7.6 and 4.4 times greater than corresponding treatment rates. To halve prevalence over 20 years nearly doubled these vaccination rates (moderate and high efficacy vaccines only) and the vaccination-to-treatment ratio increased by 20%. For all scenarios considered, required annual vaccination rates and vaccination-to-treatment ratios were at least a third lower to reduce incidence than prevalence. Baseline HCV prevalence had little effect on the vaccine's impact on prevalence or incidence, but substantially affected the vaccination-to-treatment ratios. Behavioural risk heterogeneity only had an effect if we assumed no transitions between high and low risk states and vaccinations were targeted or if PWID were high risk for their first year. **CONCLUSIONS:** Achievable coverage levels of a low efficacy prophylactic HCV vaccine could greatly reduce HCV transmission amongst PWID. Current high treatment costs ensure vaccination could still be an important intervention option.

Inhibition of HCV replication by humanized-single domain transbodies to NS4B. Glab-Ampai K1, Malik AA1, Chulanetra M2, et al. Biochem Biophys Res Commun. 2016 May 27. pii: S0006-291X(16)30817-8. doi: 10.1016/j.bbrc.2016.05.109. [Epub ahead of print]
NS4B of hepatitis C virus (HCV) initiates membrane web formation, binds RNA and other HCV proteins for viral replication complex (RC) formation, hydrolyses NTP, and inhibits innate anti-viral immunity. Thus, NS4B is an attractive target of a novel anti-HCV agent. In this study, humanized-nanobodies (VHs/VHHs) that bound to recombinant NS4B were produced by means of phage display technology. The nanobodies were linked molecularly to a cell penetrating peptide, penetratin (PEN), for making them cell penetrable (become transbodies). Human hepatic (Huh7) cells transfected with HCV JFH1-RNA that were treated with transbodies from four Escherichia coli clones (PEN-VHH7, PEN-VHH9, PEN-VH33, and PEN-VH43) had significant reduction of HCV RNA amounts in their culture fluids and intracellularly when compared to the transfected cells treated with control transbody and medium alone. The results were supported by the HCV foci assay. The transbody treated-transfected cells also had upregulation of the studied innate cytokine genes, IRF3, IFNβ and IL-28b. The transbodies have high potential for testing further as a novel anti-HCV agent, either alone, adjunct of existing anti-HCV agents/remedies, or in combination with their cognates specific to other HCV enzymes/proteins.

Application of static models to predict midazolam clinical interactions in the presence of single or multiple HCV drugs. Cheng Y1, Ma L1, Chang SY1, Humphreys G2, Li W3. Drug Metab Dispos. 2016 May 25. pii: dmd.116.070409. [Epub ahead of print]
Asunaprevir (ASV), daclatasvir (DCV), and beclabuvir (BCV) are three drugs developed for the treatment of chronic hepatitis C virus infection. Here we evaluated the CYP3A4 induction potential of each drug, as well as BCV-M1 (the major metabolite of BCV), in human hepatocytes by measuring CYP3A4 mRNA alteration. The induction responses were quantified as Induction Fold (mRNA fold change) and Induction Increase (mRNA fold increase), and then fitted with 4

non-linear regression algorithms. Reversible inhibition and time dependent inhibition (TDI) on CYP3A4 activity were determined in order to predict net drug-drug interactions (DDI). All four compounds were CYP3A4 inducers and inhibitors, with ASV demonstrating TDI. The curve fitting results demonstrated that Fold Increase is a better assessment to determine kinetic parameters for compounds inducing weak responses. By summing the contribution of each inducer, the basic static model was able to correctly predict the potential for a clinically meaningful induction signal for single or multiple perpetrators, but with over prediction of the magnitude. With the same approach, the mechanistic static model improved the prediction accuracy of DCV and BCV when including both induction and inhibition effects, but incorrectly predicted the net DDI effects for ASV alone or triple combinations. The predictions of ASV or the triple combination could be improved by only including the induction and reversible inhibition but not the ASV CYP3A4 TDI component. Those results demonstrated that static models can be applied as a tool to help project the DDI risk of multiple perpetrators using in vitro data.

HIV/HCV COINFECTION

Improving HCV cure rates in HIV-coinfected patients - a real-world perspective.
Lakshmi S, Alcaide M, Palacio AM, et al. Am J Manag Care. 2016 May;22(6 Spec No.):SP198-204.
OBJECTIVES: To study rates and predictors of hepatitis C virus (HCV) cure among human immunodeficiency virus (HIV)/HCV-coinfected patients, and then to evaluate the effect of attendance at clinic visits on HCV cure. **METHODS:** Retrospective cohort study of adult HIV/HCV-coinfected patients who initiated and completed treatment for HCV with direct-acting antivirals (DAAs) between January 1, 2014, and June 30, 2015. **RESULTS:** Eighty-four participants reported completing treatment. The median age was 58 years (interquartile ratio, 50-66); 88% were male and 50% were black. One-third were cirrhotic and half were HCV-treatment-experienced. The most commonly used regimen was sofosbuvir/ledipasvir (40%) followed by simeprevir/sofosbuvir (30%). Cure was achieved in 83.3%, 11.9% relapsed, and 2.3% experienced virological breakthrough. Two patients (2.3%) did not complete treatment based on pill counts and follow-up visit documentation. In multivariable analysis, cure was associated with attendance at follow-up clinic visits (odds ratio [OR], 9.0; 95% CI, 2.91-163) and with use of an integrase-based HIV regimen versus other non-integrase regimens, such as non-nucleoside analogues or protease inhibitors (OR, 6.22; 95% CI 1.81-141). Age, race, genotype, presence of cirrhosis, prior HCV treatment, HCV regimen, and pre-treatment CD4 counts were not associated with cure. **CONCLUSIONS:** Real-world HCV cure rates with DAAs in HCV/HIV coinfection are lower than those seen in clinical trials. Cure is associated with attendance at follow-up clinic visits and with use of an integrase-based HIV regimen. Future studies should evaluate best antiretroviral regimens, predictors of attendance at follow-up visits, impact of different monitoring protocols on medication adherence, and interventions to ensure adequate models of HIV/HCV care.

Hepatitis C virus coinfection as a risk factor for osteoporosis and fracture. Bedimo R1, Maalouf NM, Lo Re V 3rd. Curr Opin HIV AIDS. 2016 May;11(3):285-93. doi: 10.1097/COH.0000000000000259.

PURPOSE OF REVIEW: With increased survival of HIV-infected patients, osteoporotic fractures have developed as a major cause of morbidity in these patients, and chronic hepatitis C virus (HCV) coinfection has emerged as a significant contributor to this increased fracture risk. The present article reviews the epidemiologic and clinical evidence for osteoporosis and increased fracture risk among HIV/HCV coinfected patients, and potential mechanisms for these outcomes with HCV coinfection. **RECENT FINDINGS:** Epidemiologic studies suggest that HIV/HCV coinfected patients exhibit a three-fold increased fracture incidence compared with uninfected controls, and 1.2-2.4-fold increased fracture risk compared with HIV monoinfected patients. Recent reports suggest that chronic HCV coinfection is independently associated with reduced bone mineral density in HIV, but that it is not associated with significantly increased bone turnover. The deleterious impact of chronic HCV on BMD and fracture risk occurs even in the absence of advanced liver fibrosis or cirrhosis. New tools to assess bone quality, including the trabecular bone score, high-resolution peripheral quantitative computed tomography, and in-vivo microindentation, may help improve understanding of the mechanisms of HCV-associated skeletal fragility. The impact of approved antiosteoporosis medications and direct-acting antivirals for the treatment of chronic HCV infection on patients' bone health remain to be studied. **SUMMARY:** Chronic HCV infection is an independent risk factor for osteoporosis and fractures among HIV-infected patients, even before the development of cirrhosis. The underlying mechanisms are being unraveled, but major questions persist regarding the optimal evaluation and management of bone health in HIV/HCV coinfected patients.

Marijuana Use is not Associated with Progression to Advanced Liver Fibrosis in HIV/HCV Coinfected Women. Kelly EM1, Dodge JL2, Sarkar M2, et al. Clin Infect Dis. 2016 May 25. pii: ciw350. [Epub ahead of print]

BACKGROUND: Marijuana (THC) use has been associated with liver fibrosis progression in retrospective analyses of chronic hepatitis C (HCV) patients. We studied long-term effects of THC on fibrosis progression in women co-infected with HIV/HCV enrolled in Women's Interagency HIV Study (WIHS). **METHODS:** Liver fibrosis was categorized according to FIB-4 scores as none, moderate, or significant. THC and alcohol use were quantified as average exposure per week. Associations between THC use and progression to significant fibrosis were assessed using Cox proportional hazards regression. **RESULTS:** Among 575 HIV/HCV co-infected women followed for 11 (6-17) years [median (IQR)], 324 (56%) reported no THC use; 141 (25%) reported less than weekly use; 70 (12%) weekly use; and 40 (7%) daily use at WIHS entry. In univariable analysis, entry FIB-4 [HR 2.26 (1.88-2.73) p<0.001], log HCV RNA [HR 1.19 (1.02-1.38) p=0.02], tobacco use [HR 1.37 (1.02-1.85) p=0.04], CD4+ count [risk per 100 count increase HR 0.90 (0.86-0.95) p<0.001] and log HIV RNA [HR 1.18 (1.05-1.32) p=0.005] were associated with progression to significant fibrosis, as was cumulative alcohol use in follow-up [HR 1.03 (1.02-1.04) p<0.001]. In multivariable analysis, entry FIB-4, entry CD4+ count and cumulative alcohol use remained significant. Cumulative THC use was not associated with fibrosis progression [HR 1.01(95% CI 0.92-1.10) p=0.83]. **CONCLUSIONS:** In this large cohort of HIV/HCV co-infected women, THC was not associated with progression to significant liver fibrosis. Alcohol use was independently associated with liver fibrosis, and may better predict fibrosis progression in HIV/HCV co-infected women.

Cognitive impairment in HIV and HCV co-infected patients: a systematic review and meta-analysis. Fialho R1,2, Pereira M3, Bucur M2, Fisher M4,5, Whale R2,5, Rusted J1. AIDS Care. 2016 May 30:1-14. [Epub ahead of print]
Cognitive impairment has been well documented in human immunodeficiency virus (HIV) and hepatitis C virus (HCV) mono-infections. However, in the context of HIV/HCV co-infection the research is more limited. The aim of this systematic review was to describe the characteristics of cognitive impairment in HIV/HCV co-infection and to examine the differences in cognitive performance between HIV/HCV and HIV and HCV mono-infected patients. Of the 437 records initially screened, 24 papers met the inclusion criteria and were included in the systematic review. Four studies were included in the meta-analysis. Most studies indicated that HIV/HCV co-infected patients had a higher level of cognitive impairment than HIV mono-infected patients. Meta-analysis also indicated that HIV mono-infected patients had a significantly lower global deficit score than co-infected patients. The results also indicated that co-infected patients were more likely to be impaired in information processing speed than HIV mono-infected patients. These findings can be challenged by biasing factors such as the small number of included studies, heterogeneity of the samples and a large diversity of methodological procedures. Future research with consistent and comprehensive neuropsychological batteries and covering a greater diversity of risk factors is needed, in order to clarify the effects of both viruses on cognitive function and the mechanisms that underlie these effects. Because cognitive impairments may pose significant challenges to medication adherence, quality of life and overall functioning, such knowledge may have important implications to the planning and implementation of effective interventions aimed at optimising the clinical management of these infections.

Evolution of hepatitis C virus in HIV coinfected patients under antiretroviral therapy. Sede M1, Parra M1, Manrique JM2, Laufer N1, Jones LR3, Quarleri J4. Infect Genet Evol. 2016 May 24;43:186-196. doi: 10.1016/j.meegid.2016.05.032. [Epub ahead of print]
Five patients (P) were followed-up for an average of 7.73years after highly active antiretroviral therapy (HAART) initiation. Patients' immune and virological status were determined by periodical CD4+T-cell counts and HIV and HCV viral load. HCV populations were studied using longitudinal high throughput sequence data obtained in parallel by virological and immunological parameters. Two patients (P7, P28) with sub-optimal responses to HAART presented HCV viral loads significantly higher than those recorded for two patients (P1, P18) that achieved good responses to HAART. Interestingly, HCV populations from P7 and P28 displayed a stable phylogenetic structure, whereas HCV populations from P1 and P18showeda significant increase in their phylogenetic structure, followed by a decrease after achieving acceptable CD4+T-cell counts (>500 cell/μl). The fifth patient (P25) presented high HCV viral loads, preserved CD4+T-cell counts from baseline and all along the follow-up, and displayed a constant viral phylogenetic structure. These results strongly suggest that HAART-induced immune recovery induces a decrease in HCV viral load and an increase in the HCV population phylogenetic structure likely reflecting the virus diversification in response to the afresh immune response. The relatively low HCV viral load observed in the HAART responder patients suggests that once HCV is adapted it reaches a maximum number of haplotypes higher than that achieved during the initial stages of the immune response as inferred from the two recovering patients. Future studies using larger number of patients are needed to corroborate these hypotheses.

Simtuzumab treatment of advanced liver fibrosis in HIV and HCV-infected adults: Results of a 6-month open-label safety trial. Meissner EG1,2,3, McLaughlin M1, Matthews L3, et al. Liver Int. 2016 May 27. doi: 10.1111/liv.13177. [Epub ahead of print]

BACKGROUND: Chronic liver injury can result in fibrosis that may progress over years to end-stage liver disease. The most effective anti-fibrotic therapy is treatment of the underlying disease, however when not possible, interventions to reverse or slow fibrosis progression are needed. **AIM:** To study the safety and tolerability of simtuzumab, a monoclonal antibody directed against lysyl oxidase-like 2 (LOXL2) enzyme, in subjects with hepatitis C virus (HCV), human immunodeficiency virus (HIV), or HCV-HIV co-infection and advanced liver disease. **METHODS:** Eighteen subjects with advanced liver fibrosis received simtuzumab 700mg intravenously every 2 weeks for 22 weeks. Transjugular liver biopsies were performed during screening and at the end of treatment to measure hepatic venous pressure gradient (HVPG) and to stage fibrosis. **RESULTS:** Treatment was well-tolerated with no discontinuations due to adverse events. No significant changes were seen in HVPG or liver biopsy fibrosis score after treatment. Exploratory transcriptional and protein profiling using paired pre- and post-treatment liver biopsy and serum samples suggested up-regulation of TGF-β3 and IL-10 pathways with treatment. **CONCLUSION:** In this open-label, pilot clinical trial, simtuzumab treatment was well-tolerated in HCV- and HIV-infected subjects with advanced liver disease. Putative modulation of TGF-β3 and IL-10 pathways during simtuzumab treatment merits investigation in future trials.

HLA-B18 as a risk factor of short-term progression to severe liver fibrosis in HIV/HCV co-infected patients with absent or minimal fibrosis: implications for timing of therapy. Frías M1, Rodríguez-Cano D1, Cuenca-López F1, et al. Pharmacogenomics J. 2016 May 31. doi: 10.1038/tpj.2016.42. [Epub ahead of print]

Our aim was to analyze the influence of HLA-B haplotypes on liver fibrosis progression in HIV/hepatitis C virus (HCV) co-infected patients. Retrospective longitudinal study including HIV/HCV, non-cirrhotic and HCV treatment-naïve patients. The main outcome variable was liver fibrosis progression of at least one stage. One hundred and four patients constituted the study population (F0-F1: 62 (59.6%); F2: 22 (21.2%); F3: 20 (19.2%)). During a median follow-up of 54.5 months (IQR: 26.2-77), 45 patients (43.3%) showed an increase in the stage of liver fibrosis (time to event: 29 (IQR: 14-49.5) months). HLA-B18pos patients more frequently had a higher and faster fibrosis progression rate (73.3%; 24 (IQR: 8-29) months) than HLA-B18neg patients (38.2%; 34.5 (IQR: 14.7-51.2) months). This association was also observed in the development of F3-F4 fibrosis among F0-F2 patients (HLA-B18pos: 69.2%; 18 (6.5-37) months vs HLA-B18neg: 28.2%; 37 (IQR: 19-52) months). These results could impact the timing of HCV therapy in F0-F2 patients.

Hepatic Safety of Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate Fixed-Dose Single-Tablet Regimen in HIV-Infected Patients with Active Hepatitis C Virus Infection: The hEPAtic Study. Neukam K1, Espinosa N2, Collado A3, et al. PLoS One. 2016 May 19;11(5):e0155842. doi: 10.1371/journal.pone.0155842. eCollection 2016.

OBJECTIVES: The aim of this study was to evaluate the frequency of transaminase elevations (TE) and total bilirubin elevations (TBE) during the first year of therapy with a single tablet regimen including RPV/FTC/TDF (EPA) in HIV/hepatitis C virus (HCV)-coinfected subjects in clinical practice. **METHODS:** In a retrospective analysis, HIV/HCV-coinfected subjects who

started EPA at 17 centres throughout Spain were included as cases. Subjects who started an antiretroviral therapy (ART) other than EPA during the study period at the same hospitals were randomly selected as controls in a 1:2 ratio. Primary outcome variables were grade (G) 3-4 TE and G4 TBE. **RESULTS:** Of the 519 subjects included, 173 individuals started EPA. Nine (5.2%) subjects of the EPA group and 49 (14.2%) controls were naïve to ART. The median (Q1-Q3) follow-up was 11.2 (9.7-13.9) months. TE was observed in 2 [1.2%; 95% confidence interval (CI): 0.14%-4.1%] subjects receiving EPA and 11 (3.2%; 95%CI: 1.6%-5.6%) controls (p = 0.136), all events were G3. No patient discontinued ART due to TE. One (0.6%; 95%CI: 0.01%-3.1%) subject on EPA and 8 (2.3%; 95%CI: 1%-4.5%) subjects in the control group developed TBE (p = 0.141), without developing any other hepatic event during follow-up. Three (2.3%) subjects with cirrhosis versus 10 (3.1%) without cirrhosis showed G3-4 TE (p = 0.451). **CONCLUSION:** The frequency of severe liver toxicity in HIV/HCV-coinfected subjects receiving EPA under real-life conditions is very low, TE were generally mild and did not lead to drug discontinuation. All these data suggest that EPA can be safely used in this particular subpopulation.

Systemic inflammation and liver damage in HIV/hepatitis C virus coinfection. Shmagel KV1,2, Saidakova EV1,2, Shmagel NG2,3, et al. HIV Med. 2016 May 17. doi: 10.1111/hiv.12357. [Epub ahead of print]
OBJECTIVES: Chronic hepatitis C virus (HCV) and HIV viral infections are characterized by systemic inflammation. Yet the relative levels, drivers and correlates of inflammation in these settings are not well defined. **METHODS:** Seventy-nine HIV-infected patients who had been receiving antiretroviral therapy (ART) for more than 2 years and who had suppressed plasma HIV levels (< 50 HIV-1 RNA copies/mL) were included in the study. Two patient groups, HCV-positive/HIV-positive and HCV-negative/HIV-positive, and a control group comprised of healthy volunteers (n = 20) were examined. Markers of systemic inflammation [interleukin (IL)-6, interferon gamma-induced protein (IP)-10, soluble tumour necrosis factor receptor-I (sTNF-RI) and sTNF-RII], monocyte/macrophage activation [soluble CD163 (sCD163), soluble CD14 and neopterin], intestinal epithelial barrier loss [intestinal fatty acid binding protein (I-FABP) and lipopolysaccharide (LPS)] and coagulation (d-dimers) were analysed. CD4 naïve T cells and CD4 recent thymic emigrants (RTEs) were enumerated. **RESULTS:** Plasma levels of IP-10, neopterin and sCD163 were higher in HCV/HIV coinfection than in HIV monoinfection and were positively correlated with indices of hepatic damage [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and the AST to platelet ratio index (APRI)]. Levels of I-FABP were comparably increased in HIV monoinfection and HIV/HCV coinfection but LPS concentrations were highest in HCV/HIV coinfection, suggesting impaired hepatic clearance of LPS. Plasma HCV levels were not related to any inflammatory indices except sCD163. In coinfected subjects, a previously recognized relationship of CD4 naïve T-cell and RTE counts to hepatocellular injury was defined more mechanistically by an inverse relationship to sCD163. **CONCLUSIONS:** Hepatocellular injury in HCV/HIV coinfection is linked to elevated levels of certain inflammatory cytokines and an apparent failure to clear systemically translocated microbial products. A related decrease in CD4 naïve T cells and RTEs also merits further exploration.

It is vital to take into account the impact of cure on a patient's mental health and wellness. This article states that overall, patients who received treatment had less anxiety disorders than those who didn't receive treatment; and that the highest rate of drug dependence was among patient populations who have never been treated. Knowing that drug and alcohol use have a direct impact on a patient's anxiety levels, we can conclude that treating HCV + patients with substance use issues will positively impact their levels of anxiety, thereby reducing the possibility of subsequent drug use. Curing a patient of a chronic, infectious disease WILL have a positive impact on their wellbeing and future health decisions. Decisions around access to medications should NOT be based on current or former drug/alcohol use.

Psychiatric and substance use disorders in HIV/hepatitis C virus (HCV)-coinfected patients: does HCV clearance matter? [Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) HEPAVIH CO13 cohort]. Michel L1,2,3, Lions C4,5,6, Winnock M7, et al. HIV Med. 2016 May 17. doi: 10.1111/hiv.12382. [Epub ahead of print]

OBJECTIVES: The objective of this nested study was to assess the prevalence of psychiatric disorders in a sample of HIV/hepatitis C virus (HCV)-coinfected patients according to their HCV status. **METHODS:** The nested cross-sectional study, untitled HEPAVIH-Psy survey, was performed in a subset of HIV/HCV-coinfected patients enrolled in the French Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) CO13 HEPAVIH cohort. Psychiatric disorders were screened for using the Mini International Neuropsychiatric Interview (MINI 5.0.0). **RESULTS:** Among the 286 patients enrolled in the study, 68 (24%) had never received HCV treatment, 87 (30%) were treatment nonresponders, 44 (15%) were currently being treated and 87 (30%) had a sustained virological response (SVR). Of the 286 patients enrolled, 121 patients (42%) screened positive for a psychiatric disorder other than suicidality and alcohol/drug abuse/dependence, 40 (14%) screened positive for alcohol abuse/dependence, 50 (18%) screened positive for drug abuse/dependence, 50 (17.5%) were receiving an antidepressant treatment and 69 (24%) were receiving an anxiolytic. Patients with an SVR did not significantly differ from the other groups in terms of psychiatric disorders. Patients receiving HCV treatment screened positive less often for an anxiety disorder. The highest rate of drug dependence/abuse was among HCV treatment-naïve patients. **CONCLUSIONS:** Psychiatric disorders were frequent in HIV/HCV-coinfected patients and their rates were comparable between groups, even for patients achieving an SVR. Our results emphasize the need for continuous assessment and care of coinfected patients, even after HCV clearance. Drug addiction remains an obstacle to access to HCV treatment. Despite the recent advent and continued development of directly acting antiviral agents (DAAs), it is still crucial to offer screening and comprehensive care for psychiatric and addictive disorders.

Fatigue in the long term after HCV treatment in HIV-HCV-coinfected patients: functional limitations persist despite viral clearance in patients exposed to peg-interferon/ribavirin-containing regimens (ANRS CO13-HEPAVIH cohort).
Marcellin F1, Protopopescu C, Poizot-Martin I, et al. Eur J Gastroenterol Hepatol. 2016 May 12. [Epub ahead of print]

OBJECTIVES: To analyze the impact of fatigue on individuals' global, cognitive, physical, and psychosocial functioning in the long term after hepatitis C virus (HCV) treatment and its relationship with HCV clearance among patients coinfected with HIV and HCV exposed to peg-interferon/ribavirin-containing regimens. **PATIENTS AND METHODS:** The study sample included 107 coinfected patients treated for HCV during follow-up in the French ANRS CO13-

HEPAVIH cohort. Analyses used scores from the Fatigue Impact Scale (FIS), assessed before treatment initiation and at last available measure after the end of treatment (2 years in median). Patient proportions with a clinically significant improvement in fatigue impact, defined as a decrease higher than 10 points in the 160-point global FIS score, were compared between HCV clearers and chronic HCV patients (Fisher's exact test). Relationships between HCV clearance and FIS scores were analyzed in linear regression models adjusted for sex, time since end of HCV treatment, and pretreatment scores. **RESULTS:** Twenty-nine percent of patients showed a clinically significant improvement in fatigue (15/57 in HCV clearers vs. 16/50 in chronic HCV patients, P=0.52). HCV clearance was not significantly associated with FIS scores in multivariate models. **CONCLUSION:** The role of HCV clearance in coinfected patients' functional recovery in the long term after peg-interferon/ribavirin treatment may be lesser than expected. Additional studies are needed in patients treated with direct-acting antiviral agents. In the meantime, the effectiveness of palliative care and targeted psychological treatments such as cognitive-behavioral therapy in reducing fatigue impact needs to be assessed in the many HCV-cured patients with HIV exposed to suboptimal interferon-based first-generation therapies.

Liver Fibrosis Evaluation Using Real-time Shear Wave Elastography in Hepatitis C-Monoinfected and Human Immunodeficiency Virus/Hepatitis C-Coinfected Patients.
Verlinden W1, Bourgeois S2, Gigase P3, et al. J Ultrasound Med. 2016 Jun;35(6):1299-308. doi: 10.7863/ultra.15.08066. Epub 2016 May 5.
OBJECTIVES: A few studies have evaluated real-time shear wave elastography (SWE) for assessing liver fibrosis by measuring liver stiffness in patients with chronic hepatitis C virus (HCV) infection, but they excluded human immunodeficiency virus/HCV-coinfected patients. We investigated the diagnostic performance of liver stiffness measured by SWE as a noninvasive predictor of liver fibrosis in HCV using liver biopsy as a reference standard, including monoinfected and coinfected patients. **METHODS:** We measured liver stiffness in patients with HCV undergoing liver biopsy (METAVIR fibrosis staging). **RESULTS:** Eighty patients (53 monoinfected and 27 coinfected) were included. There was a significant correlation between liver stiffness and fibrosis stage ($\rho = 0.685$; $P < .001$). Areas under the receiver operating characteristic curve were 0.841, 0.879, and 0.975 when comparing fibrosis stages F0-F1 versus F2-F4, F0-F2 versus F3-F4, and F0-F3 versus F4, respectively. Suggested cutoff values were 8.5 kPa for F2, 10.4 kPa for F3, and 11.3 kPa for F4, with sensitivity and specificity of 81% and 84%, 81% and 95%, and 100% and 90%. There was no significant difference between the liver stiffness of monoinfected and coinfected patients ($P = .453$). When combining SWE with the fibrosis-4 score, accuracy increased from 82% to 88% and from 88% to 96%, with incongruent results of 26% and 29%, for F0-F1 versus F2-F4 and F0-F2 versus F3-F4. **CONCLUSIONS:** Shear wave elastography of the liver is an effective noninvasive predictor of liver fibrosis in patients with HCV. There was no significant difference between monoinfected and coinfected patients; hence, the same cutoff values can be used for both groups. Combination of SWE with the fibrosis-4 score leads to higher accuracy, although at the expense of inconclusive results in some patients.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Meta-Analysis of Combination Therapy of Chinese Herbs Plus Interferon and Ribavirin in Patients with Chronic Hepatitis C. Wang J1, Xin S1, Jin X1, et al. Med Sci Monit. 2016 May 30;22:1817-26.

BACKGROUND: We aimed to evaluate the combination therapy of Chinese herbs plus interferon and ribavirin in treatment of patients with chronic hepatitis C (CHC). **MATERIAL AND METHODS**: Related databases were searched to identify randomized controlled trials (RCTs) that evaluated biochemical response, virological response, histological response, and/or adverse reactions to combination therapy of interferon and ribavirin with and without Chinese herbs. The RR (relative risk) with a 95% confidence interval (CI) was calculated. Sensitivity analysis was conducted by omitting one study at a time. Publication bias among the eligible studies was evaluated by Egger's test. **RESULTS**: A total of 17 RCTs matched the selection criteria. Overall, combination therapies of Chinese herbs plus interferon and ribavirin achieved significantly higher ALT (alanine transaminase) and ETVR (the end-of-treatment viral response), and significantly lower levels of HA (hyaluronic acid), LN (laminin), PC III (procollagen iii peptide), IV-C (type IV collagen), decreased LC (decreasing leukocyte count), ATF (abnormal thyroid function), psychosis, and anemia in CHC patients compared with those treated without Chinese herbs. Sensitivity analysis showed no changes and no potential publication bias was found. **CONCLUSIONS:** The current evidence suggests that combination therapy of Chinese herb plus interferon and ribavirin yields better outcome and fewer adverse events in CHC patients than that of interferon plus ribavirin therapy.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Costs and spillover effects of private insurers' coverage of hepatitis C treatment. Moreno GA1, Mulligan K, Huber C, et al. Am J Manag Care. 2016 May;22(6 Spec No.):SP236-44.

OBJECTIVES: Hepatitis C virus (HCV) treatment incentives for private payers may be misaligned because payers must bear immediate costs and may not realize long-term benefits. However, these benefits may accrue to future payers, including Medicare. We examined how and to what extent private payers' current HCV treatment coverage decisions impact Medicare's and private payers' future costs. **STUDY DESIGN:** Discrete-time Markov model. **METHODS:** We modeled HCV disease progression and transmission to simulate the economic and social effects of different private-payer HCV treatment scenarios on Medicare. The model examined differences between a baseline scenario (current practice guidelines) and 2 alternative scenarios that expand treatment coverage. Spillover effects were measured as reduced HCV treatment costs and medical expenditures in Medicare. We calculated the spillover effects and net social value of each scenario (total value of quality-adjusted life-years accrued over time minus cumulative treatment and medical costs). **RESULTS:** With expanded HCV treatment coverage, private payers experience reduced medical expenditures in the 3-to-5-year time horizon; however, they still face higher treatment costs. Over a 20-year horizon, private payers experience overall savings of $10 billion to $14 billion after treatment costs. The expansion of coverage by private payers generates positive spillover benefits to Medicare of $0.3 billion to $0.7 billion over a 5-year horizon, and $4 billion to $11 billion over a 20-year horizon. **CONCLUSIONS:** When private payers increase HCV treatment coverage, they may achieve significant savings while inducing spillover benefits to Medicare. Future savings, however, may not motivate

immediate treatment investments among private payers who experience high beneficiary turnover.

We know that jails are a cesspool for a large population of HCV positive individuals; beyond testing and treatment, what are some preventative methods we can take to quell the transmission and aquisiotion of HCV amongst inmates? Education? Peer counseling? Increased sanitation practices?

Hepatitis C Screening of the "Birth Cohort" (Born 1945-1965) and Younger Inmates of New York City Jails. Akiyama MJ1, Kaba F1, Rosner Z1, Alper H1, Holzman RS1, MacDonald R1. Am J Public Health. 2016 Jul;106(7):1276-7. doi: 10.2105/AJPH.2016.303163. Epub 2016 May 19.

OBJECTIVES: To examine uptake of screening for all individuals born between 1945 and 1965 (referred to by the Centers for Disease Control and Prevention as the "birth cohort") and outline preliminary HCV prevalence data in the New York City jail system. **METHODS:** Data were extracted from electronic health records for all individuals screened for HCV between June 13, 2013, and June 13, 2014, in New York City jails. We used the Abbott EIA 2.0 HCV antibody assay for testing. **RESULTS:** In the year of study, 56 590 individuals were incarcerated; 15.1% were born between 1945 and 1965, and 84.6% were born after 1965. HCV screening was completed for 64.1% of the birth cohort and for 11.1% born after 1965, with 55.1% and 43.8% of cases found in these groups, respectively. The overall seropositivity rate was 20.6%. **CONCLUSIONS:** Birth cohort screening in a large jail system identified many HCV cases, but HCV infection was common among younger age groups. **PUBLIC HEALTH IMPLICATIONS:** Universal screening may be warranted pending further study including cost-effectiveness analyses.

Long Term Survival in Persons with Hemophilia and Chronic Hepatitis C: 40 Year Outcomes of a Large Single Center Cohort. Eyster ME1, Kong L2, Li M2, Schreibman IR3. Am J Hematol. 2016 May 23. doi: 10.1002/ajh.24427. [Epub ahead of print]

We studied the course of chronic HCV infections in a cohort of 222 persons with hemophilia (PWH) and von Willebrand disease followed at our center since 1973. Twenty two (10%) developed end stage liver disease (ESLD). Forty years after HCV infection, cumulative incidence of ESLD was 12.3% and overall survival was 45.5%. Those who were infected with HCV only (n=100) had a survival of 75.2%, while those infected with HIV (n=122) had a survival of 24% (P<.001). Survivals were significantly longer for those infected with HCV at younger age (< 15 years) compared to those infected over age 30 years (P=0.014). Cause specific deaths for ESLD and bleeding were 8.8% and 8.3% respectively. For HIV negative subjects, the annual hazard of death from ESLD and bleeding was near zero for the first 10 years, and then rose slowly over the next 20 years to 0.4/100py for ESLD and 0.2/100py for bleeding. Sixty subjects completed 79 treatment episodes. Sustained viral response rates increased from 7/21 (33%) between 1990-2001, to 17/29 (58%) between 2002-2011, and to 27/29 (93%), since 2012 with the advent of the directly acting antiviral agents. These results confirm the very slow ESLD progression rate in HIV negative PWH. However, the risk of death from both ESLD and bleeding increases steadily with longer duration of HCV infection. More aggressive surveillance to detect those with early fibrosis is needed now that curative treatment is possible in >95% of individuals.

Some payors do not want to foot the bill for an expensive HCV treatment because they will not see the benefits of curing their insuraed patient. How can discussions with insurers change by including the article below? The fact is that NOT treating their patients with HCV will result in higher costs elsewhere.

Higher all-cause hospitalization among patients with chronic hepatitis C: the Chronic Hepatitis Cohort Study (CHeCS), 2006-2013. Teshale EH1, Xing J1, Moorman A1, et al. J Viral Hepat. 2016 May 15. doi: 10.1111/jvh.12548. [Epub ahead of print]

In the United States, hospitalization among patients with chronic hepatitis C virus (HCV) infection is high. The healthcare burden associated with hospitalization is not clearly known. We analysed data from the Chronic Hepatitis Cohort Study, an observational cohort of patients receiving care at four integrated healthcare systems, collected from 2006 to 2013 to determine all-cause hospitalization rates of patients with chronic HCV infection and the other health system patients. To compare the hospitalization rates, we selected two health system patients for each chronic HCV patient using their propensity score (PS). Propensity score matching was conducted by site, gender, race, age and household income to minimize differences attributable to these characteristics. We also compared primary reason for hospitalization between chronic HCV patients and the other health system patients. Overall, 10 131 patients with chronic HCV infection and 20 262 health system patients were selected from the 1 867 802 health system patients and were matched by PS. All-cause hospitalization rates were 27.4 (27.0-27.8) and 7.4 (7.2-7.5) per 100 persons-year (PY) for chronic HCV patients and for the other health system patients, respectively. Compared to health system patients, hospitalization rates were significantly higher by site, gender, age group, race and household income among chronic HCV patients ($P < 0.001$). Compared to health system patients, chronic HCV patients were more likely to be hospitalized from liver-related conditions ($RR = 24.8$, $P < 0.001$). Hence, patients with chronic HCV infection had approximately 3.7-fold higher all-cause hospitalization rate than other health system patients. These findings highlight the incremental costs and healthcare burden of patients with chronic HCV infection associated with hospitalization.

A prescribing physician's approach to treating an HCV positive substance user is vital to the patients' successful initiation of HCV treatment. For too long, providers have approached addiction issues through a morality lens versus a medical lens thwarting any successful engagement with a patient who wants to make change but feels too much shame to talk about it. Their providers' approach reinforces their shame. Integrating the treatment of substance issues into the medical model will be vital to addressing the full wellness of every patient.

Clinicians' Views of Hepatitis C Virus Treatment Candidacy With Direct-Acting Antiviral Regimens for People Who Inject Drugs. Asher AK1,2, Portillo CJ1, Cooper BA1, et al. Subst Use Misuse. 2016 May 24:1-6. [Epub ahead of print]

BACKGROUND: Direct-acting antivirals (DAAs) are curative in most persons with chronic hepatitis C virus (HCV) infection. However, high cost and concerns about adherence and reinfection may present continued barriers to treatment, particularly for people who inject drugs (PWID). **OBJECTIVE:** To understand changes in assessments of treatment candidacy, given advances in treatment. **METHODS:** Clinicians attending the Liver Meeting® in 2014 who reported prescribing HCV treatment in the past three years were invited to complete a survey regarding HCV treatment decisions. Participants assessed their likelihood to treat HCV in PWID in association with time of abstinence from injection drug use and what impacts their decision to

provide treatment using interferon and DAAs. **RESULTS:** 108 clinicians completed the survey; 10% were willing to treat an active PWID (last injection within 30 days) using interferon-containing regimens, and 15% with all-oral regimens. For each increasing time interval of injection abstinence, there was an increase in the odds of a clinician reporting willingness to treat with DAAs (Odds Ratio (OR) 2.57, 95% CI 2.18, 3.03) and with interferon-based treatment (OR 2.22 (95% CI 1.90, 2.61), Reinfection and medication cost were cited as most important concerns when determining candidacy. **CONCLUSIONS:** A cure is now the norm in HCV treatment, and there is an increasing need to address the barriers to treating PWID, the population with the highest burden of infection. Understanding treatment candidacy assessments is essential to improving uptake. This study provides insight into how clinicians view treatment candidacy in this era of DAAs and can help identify supportive treatment environments and concurrent programs.

Value of expanding HCV screening and treatment policies in the United States. Linthicum MT1, Gonzalez YS, Mulligan K, et al. Am J Manag Care. 2016 May;22(6 Spec No.):SP227-35.
OBJECTIVES: To investigate the value of expanding screening and treatment for hepatitis C virus (HCV) infection in the United States. **STUDY DESIGN:** Discrete-time Markov model. **METHODS:** We modeled HCV progression and transmission to analyze the costs and benefits of investment in screening and treatment over a 20-year time horizon. Population-level parameters were estimated using National Health and Nutrition Examination Survey data and published literature. We considered 3 screening scenarios that vary in terms of clinical guidelines and physician awareness of guidelines. For each screening scenario, we modeled 3 approaches to treatment, varying the fibrosis stage of treatment initiation. Net social value was the key model outcome, calculated as the value of benefits from improved quality-adjusted survival and reduced transmission minus screening, treatment, and medical costs. **RESULTS:** Expanded screening policies generated the largest value to society. However, this value is constrained by the availability of treatment to diagnosed patients. Screening all individuals in the population generates $0.68 billion in social value if diagnosed patients are treated in fibrosis stages F3-F4 compared with $824 billion if all diagnosed patients in stages F0-F4 are treated. Moreover, increased screening generates cumulative net social value by year 8 to 9 under expanded treatment policies compared with 20 years if only patients in stages F3-F4 are treated. **CONCLUSIONS:** Although increasing screening for HCV may generate some value to society, only when paired with expanded access to treatment at earlier disease stages will it produce considerable value. Such a "test and treat" strategy is likely to entail higher short-term costs but also yield the greatest social benefits.

Coverage for hepatitis C drugs in Medicare Part D. Jung JK1, Feldman R, Cheong C, Du P, eslie D. Am J Manag Care. 2016 May;22(6 Spec No.):SP220-6.
OBJECTIVES: The recent arrival of new hepatitis C virus (HCV) drugs has brought fiscal pressures onto Medicare Part D; spending on HCV drugs in Part D jumped from $283 million in 2013 to $4.5 billion in 2014. We examined the current benefit designs for HCV drugs in Part D plans and analyzed patients' financial burden for those drugs. **STUDY DESIGN:** A cross-sectional analysis of CMS' July 2015 Part D Plan Formulary File and the Wolters Kluwer Health Medi-Span Electronic Drug File v.2. **METHODS:** We analyzed the type and amount of cost sharing for HCV drugs and the extent to which plans apply utilization management tools. We then estimated total out-of-pocket spending for beneficiaries to complete a course of treatment.

RESULTS: All Part D plans covered at least 1 recently introduced HCV drug, as of July 2015. Nearly all plans charged relatively high coinsurance and required prior authorization for new HCV drugs. For enrollees with no subsidy, the mean out-of-pocket spending needed to complete a course of treatment is substantial, ranging from $6297 to $10,889. For enrollees with a low-income subsidy, out-of-pocket spending varies between $10.80 and $1191. **CONCLUSIONS:** Under the current Part D benefits, HCV drug users with no subsidy face sizable financial burdens, even with catastrophic coverage and the recent in-gap discount for brand name drugs. As baby boomers-the group most likely to have HCV-join Medicare, efforts should be made to ensure patient access to these needed drugs.

Racial Disparities in Treatment Rates for Chronic Hepatitis C: Analysis of a Population-Based Cohort of 73,665 Patients in the United States. Vutien P1, Hoang J, Brooks L Jr, Nguyen NH, Nguyen MH. Medicine (Baltimore). 2016 May;95(22):e3719. doi: 10.1097/MD.0000000000003719.

Chronic hepatitis C (CHC) disproportionately affects racial minorities in the United States (US). Although prior studies have reported lower treatment rates in Blacks than in Caucasians, the rates of other minorities remain understudied. We aimed to examine antiviral treatment rates by race and to evaluate the effect of other demographic, medical, and psychiatric factors on treatment rates. We performed a population-based study of adult CHC patients identified via ICD-9CM query from OptumInsight's Data Mart from January 2009 to December 2013. Antiviral treatment was defined by pharmaceutical claims for interferon and/or pegylated-interferon. A total of 73,665 insured patients were included: 51,282 Caucasians, 10,493 Blacks, 8679 Hispanics, and 3211 Asians. Caucasians had the highest treatment rate (10.7%) followed by Blacks (8.8%), Hispanics (8.8%), and Asians (7.9%, P<.001). Hispanics had the highest cirrhosis rates compared with Caucasians, Blacks, and Asians (20.7% vs 18.3%, 17.1%, and 14.3%, respectively). Caucasians were the most likely to have a psychiatric comorbidity (20.1%) and Blacks the most likely to have a medical comorbidity (44%). Asians were the least likely to have a psychiatric (6.4%) or medical comorbidity (26.9%). On multivariate analysis, racial minority was a significant predictor of nontreatment with odds ratios of 0.82 [confidence interval (CI): 0.74-0.90] for Blacks, 0.87 (CI: 0.78-0.96) for Hispanics, and 0.73 (CI: 0.62-0.86) for Asians versus Caucasians. Racial minorities had lower treatment rates than Caucasians. Despite fewer medical and psychiatric comorbidities and higher incomes and educational levels, Asians had the lowest treatment rates. Hispanics also had lower treatment rates than Caucasians despite having higher rates of cirrhosis. Future studies should aim to identify underlying racial-related barriers to hepatitis C virus treatment besides socioeconomic status and medical or psychiatric comorbidities.

Barriers to Treatment Among New York City Residents with Chronic Hepatitis C Virus Infection, 2014. King A1, Bornschlegel K1, Johnson N1, Rude E1, Laraque F1. Public Health Rep. 2016 May-Jun;131(3):430-7.

OBJECTIVE: New, highly effective hepatitis C virus (HCV) medications recently changed the landscape of HCV treatment. Access to treatment, however, is limited. The New York City Department of Health and Mental Hygiene conducted an enhanced surveillance project to better understand the reasons patients are not treated for HCV. **METHODS:** In June 2014, we randomly selected 300 adults who were reported through routine surveillance as having a positive HCV ribonucleic acid test result and who had seen a medical provider since June 2012.

We collected information on demographics, treatment, and barriers to treatment from these 300 patients and their providers by telephone, fax, mail, and medical record review. **RESULTS:** Of 179 providers, 74 (41%) cited co-occurring conditions and 50 (28%) cited patients not keeping follow-up or referral appointments with specialists as common barriers to treatment. Forty providers (22%) reported that they do not prescribe HCV medications and instead refer patients to specialists for treatment. Of 89 patients citing barriers to treatment, 30 (34%) cited co-occurring conditions, 26 (29%) cited concerns about side effects, 21 (24%) indicated not feeling sick, 15 (17%) cited waiting for a better treatment regimen, and 12 (13%) cited medication costs or insurance issues. Only 11 providers and 10 patients denied any barriers to treatment. **CONCLUSION:** Increasing the number of New York City residents with HCV infection who are treated and cured will require programs to increase provider capacity, change provider behavior in treating patients with substance use and medical conditions, improve patient awareness of new medications, provide patient navigation and care coordination support through treatment, and initiate advocacy and policy work.

Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis.

Iyengar S1, Tay-Teo K1, Vogler S2, Beyer P1, Wiktor S1, de Joncheere K1, Hill S1. PLoS Med. 2016 May 31;13(5):e1002032. doi: 10.1371/journal.pmed.1002032. eCollection 2016.

INTRODUCTION: New hepatitis C virus (HCV) medicines have markedly improved treatment efficacy and regimen tolerability. However, their high prices have limited access, prompting wide debate about fair and affordable prices. This study systematically compared the price and affordability of sofosbuvir and ledipasvir/sofosbuvir across 30 countries to assess affordability to health systems and patients. **METHODS AND FINDINGS:** Published 2015 ex-factory prices for a 12-wk course of treatment were provided by the Pharma Price Information (PPI) service of the Austrian public health institute Gesundheit Österreich GmbH or were obtained from national government or drug reimbursement authorities and recent press releases, where necessary. Prices in Organisation for Economic Co-operation and Development (OECD) member countries and select low- and middle-income countries were converted to US dollars using period average exchange rates and were adjusted for purchasing power parity (PPP). We analysed prices compared to national economic performance and estimated market size and the cost of these drugs in terms of countries' annual total pharmaceutical expenditure (TPE) and in terms of the duration of time an individual would need to work to pay for treatment out of pocket. Patient affordability was calculated using 2014 OECD average annual wages, supplemented with International Labour Organization median wage data where necessary. All data were compiled between 17 July 2015 and 25 January 2016. For the base case analysis, we assumed a 23% rebate/discount on the published price in all countries, except for countries with special pricing arrangements or generic licensing agreements. The median nominal ex-factory price of a 12-wk course of sofosbuvir across 26 OECD countries was US$42,017, ranging from US$37,729 in Japan to US$64,680 in the US. Central and Eastern European countries had higher PPP-adjusted prices than other countries: prices of sofosbuvir in Poland and Turkey (PPP$101,063 and PPP$70,331) and of ledipasvir/sofosbuvir in Poland (PPP$118,754) were at least 1.09 and 1.63 times higher, respectively than in the US (PPP$64,680 and PPP$72,765). Based on PPP-adjusted TPE and without the cost of ribavirin and other treatment costs, treating the entire HCV viraemic population with these regimens at the PPP-adjusted prices with a 23% price reduction would amount to at least one-tenth of current TPE across the countries included in this study, ranging

from 10.5% of TPE in the Netherlands to 190.5% of TPE in Poland. In 12 countries, the price of a course of sofosbuvir without other costs was equivalent to 1 y or more of the average annual wage of individuals, ranging from 0.21 y in Egypt to 5.28 y in Turkey. This analysis relies on the accuracy of price information and infection prevalence estimates. It does not include the costs of diagnostic testing, supplementary treatments, treatment for patients with reinfection or cirrhosis, or associated health service costs. **CONCLUSIONS:** Current prices of these medicines are variable and unaffordable globally. These prices threaten the sustainability of health systems in many countries and prevent large-scale provision of treatment. Stakeholders should implement a fairer pricing framework to deliver lower prices that take account of affordability. Without lower prices, countries are unlikely to be able to increase investment to minimise the burden of hepatitis C.

Identification and Clinical Management of Persons with Chronic Hepatitis C Virus Infection - Cherokee Nation, 2012-2015. Mera J, Vellozzi C, Hariri S, et al. MMWR Morb Mortal Wkly Rep. 2016 May 13;65(18):461-6. doi: 10.15585/mmwr.mm6518a2.
An estimated 3.5 million persons in the United States are living with hepatitis C virus (HCV) infection, resulting in approximately 20,000 deaths each year, primarily from cirrhosis or hepatocellular carcinoma (1,2). American Indian/Alaska Native (AI/AN) populations have the highest incidence of acute HCV infection among all U.S. racial/ethnic groups and are at greater risk for HCV-related mortality compared with the general population (3). In 2013, new antiviral drugs became available that make possible 8-12 week treatment regimens with fewer adverse events and are able to achieve sustained virologic response (SVR) in >90% of treated patients (4), equivalent to a cure of HCV infection. Also of note, HCV testing recommendations were expanded in 2012 by CDC and in 2013 by the U.S. Preventive Services Task Force to include one-time testing of persons born during 1945-1965 (the "baby boomer" cohort) in addition to anyone at increased risk for HCV infection (5,6). Given the availability of new HCV drugs, expanded testing recommendations, and high incidence of HCV infection in AI/AN populations, in October 2012, Cherokee Nation Health Services (CNHS) implemented a tribal HCV testing policy.* As part of the policy, CNHS added a reminder in the electronic health record (EHR) for clinical decision support and provided HCV education to primary care clinicians. From October 2012 to July 2015, among 92,012 persons with at least one CNHS clinic encounter, the cumulative number who received HCV screening for the first time increased from 3,337 (3.6%) to 16,772 (18.2%). The largest percentage of HCV screening was among persons born during 1945-1965. Of 715 persons who tested positive for HCV antibodies, 488 (68.3%) were tested for HCV RNA; among those 488 persons, 388 (79.5%) were RNA positive and were thus confirmed to have chronic HCV infection. Treatment was initiated for 223 (57.5%) of the 388 with chronic infection; 201 (90.1%) completed treatment, of whom 180 (89.6%) achieved SVR. CNHS has successfully increased HCV testing and treatment and is now collaborating with CDC and other external partners to develop an HCV elimination program for the Cherokee Nation that might serve as a model for similar settings.

Birth Cohort Testing for Hepatitis C Virus - Indian Health Service 2012-2015. Reilley B, Leston J, Hariri S, Neel L, Rudd M, Galope M, Ward J, Vellozzi C. MMWR Morb Mortal Wkly Rep. 2016 May 13;65(18):467-9. doi: 10.15585/mmwr.mm6518a3.
Hepatitis C virus (HCV) infection is a substantial and largely unrecognized public health problem. An estimated 3.5 million persons in the United States are currently living with HCV

infection, at least half of whom are unaware of their infection (1-3). Persons born during 1945-1965 (the "baby boomer" birth cohort) have a sixfold higher prevalence (2.6%) than adults of other ages, and represent 81% of all persons chronically infected with HCV (4). Therefore, in addition to recommending testing for all persons at risk for HCV infection, CDC and the U.S. Preventive Services Task Force (USPSTF) recommend one-time HCV testing for the birth cohort (5,6). Compared with the national average, American Indian/Alaska Native (AI/AN) persons have approximately twofold the rate of acute HCV incidence and HCV associated mortality (2). In June 2012, the Indian Health Service (IHS) implemented HCV testing in the 1945-1965 birth cohort and created a nationally standardized performance measure to monitor implementation of the recommendation. As of June 2015, the proportion of the birth cohort screened for HCV increased from a baseline of 7.9% (14,402/182,503) to 32.5% (68,514/211,014) among the AI/AN population served by IHS nationwide; provider training and the use of clinical decision tools were associated with increases in HCV testing. With this fourfold increase in testing in just 3 years, IHS needs to prepare for the challenges associated with increased identification of persons living with HCV infection.

While alcohol is legal, there is an incredible amount of judgment and stigma that comes along with an HCV diagnosis and someone who drinks alcohol. Usually the first question is 'well, did you drink?' What is likely NOT considered, is that patients who are adults and living with HCV for many years acquired HCV through other drug use *while* consuming alcohol. The other drug use, likely the method that transmitted HCV, has stopped, but occasional alcohol use may remain. How can the topic of alcohol consumption and overall liver health be better synergized?

Association of Hepatitis C Virus With Alcohol Use Among U.S. Adults: NHANES 2003-2010. Taylor AL1, Denniston MM2, Klevens RM2, McKnight-Eily LR3, Jiles RB2. Am J Prev Med. 2016 May 2. pii: S0749-3797(16)30065-4. doi: 10.1016/j.amepre.2016.02.033. [Epub ahead of print]

INTRODUCTION: Excessive alcohol use exacerbates morbidity and mortality among hepatitis C virus (HCV)-infected people. The purpose of this study was to describe self-reported patterns of alcohol use and examine the association with HCV infection and other sociodemographic and health-related factors. **METHODS:** Data from 20,042 participants in the 2003-2010 National Health and Nutrition Examination Survey were analyzed in 2014. Estimates were derived for self-reported demographic characteristics, HCV-RNA (indicative of current HCV infection) status, and alcohol use at four levels: lifetime abstainers, former drinkers, non-excessive current drinkers, and excessive current drinkers. **RESULTS:** Former drinkers and excessive current drinkers had a higher prevalence of HCV infection (2.2% and 1.5%, respectively) than never or non-excessive current drinkers (0.4% and 0.9%, respectively). HCV-infected adults were estimated to ever drink five or more drinks/day almost every day at some time during their lifetime about 3.3 times more often (43.8% vs 13.7%, $p<0.001$) than those who were never infected with HCV. Controlling for age, sex, race/ethnicity, education, and having a usual source of health care, HCV infection was significantly associated with excessive current drinking (adjusted prevalence ratio, 1.3; 95% CI=1.1, 1.6) and former drinking (adjusted prevalence ratio, 1.3; 95% CI=1.1, 1.6). **CONCLUSIONS:** Chronic HCV infection is associated with both former and excessive current drinking. Public health HCV strategies should implement interventions with emphasis on alcohol abuse, which negatively impacts disease progression for HCV-infected individuals.

Hepatitis C Virus Testing and Linkage to Care in North Carolina and South Carolina Jails, 2012-2014. Schoenbachler BT1, Smith BD2, Seña AC3, Hilton A4, Bachman S5, Lunda M6, Spaulding AC7. Public Health Rep. 2016 May-Jun;131 Suppl 2:98-104.

OBJECTIVE: We evaluated a hepatitis C virus (HCV) testing and linkage-to-care post-release program among detainees of small- to medium-sized jails in North Carolina and South Carolina as part of the Hepatitis Testing and Linkage to Care initiative. **METHODS:** An HCV testing and linkage-to-care program was implemented in selected jails in North Carolina and South Carolina from December 2012 to March 2014. Health-care workers not affiliated with the jails conducted HCV antibody (anti-HCV) and HCV ribonucleic acid (RNA) testing and linkage-to-care activities. The North Carolina jail provided universal opt-out testing for HCV; South Carolina jails initially targeted high-risk individuals before expanding to routine testing. **RESULTS:** Of 669 detainees tested for HCV in North Carolina, 88 (13.2%) tested anti-HCV positive, of whom 81 (92.0%) received an HCV RNA test, 66 (81.5%) of whom tested HCV RNA positive (i.e., currently infected). Of the 66 detainees with current HCV infection, 18 were referred to HCV medical care post-release and 10 attended their first appointment. Of 224 detainees tested for HCV in South Carolina, 18 (8.0%) tested anti-HCV positive, of whom 13 received an HCV RNA test. Nine of 13 detainees tested HCV RNA positive, seven detainees were referred to post-release medical care, and two detainees attended their first appointment. Overall, 106 of 893 (11.9%) detainees were anti-HCV positive. **CONCLUSION:** This study demonstrated that HCV testing, identification of infection, and linkage to care are feasible among jail populations. The rate of anti-HCV positivity was lower than that found in national studies of incarcerated populations, suggesting that HCV infection prevalence in jails may vary across U.S. states or regions.

Improving Screening Methods for Hepatitis C Among People Who Inject Drugs: Findings from the HepTLC Initiative, 2012-2014. Blackburn NA1, Patel RC1, Zibbell JE2. Public Health Rep. 2016 May-Jun;131 Suppl 2:91-7.

OBJECTIVE: People who inject drugs (PWID) are at increased risk for hepatitis C virus (HCV) infection. We examined HCV testing outcomes among PWID through CDC's Hepatitis Testing and Linkage to Care initiative, which promoted viral hepatitis B and hepatitis C screening, posttest counseling, and linkage to care at 34 U.S. sites during 2012-2014. Ten grantees in nine geographically diverse cities conducted HCV testing among PWID. **METHODS:** Among those testing positive for HCV antibody (anti-HCV), we calculated the proportion who were offered a confirmatory HCV ribonucleic acid (RNA) test, positively diagnosed, and referred to a specialist for care. We stratified anti-HCV-positive people who completed each step by same-day testing (i.e., an HCV RNA test administered on the same date as an anti-HCV test) vs. person not receiving same-day testing to evaluate whether the need for follow-up testing affected diagnosis of chronic infection and linkage to care. **RESULTS:** A total of 15,274 people received an anti-HCV test at 84 testing sites targeting PWID. Of those, 11,159 (73%) reported having injected drugs in their lifetime, 7,789 (51%) reported injecting drugs in the past 12 months, and 3,495 (23%) tested anti-HCV positive. A total of 1,630 people received testing for HCV RNA, of whom 1,244 (76%) were HCV RNA positive. When not receiving both tests on the same day, 601 of 2,465 (24%) anti-HCV-positive people received an HCV RNA test. **CONCLUSION:** Strategies to diagnose PWID for HCV infection are needed to reduce associated morbidity and mortality. Agencies can substantially increase the number of PWID who are diagnosed and

informed of their HCV infection by administering both anti-HCV and HCV RNA tests during a single testing event.

High-Yield Birth-Cohort Hepatitis C Virus Screening and Linkage to Care Among Underserved African Americans, Atlanta, Georgia, 2012-2013. Miller LS1, Rollin F1, Fluker SA1, Lundberg KL1, Park B1, Quairoli K2, Niyibizi NK3, Spaulding AC3. Public Health Rep. 2016 May-Jun;131 Suppl 2:84-90.

OBJECTIVE: Hepatitis C virus (HCV) infection disproportionately affects certain populations, including those born between 1945 and 1965 (i.e., baby boomers) and African Americans. As part of the Hepatitis Testing and Linkage to Care initiative, which promoted hepatitis B and hepatitis C screening, posttest counseling, and linkage to care at 34 U.S. sites, we conducted routine HCV screening to identify previously undiagnosed, primarily African American baby boomers with chronic hepatitis C infection and link them to care. **METHODS:** We launched the Internal Medicine Trainees Identifying and Linking to Treatment for Hepatitis C (TILT-C) initiative at the Grady Memorial Hospital Primary Care Center and Grady Liver Clinic in Atlanta, Georgia, in October 2012, and present results from the first year. TILT-C faculty implemented an electronic medical record prompt and conducted educational sessions to boost HCV screening. A project coordinator tracked testing outcomes and linked HCV-positive patients to care. **RESULTS:** Of 2,894 patients tested for anti-HCV, 201 (6.9%) tested positive. Men had a significantly higher ($p<0.001$) prevalence of HCV infection than women, with 106 of 1,091 (9.7%) men compared with 95 of 1,803 (5.3%) women testing anti-HCV positive. A total of 174 of 201 (86.6%) anti-HCV-positive patients received HCV ribonucleic acid (RNA) testing. Of 124 patients with a positive HCV RNA test, 122 were referred to care and 120 attended the first appointment. **CONCLUSION:** The TILT-C screening program was feasible and effective in detecting previously undiagnosed HCV infection and linking patients to care. The unexpectedly high prevalence of HCV infection in this primarily African American, baby boomer population underscores the need for aggressive HCV screening efforts in similar populations.

Hospital-Based Hepatitis C Screening of Baby Boomers in a Majority Hispanic South Texas Cohort: Successes and Barriers to Implementation. Taylor BS1, Hanson JT2, Veerapaneni P3, Villarreal R4, Fiebelkorn K5, Turner BJ6. Public Health Rep. 2016 May-Jun;131 Suppl 2:74-83.

OBJECTIVE: To comply with the 2012 CDC recommendations for hepatitis C virus (HCV) screening, we implemented a new HCV screening program for patients born between 1945 and 1965 at a South Texas safety-net hospital. **METHODS:** Patients with no HCV diagnosis or prior HCV test received an automated order for HCV antibody (anti-HCV) tests combined with reflex HCV ribonucleic acid (RNA) polymerase chain reaction. An inpatient counselor educated anti-HCV-positive patients. A bilingual patient navigator assisted newly diagnosed chronic HCV patients with linkage to primary and specialty care. We examined results for Hispanic vs. non-Hispanic patients in the first 10 months of project implementation in 2013-2014. **RESULTS:** Of 2,327 patients screened for HCV, the 192 (8%) patients who tested anti-HCV positive were younger than those who tested negative (56 vs. 58 years, respectively, $p<0.001$) and more likely to be male ($p<0.001$). Of the 167 anti-HCV-positive patients tested for HCV RNA, 108 (65%) were HCV RNA positive (5% of cohort). Barriers to care for HCV RNA-positive patients included a lack of health insurance, current substance abuse, incarceration, and homelessness.

Hispanic HCV RNA-positive patients were more likely than non-Hispanic HCV RNA-positive patients to be substance abusers or incarcerated. Of all HCV RNA-positive patients, 103 patients (95%) received counseling, 94 patients (87%) were linked to primary care, 47 patients (44%) were linked to specialty care, and eight patients (7%) started treatment. **CONCLUSION:** The prevalence of anti-HCV-positive and chronically HCV-infected patients was higher than many Hispanic or non-Hispanic white cohorts. Most Hispanic patients newly diagnosed with chronic HCV had barriers to care for HCV infection that must be overcome if HCV screening is to reduce morbidity and mortality in this population.

Integrating Routine HCV Testing in Primary Care: Lessons Learned from Five Federally Qualified Health Centers in Philadelphia, Pennsylvania, 2012-2014. Coyle C1, Kwakwa H2, Viner K3.
OBJECTIVE: An estimated 2.7-3.9 million Americans are infected with hepatitis C virus (HCV). Despite being the most common blood-borne virus in the United States, routine HCV testing is not commonly practiced. To address this gap, we measured the impact of integrated routine HCV testing on patient care. **METHODS:** As part of CDC's Hepatitis Testing and Linkage to Care initiative, which promoted viral hepatitis B and hepatitis C screening, posttest counseling, and linkage to care at 34 U.S. sites, National Nursing Centers Consortium integrated a routine opt-out HCV testing and linkage-to-care model at five federally qualified health centers in Philadelphia, Pennsylvania, from October 1, 2012, to June 30, 2014. The model included medical assistant-initiated testing, reflex laboratory-based HCV tests, and electronic health record modifications to prompt, track, and facilitate reimbursement for tests performed on uninsured patients. **RESULTS:** During the study period, 4,207 unique patients received HCV antibody (anti-HCV) testing, of whom 488 (11.6%) tested anti-HCV positive. Of those testing positive, 433 (88.7%) received a confirmatory HCV RNA test; of these 433 recipients, 313 (72.3%) were diagnosed with current infection (overall prevalence = 7.4%), of which 243 (77.6%) received their HCV RNA-positive results, 184 (58.8%) were referred to an HCV care provider, and 121 (38.7%) were linked to care. The highest rates of current infection were among non-Hispanic white patients (18.1%, 90/496); patients from the Public Health Management Corporation Care Clinic, which treats HIV and HCV patients on-site (14.3%, 200/1,394); and patients aged 50-69 years (10.7%, 189/1,767). **CONCLUSION:** Our model successfully integrated HCV testing and linkage to care into routine primary care. This study also identified potential successes and barriers that may be experienced by other primary care health centers that are integrating HCV testing.

The Significance of Harm Reduction as a Social and Health Care Intervention for Injecting Drug Users: An Exploratory Study of a Needle Exchange Program in Fresno, California. Clarke K1, Harris D1, Zweifler JA2, Lasher M2, Mortimer RB2, Hughes S2. Soc Work Public Health. 2016 May 11:1-10. [Epub ahead of print]
Infectious disease remains a significant social and health concern in the United States. Preventing more people from contracting HIV/AIDS or Hepatitis C (HCV), requires a complex understanding of the interconnection between the biomedical and social dimensions of infectious disease. Opiate addiction in the US has skyrocketed in recent years. Preventing more cases of HIV/AIDS and HCV will require dealing with the social determinants of health. Needle exchange programs (NEPs) are based on a harm reduction approach that seeks to minimize the risk of infection and damage to the user and community. This article presents an exploratory

small-scale quantitative study of the injection drug using habits of a group of injection drug users (IDUs) at a needle exchange program in Fresno, California. Respondents reported significant decreases in high risk IDU behaviors, including sharing of needles and to a lesser extent re-using of needles. They also reported frequent use of clean paraphernalia. Greater collaboration between social and health outreach professionals at NEPs could provide important frontline assistance to people excluded from mainstream office-based services and enhance efforts to reduce HIV/AIDS or HCV infection

LIVER CANCER

Proposal and validation of a new model to estimate survival for hepatocellular carcinoma patients. Liu PH1, Hsu CY2, Hsia CY3, et al. Eur J Cancer. 2016 May 31;63:25-33. doi: 10.1016/j.ejca.2016.04.023. [Epub ahead of print]
BACKGROUND AND AIMS: The survival of hepatocellular carcinoma (HCC) patients is heterogeneous. We aim to develop and validate a simple prognostic model to estimate survival for HCC patients (MESH score). **METHODS:** A total of 3182 patients were randomised into derivation and validation cohort. Multivariate analysis was used to identify independent predictors of survival in the derivation cohort. The validation cohort was employed to examine the prognostic capabilities. **RESULTS:** The MESH score allocated 1 point for each of the following parameters: large tumour (beyond Milan criteria), presence of vascular invasion or metastasis, Child-Turcotte-Pugh score ≥6, performance status ≥2, serum alpha-fetoprotein level ≥20 ng/ml, and serum alkaline phosphatase ≥200 IU/L, with a maximal of 6 points. In the validation cohort, significant survival differences were found across all MESH scores from 0 to 6 (all $p < 0.01$). The MESH system was associated with the highest homogeneity and lowest corrected Akaike information criterion compared with Barcelona Clínic Liver Cancer, Hong Kong Liver Cancer (HKLC), Cancer of the Liver Italian Program, Taipei Integrated Scoring and model to estimate survival in ambulatory HCC Patients systems. The prognostic accuracy of the MESH scores remained constant in patients with hepatitis B- or hepatitis C-related HCC. The MESH score can also discriminate survival for patients from early to advanced stages of HCC. **CONCLUSIONS:** This newly proposed simple and accurate survival model provides enhanced prognostic accuracy for HCC. The MESH system is a useful supplement to the BCLC and HKLC classification schemes in refining treatment strategies.

Alcohol intake increases the risk of hepatocellular carcinoma in patients with hepatitis C virus-related compensated cirrhosis: a prospective study. Vandenbulcke H1, Moreno C2, Colle I3, et al. J Hepatol. 2016 May 12. pii: S0168-8278(16)30184-2. doi: 10.1016/j.jhep.2016.04.031. [Epub ahead of print]
Whether alcohol intake increases the risk of complications in patients with HCV-related cirrhosis remains unclear.
AIM: To determine the impact of alcohol intake and viral eradication on the risk of hepatocellular carcinoma (HCC), decompensation of cirrhosis and death. **PATIENTS AND METHODS:** Data on alcohol intake and viral eradication were prospectively collected in 192 patients with compensated HCV-related cirrhosis. **RESULTS:** 74 patients consumed alcohol (median alcohol intake: 15 g/day); 68 reached viral eradication. During a median follow-up of 58 months, 33 patients developed HCC, 53 experienced at least one decompensation event, and 39 died. The 5-year cumulative incidence rate of HCC was 10.6% (95% CI: 4.6-16.6) in abstainers

vs. 23.8% (95% CI: 13.5-34.1) in consumers (p=0.087), and 2.0% (95% CI: 0-5.8) vs. 21.7% (95% CI: 14.2-29.2) in patients with and without viral eradication (p=0.002), respectively. The lowest risk of HCC was observed for patients without alcohol intake and with viral eradication (0%) followed by patients with alcohol intake and viral eradication (6.2% [95% CI: 0-18.4]), patients without alcohol intake and no viral eradication (15.9% [95% CI: 7.1-24.7]), and patients with alcohol intake and no viral eradication (29.2% [95% CI: 16.5-41.9]) (p=0.009). In multivariate analysis, lack of viral eradication and alcohol consumption were associated with the risk of HCC (hazard ratio for alcohol consumption: 3.43, 95% CI: 1.49-7.92, p=0.004). Alcohol intake did not influence the risk of decompensation or death. **CONCLUSION:** Light-to-moderate alcohol intake increases the risk of HCC in patients with HCV-related cirrhosis. Patient care should include measures to ensure abstinence

Links between Human LINE-1 Retrotransposons and Hepatitis Virus-Related Hepato-cellular Carcinoma. Honda T1. Front Chem. 2016 May 11;4:21. doi: 10.3389/fchem.2016.00021. eCollection 2016.
Hepatocellular carcinoma (HCC) accounts for approximately 80% of liver cancers, the third most frequent cause of cancer mortality. The most prevalent risk factors for HCC are infections by hepatitis B or hepatitis C virus. Findings suggest that hepatitis virus-related HCC might be a cancer in which LINE-1 retrotransposon, often termed L1, activity plays a potential role. Firstly, hepatitis viruses can suppress host defense factors that also control L1 mobilization. Secondly, many recent studies also have indicated that hypomethylation of L1 affects the prognosis of HCC patients. Thirdly, endogenous L1 retrotransposition was demonstrated to activate oncogenic pathways in HCC. Fourthly, several L1 chimeric transcripts with host or viral genes are found in hepatitis virus-related HCC. Such lines of evidence suggest a linkage between L1 retrotransposons and hepatitis virus-related HCC. Here, I briefly summarize current understandings of the association between hepatitis virus-related HCC and L1. Then, I discuss potential mechanisms of how hepatitis viruses drive the development of HCC via L1 retrotransposons. An increased understanding of the contribution of L1 to hepatitis virus-related HCC may provide unique insights related to the development of novel therapeutics for this disease.

Clinical significance and diagnostic value of serum dickkopf-1 in patients with hepato-cellular carcinoma. Fouad YM1, Mohamed HI1, Kamal EM1, Rasek MA2. Scand J Gastroenterol. 2016 May 10:1-5. [Epub ahead of print]
BACKGROUND: Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide. It has been widely established that the early detection of HCC enables more treatment options and translates to improved survival. **AIM:** To assess the diagnostic accuracy of DKK1 as a serum protein marker for HCC by examining its diagnostic sensitivity and specificity in HCC. **METHODS:** We analyzed data for 50 patients with hepatitis C virus (HCV) related HCC as the studied group. Twenty patients with chronic hepatitis C and 20 patients with HCV-related liver cirrhosis will serve as control group. DKK1 was measured in serum by ELISA. We used receiver operating characteristics (ROC) to calculate its diagnostic accuracy. **RESULTS:** We assessed serum DKK1 in 90 participants: 50 with HCC (studied group), 20 with chronic HCV infection, and 20 with liver cirrhosis (as control group). Serum concentration of DKK1 was significantly higher in HCC group and values did not differ significantly between the two control groups. We performed multivariate regression analysis using AFP level, number of focal lesions,

focal lesion size and Portal vein thrombosis as an independent variable. ROC curves showed the optimum diagnostic cut off was 1.5 ng/mL (sensitivity 67.5%, specificity 89.3%).
CONCLUSION: Serum DKK1 could potentially be used for early diagnosis of HCC and complement measurement of AFP in the diagnosis of HCC.

Development of hepatocellular carcinoma in patients with hepatitis C virus infection who achieved sustained virological response following interferon therapy: A large-scale, long-term cohort study. Nagaoki Y1, Aikata H1, Nakano N1, et al. J Gastroenterol Hepatol. 2016 May;31(5):1009-15. doi: 10.1111/jgh.13236.
BACKGROUND: We assessed the risk factors for the development of hepatocellular carcinoma (HCC) following successful eradication of hepatitis C virus (HCV) with interferon (IFN) therapy in a long-term, large-scale cohort study. **METHODS:** We reviewed 1094 consecutive patients with HCV who achieved sustained virological response (SVR) following IFN therapy between January 1995 and September 2013. **RESULTS:** During the observation period (median 50 months: range 13-224), 36 (3%) of 1094 patients developed HCC after SVR. The median period from SVR to diagnosis of HCC was 37 months (range 17-141), and the cumulative rates of HCC at 5, 10, and 15 years were 4%, 6%, and 12%, respectively. Multivariate analysis identified old age (≥60 years, HR, 3.1: 95%CI, 1.3-6.6: $P = 0.009$), male sex (HR, 12.0: 95%CI, 2.8-50.0: $P < 0.0001$), advanced fibrosis stage (F3/4, HR, 3.2: 95%CI, 1.6-7.2: $P < 0.0001$), and alpha-fetoprotein ≥10 ng/mL at 1 year after SVR (HR, 7.8: 95%CI, 2.9-16.8: $P < 0.0001$) as significant and independent risk factors for post-SVR HCC. **CONCLUSIONS:** Older age and male sex (host factors), advanced fibrosis stage (pre-IFN treatment factor), and higher alpha-fetoprotein values (post-treatment factor) were significantly associated with HCC development after HCV eradication.