
BACKGROUND: Novel interferon- and ribavirin-free regimens are needed to treat hepatitis C virus (HCV) infection. OBJECTIVE: To evaluate the safety and efficacy of grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A inhibitor) in treatment-naive patients. DESIGN: Randomized, blinded, placebo-controlled trial. (ClinicalTrials.gov: NCT02105467).

SETTING: 60 centers in the United States, Europe, Australia, Scandinavia, and Asia.

PATIENTS: Cirrhotic and noncirrhotic treatment-naive adults with genotype 1, 4, or 6 infection. INTERVENTION: Oral, once-daily, fixed-dose grazoprevir 100 mg/elbasvir 50 mg for 12 weeks, stratified by fibrosis and genotype. Patients were randomly assigned 3:1 to immediate or deferred therapy. MEASUREMENTS: Proportion of patients in the immediate-treatment group achieving unquantifiable HCV RNA 12 weeks after treatment (SVR12); adverse events in both groups. RESULTS: Among 421 participants, 194 (46%) were women, 157 (37%) were nonwhite, 382 (91%) had genotype 1 infection, and 92 (22%) had cirrhosis. Of 316 patients receiving immediate treatment, 299 of 316 (95% [95% CI, 92% to 97%]) achieved SVR12, including 144 of 157 (92% [CI, 86% to 96%]) with genotype 1a, 129 of 131 (99% [CI, 95% to 100%]) with genotype 1b, 18 of 18 (100% [CI, 82% to 100%]) with genotype 4, 8 of 10 (80% [CI, 44% to 98%]) with genotype 6, 68 of 70 (97% [CI, 90% to 100%]) with cirrhosis, and 231 of 246 (94% [CI, 90% to 97%]) without cirrhosis. Virologic failure occurred in 13 patients (4%), including 1 case of breakthrough infection and 12 relapses, and was associated with baseline NS5A polymorphisms and emergent NS3 or NS5A variants or both. Serious adverse events occurred in 9 (2.8%) and 3 (2.9%) patients in the active and placebo groups, respectively (difference <0.05 percentage point [CI, -5.4 to 3.1 percentage points]); none were considered drug related. The most common adverse events in the active group were headache (17%), fatigue (16%), and nausea (9%). LIMITATION: The study lacked an active-comparator control group and included relatively few genotype 4 and 6 infections. CONCLUSION: Grazoprevir-elbasvir achieved high SVR12 rates in treatment-naive cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection. This once-daily, all-oral, fixed-combination regimen represents a potent new therapeutic option for chronic HCV infection.

BACKGROUND: Worldwide, although predominantly in low-income countries in the Middle East and Africa, up to 13% of hepatitis C virus (HCV) infections are caused by HCV genotype 4. For patients with HCV genotype 1, the combination of ledipasvir and sofosbuvir has been shown to cure high proportions of patients with excellent tolerability, but this regimen has not been assessed for the treatment of HCV genotype 4. We assessed the efficacy, safety, and tolerability of 12 weeks of combination therapy with ledipasvir and sofosbuvir for patients with chronic HCV genotype 4 infections. METHODS: In this single-centre, open-label cohort, phase 2a trial, patients with HCV genotype 4 who were treatment naive or interferon treatment experienced (HIV-negative) were sequentially enrolled at the Clinical Center of the National Institutes of Health, Bethesda, MD, USA. We gave patients 12 weeks of ledipasvir (90 mg) and sofosbuvir (400 mg) as a single combination tablet once per day. The primary efficacy endpoint was sustained viral response at 12 weeks (SVR12), as measured by the proportion of patients with HCV RNA concentrations less than the lower limit of quantification (COBAS TaqMan HCV test, version 1.0, 43 IU/mL). The primary safety endpoint was the frequency and severity of adverse events. We did our analyses on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT01805882. FINDINGS: Between Sept 16, 2013, and Nov 2, 2014, we recruited 21 patients. 20 (95%) of 21 patients completed 12 weeks of treatment and achieved SVR12 (95% CI 76-100), including seven patients with cirrhosis. One patient was non-adherent to study drugs and withdrew from the study, but was included in the intention-to-treat analysis. No patients discontinued treatment because of adverse events and no grade 3 or 4 adverse events occurred that were related to study medications. The most common adverse events were diarrhoea (two patients), fatigue (three patients), nausea (two patients), and upper respiratory infections (two patients). INTERPRETATION: Ledipasvir and sofosbuvir treatment for 12 weeks was well tolerated by patients with HCV genotype 4 and resulted in 100% SVR for all patients who received all 12 weeks of study drugs, irrespective of previous treatment status and underlying liver fibrosis. This is the first report of a single-pill, all-oral, interferon-free, ribavirin-free treatment for patients with HCV genotype 4. FUNDING: NIAID, National Cancer Institute and Clinical Center Intramural Program. The study was also supported in part by a Cooperative Research and Development Agreement between NIH and Gilead Sciences.


BACKGROUND: Alisporivir (ALV) is an oral, host-targeting agent with pangenotypic anti-hepatitis C virus (HCV) activity and a high barrier to resistance. AIM: To evaluate efficacy and safety of ALV plus peginterferon-α2a and ribavirin (PR) in treatment-naïve patients with chronic HCV genotype 1 infection. METHODS: Double-blind, randomised, placebo-controlled, Phase 3 study evaluating ALV 600 mg once daily [response-guided therapy (RGT) for 24 or 48 weeks or 48 weeks fixed duration] or ALV 400 mg twice daily RGT with PR, compared to PR alone. Following a Food and Drug Administration partial clinical hold, ALV/placebo was discontinued and patients completed treatment with PR only. At that time, 87% of patients had received ≥12
weeks and 20% had received ≥24 weeks of ALV/PR triple therapy. **RESULTS:** A total of 1081 patients were randomised (12% cirrhosis, 55% CT/TT IL28B). Addition of ALV to PR improved virological response in a dose-dependent fashion. Overall, sustained virological response (SVR12; primary endpoint) was 69% in all ALV groups vs. 53% in PR control. Highest SVR12 (90%) was achieved in patients treated with ALV 400 mg twice daily and PR for >24 weeks. Seven cases of pancreatitis were reported, with similar frequency between ALV/PR and PR control groups (0.6% vs. 0.8% respectively). Adverse events seen more frequently with ALV/PR than with PR alone were anaemia, thrombocytopenia, hyperbilirubinaemia and hypertension. **CONCLUSIONS:** Alisporivir, especially the 400 mg twice daily regimen, increased efficacy of PR therapy in treatment-naïve patients with HCV genotype 1 infection. The mechanism of action and pangenotypic activity suggest that alisporivir could be useful in interferon-free combination regimens.

**Effect of Peginterferon or Ribavirin Dosing on Efficacy of Therapy With Telaprevir in Treatment-Experienced Patients With Chronic Hepatitis C and Advanced Liver Fibrosis: A Multicenter Cohort Study.** Janczewska E1, Flisiak R, Zarebska-Michaluk D, et al. Medicine (Baltimore). 2015 Sep;94(38):e1411. doi: 10.1097/MD.0000000000001411. We investigated the safety, efficacy, and impact of ribavirin and peginterferon dose reduction on complete early virologic response and sustained virologic response (SVR) to triple therapy with telaprevir in treatment-experienced patients with advanced liver fibrosis. Treatment was initiated for 211 patients who failed treatment with peginterferon and ribavirin, with bridging fibrosis (F3, n=68) or cirrhosis (F4, n=143), including 103 (49%) null-responders (NR), 30 (14%) partial responders (PR), and 78 (37%) relapers (REL). Impaired liver function (ILF) platelets <100,000/mm or albumin <35 g/L were present in 40 patients. The distribution of hepatitis C virus subtypes was: 1a, 1b, or 1, with undetermined subtype for 10 (5%), 187 (89%), and 14 (6%) patients, respectively. Treatment was started with peginterferon alpha-2a or alpha-2b, ribavirin, and telaprevir at standard doses. The overall SVR24 rate was 56% and was lower in cirrhotic patients (NR: 35%, PR: 40%, and REL: 63%, respectively) than in patients with bridging fibrosis (NR: 50%, PR: 75%, and REL: 75%, respectively). The lowest probability of SVR24 was in NRs with ILF (26%). The SVR24 rate significantly decreased in NRs receiving <60% vs >60% of the total ribavirin dose (23% vs 44%, respectively) or <80% vs >80% of the total ribavirin dose (33% vs 48%, respectively). A significant SVR24 decrease was noted subsequent to a total peginterferon dose reduction, both when comparing patients who received <60% vs >60% of the total dose (NR: 0% vs 44%; REL: 33% vs 68%) and patients who received <80% vs >80% of the total dose (NR: 17% vs 50%; REL: 46% vs 71%). Serious adverse events were observed in 31 patients (15%). Deaths occurred in 4 patients. All of the deceased subjects were cirrhotic members of the ILF (baseline serum albumin level <35 g/L and/or platelet count <100,000/mm) group. Ribavirin dose reduction did not affect efficacy in REL but did in NR. Peginterferon dose reduction decreased the SVR24 rate for all groups, particularly in prior NR. ILF increased the risk of fatal complications with a low probability to achieve SVR24. One solution might be to provide wide and early access to novel, efficient, and safe interferon-free combinations to treatment-experienced patients, particularly those with liver cirrhosis.
How can an analysis in cost-effective models be utilized on the ground with various payers and stakeholders to create an increased access to HCV treatment? What are some specific tactics?


BACKGROUND: The standard care of treatment of interferon plus ribavirin (plus protease inhibitor for genotype 1) are effective in 50% to 70% of patients with CHC. Several new treatments including Harvoni, Olysio + Sovaldi, Viekira Pak, Sofosbuvir-based regimens characterized with potent inhibitors have been approved by the Food and Drug Administration (FDA) providing more options for CHC patients. Trials have shown that the new treatments increased the rate to 80% to 95%, though with a substantial increase in cost. In particular, current market pricing of a 12-week course of sofosbuvir is approximately US$84,000. We determine the cost-effectiveness of new treatments in comparison with the standard care of treatments.

METHODS: A Markov simulation model of CHC disease progression is used to evaluate the cost-effectiveness of different treatment strategies based on genotype. The model calculates the expected lifetime medical costs and quality adjusted life years (QALYs) of hypothetical cohorts of identical patients receiving certain treatments. For genotype 1, we compare: (1) peginterferon + ribavirin + telaprevir for 12 weeks, followed by 12 or 24 weeks treatment of peginterferon + ribavirin dependent on HCV RNA level at week 12; (2) Harvoni treatment, 12 weeks; (3) Olysio + Sovaldi, 12 weeks for patients without cirrhosis, 24 weeks for patients with cirrhosis; (4) Viekira Pak + ribavirin, 12 weeks for patients without cirrhosis, 24 weeks for patients with cirrhosis; (5) sofosbuvir + peginterferon + ribavirin, 12 weeks for patients with or without cirrhosis. For genotypes 2 and 3, treatment strategies include: (1) peginterferon + ribavirin, 24 weeks for treatment-naïve patients; (2) sofosbuvir + ribavirin, 12 weeks for patients with genotype 2, 24 weeks for genotype 3; (3) peginterferon + ribavirin as initial treatment, 24 weeks for patients with genotype 2/3, follow-up treatment with sofosbuvir + ribavirin for 12/16 weeks are performed on non-responders and relapsers.

RESULTS: Viekira Pak is cost-effective for genotype 1 patients without cirrhosis, whereas Harvoni is cost-effective for genotype 1 patients with cirrhosis. Sofosbuvir-based treatments for genotype 1 in general are not cost-effective due to its substantial high costs. Two-phase treatments with 12-week and 16-week follow-ups are cost-effective for genotype 3 patients and for genotype 2 patients with cirrhosis. The results were shown to be robust over a broad range of parameter values through sensitivity analysis. CONCLUSIONS: For genotype 1, sofosbuvir-based treatments are not cost-effective compared to Viekira Pak and Harvoni, although a 30% reduction in sofosbuvir price would change this result. Sofosbuvir + ribavirin are cost-effective as second-phase treatments following peginterferon + ribavirin initial treatment for genotypes 2 and 3. However, there is limited data on sofosbuvir-involved treatment, and the results obtained in this study must be interpreted within the model assumptions.

Studies show that despite stigma and social misrepresentations of people who use drugs, successful treatment adherence and cure rates are achieved at the same rate as other patients without substance use disorders. Despite literature proving treatment can be successful with people who use drugs, access is limited. What are some effective ‘home grown’ models for the identification of, linkage to, and treatment of HCV within addictions treatment?

How can we leverage the otherwise ‘anonymous’ addiction community (AA, NA, etc.) to convene around access to care for HCV positive patients?
Caring Ambassadors Program Hepatitis C Literature Review © 2015


BACKGROUND: People who inject drugs (PWID) constitute 10 million people globally with hepatitis C virus, including many opioid agonist treatment patients. Little data exist describing clinical outcomes for patients receiving HCV treatment with direct-acting antiviral agents (DAAs) in opioid agonist treatment settings. METHODS: In this retrospective observational study, we describe clinical outcomes for 50 genotype-1 patients receiving HCV treatment with triple therapy: telaprevir (n=42) or boceprevir (n=8) in combination with pegylated interferon and ribavirin on-site in an opioid agonist treatment program. RESULTS: Overall, 70% achieved an end of treatment response (ETR) and 62% achieved a sustained virological response (SVR). These treatment outcomes are nearly equivalent to previously published HCV outcomes shown in registration trials, despite high percentages of recent drug use prior to treatment (52%), ongoing drug use during treatment (45%) and psychiatric comorbidity (86%). Only 12% (n=6) discontinued antiviral treatment early for non-virological reasons. Four patients received a blood transfusion, and one discontinued telaprevir due to severe rash. CONCLUSIONS: These data demonstrate that on-site HCV treatment with direct-acting antiviral agents is effective in opioid agonist treatment patients including patients who are actively using drugs. Future interferon-free regimens will likely be even more effective. Opioid agonist treatment programs represent an opportunity to safely and effectively treat chronic hepatitis C, and PWID should have unrestricted access to DAAs.


BACKGROUND & AIMS: Fatigue is a disturbing symptom of chronic hepatitis C virus (HCV) infection. We assessed the effects of sustained virologic response 12 weeks after the end of therapy (SVR12) on fatigue. METHODS: We performed a retrospective analysis of 100 patients with chronic HCV infection who achieved an SVR12 after treatment with ledipasvir and sofosbuvir, with or without ribavirin. Data were collected on fatigue-related patient-reported outcomes (PROs) and assessed by using the Functional Assessment of Cancer Therapy-Fatigue scoring system and the Vitality subscale of Short Form 36. We measured levels of cytokines and growth factors in frozen serum samples collected at baseline, week 12 of treatment, and 4 weeks after treatment. Central fatigue and peripheral or muscle fatigue (PF) were determined by using items from PROs. Serum levels of cytokines, growth factors, serotonin, alanine aminotransferase, and aspartate aminotransferase were measured by using the Bio-Plex, enzyme-linked immunosorbent, and enzymatic assays. RESULTS: Compared with baseline, 4 weeks after the end of treatment, all fatigue-associated PROs improved significantly. Baseline PROs correlated inversely with serum level of interferon-γ; level of platelet-derived growth factor correlated with PF, central fatigue, and total fatigue score. Only PF correlated with serum level of serotonin. At baseline, high PF scores correlated with high serum levels of serotonin and low levels of interleukin-10 and tumor necrosis factor-α. In multivariate analysis, serum level of interleukin-8 was associated with greater fatigue (P < .02). Reductions in levels of chemokine (C-C motif) ligand 2 (also called monocyte chemotactic protein 1) were associated with fatigue after
treatment (P = .0165). **CONCLUSIONS:** In an analysis of data from patients with chronic HCV infection participating in a clinical trial of ledipasvir and sofosbuvir, SVR12 was associated with reduced fatigue, compared with baseline. High baseline serum levels of interferon-γ were associated with fatigue. Reductions in levels of chemokine (C-C motif) ligand 2 were associated with persistent fatigue after SVR12. Central and peripheral fatigue each associated with different biomarkers, suggesting differentpathogenic pathways.


Risks and benefits of simeprevir plus sofosbuvir (SIM+SOF) in patients with advanced cirrhosis are unknown. We assessed the safety and sustained virological responses (SVR) of SIM+SOF with and without ribavirin (RBV) in patients with Child-Pugh (CP)-B/C versus CP-A cirrhosis and compared to matched untreated controls. This study was of a multicenter cohort of adults with hepatitis C virus genotype 1 and cirrhosis treated with SIM+SOF with/without RBV for 12 weeks. Controls were matched on treatment center, age, CP class, and Model for End-Stage Liver Disease (MELD) score. Of 160 patients treated with SIM+SOF with/without RBV, 35% had CP-B/C and 64% had CP-A, with median baseline MELD 9 (interquartile range, 8-11).

Sustained virological response at week 12 (SVR12) was achieved by 73% of CP-B/C versus 91% of CP-A (P < 0.01). CP-B/C versus CP-A had more early treatment discontinuations (11% vs. 1%), adverse events (AEs) requiring hospitalization (22% vs. 2%), infections requiring antibiotics (20% vs. 1%), and hepatic decompensating events (20% vs. 3%; all P < 0.01). There were 2 deaths: 1 CP-B/C (liver related) and 1 CP-A (not liver related). In multivariate analysis, CP-B/C independently predicted lack of SVR12 (odds ratio, 0.27; 95% confidence interval: 0.08-0.92). In comparing SIM+SOF-treated patients versus matched untreated controls, AEs requiring hospitalization (9% vs. 13%; P = 0.55), infections (8% vs. 6%; P = 0.47), and events of decompensation (9% vs. 10%; P = 0.78) occurred at similar frequency. **CONCLUSIONS:** SIM+SOF with/without RBV has lower efficacy and higher rates of AEs in patients with CP-B/C cirrhosis, compared to CP-A. Frequency of adverse safety outcomes were similar to matched untreated controls, suggesting that safety events reflect the natural history of cirrhosis and are not related to treatment.


**BACKGROUND:** Combination antiviral therapy involving sofosbuvir and simeprevir is a treatment option in patients with genotype 1 chronic hepatitis C; however, the safety of this regimen in patients with decompensated cirrhosis is not established. Data from a combined treatment cohort of two large hepatology referral centers were evaluated to assess for safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with Child's B or C cirrhosis. **METHODS:** All (n=42) patients included in analysis had Child's B (n=35) or C (n= 7) cirrhosis and received sofosbuvir 400mg daily plussimeprevir 150mg daily, with (n=7) or without (n= 35) ribavirin, for 12 weeks. **RESULTS:** Of the 42 patients in this cohort, 31 (74%) were male, 22 (52%) had failed prior treatment and 28 (67%) were genotype 1A. Prior decompensating events included encephalopathy (53%), fluid overload (89%), or variceal hemorrhage (22%). Median MELD score was 12 (range 6-25). Treatment was well-tolerated.
overall with more than one-half (57%) reporting no adverse events. In those reporting adverse events, the most common were fatigue (n=7), insomnia (n=4), headache (n=4), nausea (n=4), and grade 1 rash (n=2). One patient developed chemical pancreatitis that did not require treatment discontinuation. 3 of 7 patients who received ribavirin developed anemia; 2 requiring blood transfusions & 1 dose reduction. No episodes of decompensation requiring hospitalization or deaths occurred on treatment. 38 of 42 patients (90%) had negative viral load at end of treatment and 31 of 42 patients (74%) achieved sustained virological response 12 weeks after end of treatment. 10 of 10 patients (100%) with hepatitis C genotype 1b achieved SVR12.

CONCLUSION: Sofosbuvir plus simeprevir was very well tolerated in patients with advanced Child's B/C decompensated cirrhosis. Overall, 74% of patients achieved SVR12. 100% of patients with genotype 1b decompensated cirrhosis achieved SVR12. This article is protected by copyright. All rights reserved.

Statin use and the risk of cirrhosis development in patients with hepatitis C virus infection.

BACKGROUND & AIMS: Several animal studies have shown that statins can inhibit the progression of cirrhosis; however, few clinical studies have been conducted. Previous studies have indicated that statins can prevent the progression of hepatic fibrosis in patients with hepatitis C virus (HCV) infection and advanced hepatic fibrosis, however data is lacking on patients who have yet to progress to cirrhosis. This study investigated the association between the use of statin and the risk of cirrhosis development in patients with HCV infection.

METHODS: We conducted a population-based cohort study by using the Taiwan National Health Insurance Research Database. A total of 226,856 patients with HCV infection were included as the study cohort. Each patient was followed from 1997 to 2010 to identify incident cases of cirrhosis. A Cox proportional hazard regression was performed to evaluate the association between statin use and cirrhosis risk. RESULTS: A total of 34,273 cases of cirrhosis were identified in the cohort with HCV infection during the follow-up period of 2,874,031.7 person-years. The incidence rate was 445.5 cases of cirrhosis per 100,000 person-years (95% confidence interval (CI), 423.3 to 465.7) for statin users (defined as those who used more than 28 cumulative defined daily doses (cDDD)), and 1311.2 cirrhosis cases per 100,000 person-years (95% CI, 1297.1 to 1325.6) for non-users. A dose-response relationship between statin use and cirrhosis risk was observed. The adjusted hazard ratios were 0.33 (95% CI, 0.31 to 0.36), 0.24 (95% CI, 0.22 to 0.25), and 0.13 (95% CI, 0.12 to 0.15) for statin use of 28 to 83, 84 to 365, and more than 365 cDDD, respectively, relative to no statin use (<28 cDDD). CONCLUSION: Among the patients with HCV infection, statin use was associated with a reduced risk of cirrhosis development in a dose-dependent manner. Further clinical research is required.

Reuse of Insulin Pens Among Multiple Patients at 2 Veterans Affairs Medical Centers.

OBJECTIVE: To determine whether reuse of insulin pens among multiple patients resulted in transmission of bloodborne pathogens (BBP). DESIGN Retrospective cohort study. SETTING Two Veterans Affairs medical centers. PATIENTS: Veterans who received insulin via insulin pens from 2010 to 2013. METHODS: Patients were identified through electronic health records, notified of possible exposure, and serotested for human immunodeficiency virus, hepatitis C
virus (HCV), and hepatitis B virus. Newly discovered case patients were assessed in relation to potential proximate patients to determine viral strain relatedness by HCV envelope (env) gene sequencing. **RESULTS:** Of 1,791 hospitalized veterans who received insulin via insulin pen, 1,155 were tested for at least 1 viral infection after exposure. Of these, 67 patients were newly diagnosed with 1 or more viral BBPs. For human immunodeficiency virus and hepatitis B virus no additional strain testing of case or proximate patients was possible; 8 HCV cases and 45 proximates (40 unique patients; 5 patients were positive for 2 genotypes) were identified as needing strain testing. Only 3 cases and their 19 proximates had samples available for further testing. None of the 26 remaining proximate patients had blood available for further testing. Median genetic distance between the HCV env sequences of those available for additional testing ranged from 14% to 24%, indicating nonrelatedness. **CONCLUSIONS:** Our investigation revealed that exposure to insulin pen reuse did not result in HCV transmission among patients who had viral genetic analysis performed. Analysis for any additional potential transmission of blood-borne pathogens was limited by the available samples.


**BACKGROUND:** Achievement of sustained virologic response (SVR) and factors associated with treatment failure in hepatitis C virus (HCV) genotype 3 have been described in tertiary and referral care settings, with rates of SVR reported to range between 72% and 89%. Fewer data exist on SVR outside of these settings. **OBJECTIVE:** To describe rates of SVR and characterize factors associated with achievement of SVR within an integrated health care delivery system. **METHODS:** A retrospective cohort study of genotype 3 HCV patients treated with dual therapy (pegylated interferon-alpha plus ribavirin) was conducted at Kaiser Permanente Southern California. Adult patients diagnosed with HCV and testing positive for HCV-RNA genotype 3 were identified from electronic medical records. Data were collected on patient demographics, baseline health status, and comorbid conditions. A multivariate logistic regression model was used to determine the association between baseline patient factors and SVR. **RESULTS:** A total of 484 HCV genotype 3 patients met the eligibility criteria. The median age was 49 years, and 65.7% were male. Overall, 252 (52.1%) achieved SVR. Aged ≥ 45 years and male gender were associated with lower rates of SVR; cirrhosis and chronic diseases (diabetes and chronic obstructive pulmonary disease) were also associated with lower rates of SVR. **CONCLUSIONS:** SVR was lower in patients within an integrated care delivery system than in those in tertiary and referral centers. Males and older patients had lower rates of SVR, as well as patients with cirrhosis, diabetes, and chronic obstructive pulmonary disease.


**BACKGROUND:** Antiviral treatment with sustained virologic response (SVR) improves survival in liver transplant (LT) recipients, and is especially relevant to patients with advanced recurrent hepatitis C virus (HCV). We assessed the safety and efficacy of protease inhibitor-based triple therapy in patients with recurrent advanced fibrosis and cholestatic hepatitis.
**METHODS:** The LT recipients with genotype 1 HCV and advanced fibrosis (F3-4/4) or cholestatic hepatitis treated with telaprevir- or boceprevir-based triple therapy at 6 centers (CRUSH-C consortium) were retrospectively assessed. The primary endpoints were SVR at 12 weeks (SVR12) and safety. **RESULTS:** Forty-five patients with advanced fibrosis and 9 with cholestatic hepatitis (74% men, 57% genotype 1a, 63% previous nonresponders) were included. SVR12 occurred in 51% with advanced fibrosis and 44% with cholestatic hepatitis. Extended rapid virologic response was highly predictive of SVR12. Hispanic ethnicity (odds ratio, 0.16; P = 0.03), previous null/partial response (0.24; P = 0.02), IL28B genotype CC (7.0; P = 0.02), albumin (3.87; P = 0.03), platelet count (1.01; P = 0.02), and steroid use (0.21; P = 0.03) were associated with SVR12. Six (11%) patients died, and hepatic decompensation occurred in 22% with advanced fibrosis and 33% with cholestatic hepatitis. Albumin (0.02; P = 0.001), encephalopathy (12.0; P = 0.04) and Hispanic ethnicity (odds ratio, 6.17; P = 0.01) were associated with death or decompensation. **CONCLUSIONS:** For LT recipients with recurrent advanced HCV and at greatest need of cure, protease inhibitor-based triple therapy achieved approximately 50% SVR12. However, there is significant risk of serious adverse events, arguing for earlier intervention. The availability of treatments with better efficacy and safety is of particular importance for posttransplant patients with advanced disease.


**BACKGROUND AND AIM:** The addition of hepatitis C virus (HCV) NS3/4A protease inhibitors to the pegylated interferon (PEG-IFN) α and ribavirin combination regimen (triple therapy) has dramatically improved treatment outcome. Unfortunately, anemia remains a common adverse effect. This study was done to compare the development of severe anemia during simeprevir- or telaprevir-based triple therapy. **METHODS:** This retrospective multicenter study consisted of 837 consecutive Japanese HCV genotype 1 patients treated in a real-world clinical setting, 811 of whom were enrolled (simeprevir 281, telaprevir 530). The inosine triphosphate pyrophosphatase (ITPA) genotype at rs1127354 was determined for all studied patients. Logistic regression was done after propensity score matching to assess the risk of development of severe anemia. **RESULTS:** Propensity score matching of the entire study population yielded 266 matched pairs. Severe anemia (nadir hemoglobin < 9.0 g/dL) was developed during the treatment period by 81 (30.5%) and 144 (54.1%) patients treated with simeprevir and telaprevir, respectively. Treatment with simeprevir was independently associated with a lower risk of severe anemia (odds ratio 0.25, 95% confidence interval 0.16-0.38, P < 0.0001). Moreover, ITPA genotype, age, hemoglobin level, and estimated glomerular filtration rate at baseline were also independent factors associated with the development of severe anemia. **CONCLUSIONS:** Patients treated with simeprevir-based triple therapy have a lower risk of the development of severe anemia than those treated with telaprevir. Moreover, ITPA genotype and age may be useful for individualizing treatment to reduce the risk of anemia-related adverse effects.

BACKGROUND AND AIM: Thrombocytopenia is frequently observed in patients with chronic hepatitis C virus (HCV) infection and cirrhosis, although it can also be observed in patients without cirrhosis by a virus-mediated phenomenon. This study assessed the prevalence, characteristics, and outcomes of antiviral therapy in patients with chronic HCV infection and thrombocytopenia not associated with cirrhosis. METHODS: The study included 1268 patients with HCV infection and thrombocytopenia enrolled in the phase 3 ENABLE studies that assessed the impact of eltrombopag on achieving a sustained virologic response to pegylated interferon and ribavirin. The study population was subdivided according to baseline FibroSURE test results into patients with non-cirrhosis (FibroSURE < 0.4) and cirrhosis-related (FibroSURE ≥ 0.75) thrombocytopenia. RESULTS: Compared with patients with cirrhosis-related thrombocytopenia (n = 995; 78.5%), non-cirrhotic patients with thrombocytopenia (n = 59; 4.6%) were younger (mean age [95% confidence interval (CI)]: 43.9 [40.7-47.2] vs 52.7 [52.2-53.3] years; P < 0.0001), predominantly female (64% [51-76] vs 30% [27-33]; P < 0.0001), and less frequently had a Model for End-Stage Liver Disease score ≥ 10 (24% [14-37] vs 45% [42-49]; P = 0.0012), low albumin levels (≤ 35 g/L; 2% [0-9] vs 32% [29-35]; P < 0.0001), and prevalence of diabetes mellitus (3% [0-12] vs 21% [19-24]; P = 0.0005). The sustained virologic response rate was higher in non-cirrhotic patients with thrombocytopenia (46% [95% CI, 33-59] vs 16% [95% CI, 14-18]; P < 0.0001). CONCLUSIONS: Patients with thrombocytopenia associated with HCV who have lower FibroSURE test results may have better preserved liver function and higher sustained virologic response rates than patients with cirrhosis.

Peginterferon plus weight-based ribavirin for treatment-naive hepatitis C virus genotype 2 patients not achieving rapid virologic response: a randomized trial. Liu CH1, Huang CF2, Liu CJ3, et al. Sci Rep. 2015 Jul 1;5:11710. doi: 10.1038/srep11710. Hepatitis C virus genotype 2 (HCV-2) slow responders poorly respond to 24 weeks of peginterferon (Peg-IFN) plus ribavirin (RBV). We evaluated the efficacy of extended 48-week regimen and the role of interleukin-28B (IL-28B) genotype in this clinical setting. Treatment-naive HCV-2 patients not achieving rapid virologic response (RVR) by Peg-IFN alfa-2a 180 μg/week plus weight-based RBV (1,000-1,200 mg/day, cutoff body weight of 75 kg) were randomly assigned to receive a total duration of 48 (n = 94) or 24 (n = 93) weeks of therapy. The primary endpoint was sustained virologic response (SVR). Baseline patient characteristics to predict SVR were analyzed. Patients receiving 48 weeks of treatment had a greater SVR rate than those receiving 24 weeks of treatment (70.2% versus 46.2%, P = 0.001). Compared to patients treated for 24 weeks, the SVR rate in those treated for 48 weeks increased by 10.9% [95% CI: -5.9% to 27.7%] and 65.6% [95% CI: 44.5% to 86.7%] if they had IL-28B rs8099917 TT genotype, and GT/GG genotype, respectively (interaction P = 0.002). In conclusion, 48-week treatment with Peg-IFN plus weight-based RBV provides a greater SVR rate than 24-week treatment in treatment-naive HCV-2 patients with unfavorable IL-28B genotypes who fail to achieve RVR.

Major depression is a serious side effect of interferon-α (IFN-α), which is used in the therapy of hepatitis C virus (HCV) infection. Due to the lack of reproducible animal models, the mechanisms underlying IFN-α-related depression are largely unknown. We herein established a mouse model, in which murine IFN-α (250 IU/day) and polyinosinic/polycytidylic acid (poly(I:C); 1 μg/day), a toll-like receptor-3 (TLR3) agonist that mimics the effect of HCV double-strand RNA, were continuously infused into the lateral ventricle via miniosmotic pumps over up to 14 days. The delivery of IFN-α and poly(I:C), but not of IFN-α or poly(I:C) alone, resulted in a reproducible depression-like state that was characterized by reduced exploration behavior in open-field tests, increased immobility in tail suspension and forced swimming tests, and a moderate loss of body weight. In the hippocampus and prefrontal cortex, the pro-inflammatory genes TNF-α, IL-6, tissue inhibitor of metalloproteinases-1 (Timp-1), CXC motif ligand-1 (Cxcl1), Cxcl10, and CC motif ligand-5 (Ccl5) were synergistically induced by IFN-α and poly(I:C), most pronounced after 14-day exposure. In comparison, the interferon-inducible genes of signal transducer and activator of transcription-1 (Stat1), guanylate binding protein-1 (Gbp1), proteasome subunit-β type-9 (Psmb9), ubiquitin-conjugating enzyme E2L-6 (Ube2l6), receptor transporter protein-4 (Rtp4), and GTP cyclohydrolase-1 (Gch1), which had previously been elevated in the blood of IFN-α-treated patients developing depression, in the brains of suicidal individuals, and in primary neurons exposed to IFN-α and poly(I:C), were induced even earlier, reaching maximum levels mostly after 24 hours. We propose that interferon-inducible genes might be useful markers of imminent depression.

This abstract points to our further understanding of HOW ribavirin works!


Ribavirin is used as a component of combination therapies for the treatment of chronic hepatitis C virus (HCV) infection together with pegylated interferon and/or direct-acting antiviral drugs. Its mechanism of action, however, is not clear. Direct antiviral activity and immunomodulatory functions have been implicated. Plasmacytoid dendritic cells (pDCs) are the principal source of type 1 interferon during viral infection. The interaction of pDCs with HCV-infected hepatocytes is the subject of intense recent investigation, but the effect of ribavirin on pDC activation has not been evaluated. In this study we showed that ribavirin augments toll-like receptors 7 and 9-mediated IFNα/β expression from pDCs and up-regulated numerous interferon-stimulated genes. Using the H77S.3 HCV infection and replication system, we showed that ribavirin enhanced the ability of activated pDCs to inhibit HCV replication, correlated with elevated induction of IFNα. Our findings provide novel evidence that ribavirin contributes to HCV inhibition by augmenting pDCs-derived type 1 IFN production.

The small GTPase Rab27a has been shown to control membrane trafficking and microvesicle transport pathways, in particular the secretion of exosomes. In the liver, high expression of Rab27a correlates with the development of hepatocellular carcinoma. We discovered that low abundance of Rab27a resulted in decreased hepatitis C virus (HCV) RNA and protein abundances in virus-infected cells. Curiously, both cell-associated and extracellular virus yield decreased in Rab27a depleted cells, suggesting that reduced exosome secretion did not cause the observed effect. Instead, Rab27a enhanced viral RNA replication by a mechanism that involves the liver-specific microRNA miR-122. Rab27a surrounded lipid droplets and was enriched in membrane fractions that harbor viral replication proteins, suggesting a supporting role for Rab27a in viral gene expression. Curiously, Rab27a depletion decreased the abundance of miR-122, whereas overexpression of miR-122 in Rab27a-depleted cells rescued HCV RNA abundance. Because intracellular HCV RNA abundance is enhanced by the binding of two miR-122 molecules to the extreme 5' end of the HCV RNA genome, the diminished amounts of miR-122 in Rab27a-depleted cells could have caused destabilization of HCV RNA. However, the abundance of HCV RNA carrying mutations on both miR-122-binding sites and whose stability was supported by ectopically expressed miR-122 mimetics with compensatory mutations also decreased in Rab27a-depleted cells. This result indicates that the effect of Rab27a depletion on HCV RNA abundance does not depend on the formation of 5' terminal HCV/miR-122 RNA complexes, but that miR-122 has a Rab27a-dependent function in the HCV lifecycle, likely the downregulation of a cellular inhibitor of HCV gene expression. These findings suggest that the absence of miR-122 results in a vulnerability not only to exoribonucleases that attack the viral genome, but also to upregulation of one more cellular factor that inhibit viral gene expression.


BACKGROUND: Hepatitis C virus (HCV) infection is associated with chronic inflammation; yet studies show greater interleukin (IL)-6, but lower C-reactive protein (CRP) levels. We determined whether liver fibrosis severity and HCV replication affect the ability of IL-6 to stimulate the production of CRP from the liver. METHODS: We used multivariable generalized linear regression to examine the association of HIV, HCV and transient elastography-measured liver stiffness with IL-6 and CRP in participants (164 HIV-monoinfected; 10 HCV-monoinfected; 73 HIV/HCV-coinfected; 59 neither infection) of the Women's Interagency HIV Study. Significant fibrosis was defined as liver stiffness greater than 7.1 kPa. RESULTS: IL-6 was positively correlated with CRP levels in all women, but CRP levels were lower in HCV-infected women (with and without HIV infection) at all levels of IL-6. HCV-infected women with fibrosis had nearly 2.7-fold higher IL-6 levels compared to controls [95% confidence interval (CI 146%, 447%); HCV-infected women without fibrosis had IL-6 levels that were similar to controls. By contrast, CRP was 28% lower in HCV-infected women with fibrosis (95% CI -55%, 15%) and 47% lower in HCV-infected women without fibrosis (95% CI -68%, -12%). Among the HCV-infected women, higher HCV-RNA levels were associated with 9% lower CRP levels per doubling (95% CI -18%, 0%). CONCLUSION: Liver fibrosis severity is associated with greater IL-6 levels, but the stimulatory effect of IL-6 on CRP appears to be blunted by HCV
replication rather than by liver fibrosis severity. Investigation of the potential CRP rebound after HCV-RNA eradication and persistent liver fibrosis on organ injury is needed.

**HIV/HCV COINFECTION**


**BACKGROUND:** Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality in patients with HIV-1. The C-EDGE CO-INFECTION study assessed the efficacy, safety, and tolerability of grazoprevir (MK-5172) plus elbasvir (MK-8742) in patients with HCV and HIV co-infection. **METHODS:** In this uncontrolled, non-randomised, phase 3, open-label, single-arm study, treatment-naïve patients with chronic HCV genotype 1, 4, or 6 infection and HIV co-infection, with or without cirrhosis, were enrolled from 37 centres in nine countries across Europe, the USA, and Australia. Patients were either naïve to treatment with any antiretroviral therapy (ART) or stable on ART for at least 8 weeks. All patients received grazoprevir 100 mg plus elbasvir 50 mg in a fixed-dose combination tablet once daily for 12 weeks. The primary endpoint was sustained virological response (HCV RNA <15 IU/mL) 12 weeks after the end of therapy (SVR12). The primary population for efficacy analyses was all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT02105662. **FINDINGS:** Between June 11, 2014, and Aug 29, 2014, 218 patients were enrolled and received grazoprevir plus elbasvir for 12 weeks, all of whom completed follow-up at week 12. SVR12 was achieved by 210 (96%) of 218 patients (95% CI 92.9-98.4). One patient did not achieve SVR12 because of a non-virological reason, and seven patients without cirrhosis relapsed (two subsequently confirmed as reinfections). All 35 patients with cirrhosis achieved SVR12. The most common adverse events were fatigue (29; 13%), headache (27; 12%), and nausea (20; 9%). No patient discontinued treatment because of an adverse event. Two patients receiving ART had transient HIV viraemia. **INTERPRETATION:** This HCV treatment regimen seems to be effective and well tolerated for patients co-infected with HIV with or without cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population. This regimen continues to be studied in phase 3 trials. **FUNDING:** Merck Sharp & Dohme Corp.

**Immunologic Predictors of Liver Transplantation Outcomes in HIV-HCV Co-Infected Persons.** Balagopal A1, Barin B2, Quinn J1, Rogers R3, Sulkowski MS1, Stock PG3. PLoS One. 2015 Aug 27;10(8):e0135882. doi: 10.1371/journal.pone.0135882. eCollection 2015. Liver disease is a leading cause of mortality among HIV-infected persons in the highly active anti-retroviral therapy (HAART) era. Hepatitis C Virus (HCV) co-infection is prevalent in, and worsened by HIV; consequently many co-infected persons require liver transplantation (LT). Despite the need, post-LT outcomes are poor in co-infection. We examined predictors of outcomes post-LT. Immunologic biomarkers of immune activation, microbial translocation, and Th1/Th2 skewing were measured pre-LT in participants enrolled in a cohort of HIV infected persons requiring solid organ transplant (HIVTR). Predictive biomarkers were analyzed in Cox-proportional hazards models; multivariate models included known predictors of outcome and biomarkers from univariate analyses. Sixty-nine HIV-HCV co-infected persons with available
pre-LT samples were tested: median (IQR) CD4+ T-cell count was 286 (210-429) cells mm-3; 6 (9%) had detectable HIV RNA. Median (IQR) follow-up was 2.1 (0.7-4.0) years, 29 (42%) people died, 35 (51%) had graft loss, 22 (32%) were treated for acute rejection, and 14 (20%) had severe recurrent HCV. In multivariate models, sCD14 levels were significantly lower in persons with graft loss post-LT (HR 0.10 [95%CI 0.02-0.68]). IL-10 levels were higher in persons with rejection (HR 2.10 [95%CI 1.01-4.34]). No markers predicted severe recurrent HCV. Monocyte activation pre-LT may be mechanistically linked to graft health in HIV-HCV co-infection.


**BACKGROUND:** End-stage liver disease (ESLD) is an important cause of morbidity among human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients. Quantifying the risk of this outcome over time could help determine which coinfected patients should be targeted for risk factor modification and HCV treatment. We evaluated demographic, clinical, and laboratory variables to predict risk of ESLD in HIV/HCV-coinfected patients receiving antiretroviral therapy (ART). **METHODS:** We conducted a retrospective cohort study among 6016 HIV/HCV-coinfected patients who received ART within the Veterans Health Administration between 1997 and 2010. The main outcome was incident ESLD, defined by hepatic decompensation, hepatocellular carcinoma, or liver-related death. Cox regression was used to develop prognostic models based on baseline demographic, clinical, and laboratory variables, including FIB-4 and aspartate aminotransferase-to-platelet ratio index, previously validated markers of hepatic fibrosis. Model performance was assessed by discrimination and decision curve analysis. **RESULTS:** Among 6016 HIV/HCV patients, 532 (8.8%) developed ESLD over a median of 6.6 years. A model comprising FIB-4 and race had modest discrimination for ESLD (c-statistic, 0.73) and higher net benefit than alternative strategies of treating no or all coinfected patients at relevant risk thresholds. For FIB-4 >3.25, ESLD risk ranged from 7.9% at 1 year to 26.0% at 5 years among non-blacks and from 2.4% at 1 year to 14.0% at 5 years among blacks. **CONCLUSIONS:** Race and FIB-4 provided important predictive information on ESLD risk among HIV/HCV patients. Estimating risk of ESLD using these variables could help direct HCV treatment decisions among HIV/HCV-coinfected patients.


**INTRODUCTION:** Hepatic fibrosis progression in patients with chronic hepatitis C virus infections has been associated with viral and host factors, including genetic polymorphisms. Human platelet antigen polymorphisms are associated with the rapid development of fibrosis in HCV-mono-infected patients. This study aimed to determine whether such an association exists in human immunodeficiency virus-1/hepatitis C virus-coinfected patients. **METHODS:** Genomic deoxyribonucleic acid from 36 human immunodeficiency virus-1/hepatitis C virus-coinfected patients was genotyped to determine the presence of human platelet antigens-1, -3, or -5 polymorphisms. Fibrosis progression was evaluated using the Metavir scoring system, and the
patients were assigned to two groups, namely, G1 that comprised patients with F1, portal fibrosis without septa, or F2, few septa (n = 23) and G2 that comprised patients with F3, numerous septa, or F4, cirrhosis (n = 13). Fisher's exact test was utilized to determine possible associations between the human platelet antigen polymorphisms and fibrosis progression. **RESULTS:** There were no deviations from the Hardy-Weinberg equilibrium in the human platelet antigen systems evaluated. Statistically significant differences were not observed between G1 and G2 with respect to the distributions of the allelic and genotypic frequencies of the human platelet antigen systems. **CONCLUSION:** The greater stimulation of hepatic stellate cells by the human immunodeficiency virus and, consequently, the increased expression of transforming growth factor beta can offset the effect of human platelet antigen polymorphism on the progression of fibrosis in patients coinfected with the human immunodeficiency virus-1 and the hepatitis C virus.


**BACKGROUND:** Hepatitis C virus (HCV) infection may increase the risk of cardiovascular disease (CVD). We evaluated the association of chronic HCV infection and coronary atherosclerosis among participants in the Multicenter AIDS Cohort Study. **METHODS:** We assessed 994 men with or without human immunodeficiency virus (HIV) infection (87 of whom had chronic HCV infection) for coronary plaque, using noncontrast coronary computed tomography (CT); 755 also underwent CT angiography. We then evaluated the associations of chronic HCV infection and HIV infection with measures of plaque prevalence, extent, and stenosis. **RESULTS:** After adjustment for demographic characteristics, HIV serostatus, behaviors, and CVD risk factors, chronic HCV infection was significantly associated with a higher prevalence of coronary artery calcium (prevalence ratio, 1.29; 95% confidence interval [CI], 1.02-1.63), any plaque (prevalence ratio, 1.26; 95% CI, 1.09-1.45), and noncalcified plaque (prevalence ratio, 1.42; 95% CI, 1.16-1.75). Chronic HCV infection and HIV infection were independently associated with the prevalence of any plaque and of noncalcified plaque, but there was no evidence of a synergistic effect due to HIV/HCV coinfection. The prevalences of coronary artery calcium, any plaque, noncalcified plaque, a mixture of noncalcified and calcified plaque, and calcified plaque were significantly higher among men with an HCV RNA load of ≥2 × 106 IU/mL, compared with findings among men without chronic HCV infection. **CONCLUSIONS:** Chronic HCV infection is associated with subclinical CVD, suggesting that vigilant assessments of cardiovascular risk are warranted for HCV-infected individuals. Future research should determine whether HCV infection duration or HCV treatment influence coronary plaque development.


**OBJECTIVE:** The objective of this study is to evaluate the impact of hepatitis C virus (HCV) serostatus on the evolution of CD8 cells and CD4 : CD8 ratio in HIV-infected patients on combined antiretroviral therapy (cART) who achieve sustained undetectable viral load (HIV-pVL). **DESIGN AND METHODS:** A longitudinal study performed in an outpatient HIV-unit...
following 1495 HIV-infected patients. Data of patients on cART achieving undetectable HIV-pVL for at least 3 years were collected retrospectively from our medical e-database NADIS from January 1997 to April 2005, a period defined in order to select patients who were naive of hepatitis treatment. T-cell counts were assessed every 6 months from HIV-suppression over the study period. RESULTS: Two hundred and twenty-six HIV mono-infected (group 1) and 130 HCV-coinfected patients (group 2; genotype prevalence: 42% HCV-G1, 26% HCV-G3, 11% HCV-G4 and 21% HCV-G2) fulfilled the selection criteria. cART regimens were comparable between the groups, as were CD4 and CD8 cell counts at the first undetectable HIV-pVL. After 3 years, both groups displayed similar CD4 cell reconstitution, although CD4 percentage was higher in group 1 (30.3±1.1 vs. 27±1.1%; P<0.001). HIV suppression led to a significant drop of median CD8 cell counts in group 1 (P=0.027), but not in group 2, which displayed higher CD8 cell counts all through the follow-up (mean diff.=135.71±26.89 cells/μl, P<0.001). Moreover, the fraction of patients reaching CD4 : CD8 ratio≥1 was lower in group 2 (14 vs. 27.7%; P<0.05). CONCLUSION: Despite sustained HIV suppression under cART, HCV coinfection was found to hamper CD8 downregulation. Further studies will determine the impact of treatment with direct-acting antiviral agents on the CD8 pool, and the advantage of systematic HCV-targeted therapy for HIV/HCV-coinfected patients.

Reinfecction is an argument used to prevent the treatment of HCV positive substance users even though research points to low reinfecion rates. What are key elements that would be vital within a package of interventions in preventing re-infection amongst cured HCV patients?


**OBJECTIVES:** To assess the incidence of hepatitis C virus (HCV) reinfections after therapy-induced clearance in HIV-coinfected patients with prior chronic hepatitis C. **METHODS:** Eighty-four HIV-infected subjects, who had previously achieved sustained virological response (SVR) after being treated of chronic hepatitis C, were analyzed. In all of them, at least yearly HCV RNA determinations were carried out during a median (range) of 34 (12-146) months. **RESULTS:** Seventy-two (86%) subjects had been people who inject drugs (PWID), of whom 11 (15%) continued to use snorted or injected drugs during the follow-up. Four (4.76%) patients showed HCV reinfection (incidence 1.21 [95% confidence interval: 0.3-3.09] cases per 100 person-years). These patients maintained risk factors for HCV infection. In three cases, HCV genotype switched. Phylogenetic analysis of the remaining case suggested reinfection from his sexual partner. **CONCLUSION:** The incidence of HCV reinfection in the overall population of HIV-coinfected patients who achieved SVR after being treated against chronic hepatitis C is low. A low frequency of risk behavior is the main factor accounting for this modest rate of reinfection. The possibility of reinfection should not be considered a reason against treatment of HCV infection with direct acting antivirals in PWID.


**BACKGROUND:** Effective treatment for hepatitis C virus (HCV) in patients coinfected with human immunodeficiency virus type 1 (HIV-1) remains an unmet medical need. **METHODS:** We conducted a multicenter, single-group, open-label study involving patients coinfected with HIV-1 and genotype 1 or 4 HCV receiving an antiretroviral regimen of tenofovir and
emtricitabine with efavirenz, rilpivirine, or raltegravir. All patients received ledipasvir, an NS5A inhibitor, and sofosbuvir, a nucleotide polymerase inhibitor, as a single fixed-dose combination for 12 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy. **RESULTS:** Of the 335 patients enrolled, 34% were black, 55% had been previously treated for HCV, and 20% had cirrhosis. Overall, 322 patients (96%) had a sustained virologic response at 12 weeks after the end of therapy (95% confidence interval [CI], 93 to 98), including rates of 96% (95% CI, 93 to 98) in patients with HCV genotype 1a, 96% (95% CI, 89 to 99) in those with HCV genotype 1b, and 100% (95% CI, 63 to 100) in those with HCV genotype 4. Rates of sustained virologic response were similar regardless of previous treatment or the presence of cirrhosis. Of the 13 patients who did not have a sustained virologic response, 10 had a relapse after the end of treatment. No patient had confirmed HIV-1 virologic rebound. The most common adverse events were headache (25%), fatigue (21%), and diarrhea (11%). No patient discontinued treatment because of adverse events. **CONCLUSIONS:** Ledipasvir and sofosbuvir for 12 weeks provided high rates of sustained virologic response in patients coinfected with HIV-1 and HCV genotype 1 or 4.


Chronic hepatitis C infection frequently coexists with human immunodeficiency virus (HIV) and together are associated with increased hepatic steatosis. Steatosis is a risk factor for progression of liver disease and may persist despite a sustained virologic response to hepatitis C treatment. Therefore, therapies to target hepatic steatosis are important for individuals with HIV and hepatitis C virus (HCV) coinfection. We completed a 48-week, randomized, double-blind, placebo-controlled trial of pioglitazone (45 mg/day) in 13 subjects with HIV/HCV coinfection. The primary outcome variable was hepatic fat content, measured by magnetic resonance spectroscopy (MRS) imaging. Individuals randomized to pioglitazone had a significant decrease in hepatic fat content measured by MRS from baseline (15.1 ± 7.0%) to week 48 (7.6 ± 3.9%), with a mean difference of -7.4% (p = 0.02, n = 5). There was no significant change in hepatic fat content with placebo. Glycemic control as measured by oral glucose challenge improved significantly with pioglitazone (p = 0.047). Though not statistically significant, there were trends toward improved alanine aminotransferase (ALT) and histopathologic grade of steatosis in subjects who received pioglitazone. Pioglitazone was well tolerated and no one discontinued due to side effects. This study demonstrates that 48 weeks of pioglitazone therapy, and not placebo, results in significant reductions in hepatic fat content as measured by MRS in subjects with HIV and HCV coinfection and hepatic steatosis. This small study shows that pioglitazone helps ameliorate steatosis in the context of HIV/HCV coinfection.

HIV populations were once considered ‘special populations’ within HCV communities because of treatment challenges. With current successful treatment regimens, what group might now take the ‘special population’ place of HIV+ individuals within the HCV world?


A substantial proportion of individuals with chronic hepatitis C virus (HCV) are co-infected with human immunodeficiency virus (HIV). Co-infected individuals are traditionally considered as one of the "special populations" amongst those with chronic HCV, mainly because of faster
progression to end-stage liver disease and suboptimal responses to treatment with pegylated interferon alpha and ribavirin, the benefits of which are often outweighed by toxicity. The advent of the newer direct acting antivirals (DAAs) has given hope that the majority of co-infected individuals can clear HCV. However the "special population" designation may prove an obstacle for those with co-infection to gain access to the new agents, in terms of requirement for separate pre-licensing clinical trials and extensive drug-drug interaction studies. We review the global epidemiology, natural history and pathogenesis of chronic hepatitis C in HIV co-infection. The accelerated course of chronic hepatitis C in HIV co-infection is not adequately offset by successful combination antiretroviral therapy. We also review the treatment trials of chronic hepatitis C in HIV co-infected individuals with DAAs and compare them to trials in the HCV mono-infected. There is convincing evidence that HIV co-infection no longer diminishes the response to treatment against HCV in the new era of DAA-based therapy. The management of HCV co-infection should therefore become a priority in the care of HIV infected individuals, along with public health efforts to prevent new HCV infections, focusing particularly on specific patient groups at risk, such as men who have sex with men and injecting drug users.

**Extrahepatic comorbidities associated with hepatitis C virus in HIV-infected patients.**

**PURPOSE OF REVIEW:** HIV infection facilitates progression of hepatitis C virus (HCV)-related liver fibrosis, thus increasing the risk of cirrhosis and decompensated liver disease. Although the primary target of HCV infection is the liver, extrahepatic manifestations related to HCV contribute significantly to morbidity and mortality in patients with chronic hepatitis C. We review current data on extrahepatic comorbidities associated with HCV in HIV-infected patients.

**RECENT FINDINGS:** A large proportion of individuals coinfected with HIV/HCV has extrahepatic manifestations that may be indirectly or directly related to HCV infection. Extrahepatic manifestations include autoimmune and/or lymphoproliferative disorders, and cardiovascular, renal, metabolic, and central nervous system manifestations. Chronic immune activation and systemic inflammation, hallmarks of both HIV and HCV infection, may contribute greatly to extrahepatic comorbidities of HCV in this population group. There is substantial evidence that successful antiviral therapy might reduce both hepatic and extrahepatic manifestations of HCV infection in patients coinfected with HIV/HCV. **SUMMARY:** A substantial burden of the morbidity and the mortality related to HCV in patients with or without HIV infection depends on its extrahepatic manifestations. HCV eradication following successful antiviral therapy might reduce both.


**AIM:** To evaluate virological response to telaprevir or boceprevir in combination with pegylated interferon and ribavirin and resistance mutations to NS3/4A inhibitors in hepatitis C virus-human immunodeficiency virus (HCV-HIV) coinfected patients in a real life setting. **METHODS:** Patients with HCV genotype 1-HIV coinfection followed in Nice University Hospital internal medicine and infectious diseases departments who initiated treatment including pegylated interferon and ribavirin (PegIFN/RBV) + telaprevir or boceprevir, according to standard treatment protocols, between August 2011 and October 2013 entered this observational study.
Patient data were extracted from an electronic database (Nadis®). Liver fibrosis was measured by elastometry (Fibroscan®) with the following cut-off values: F0-F1: < 7.1 kPa, F2: 7.1-9.5 kPa, F3: 9.5-14.5 kPa, F4: ≥ 14.5 kPa. The proportion of patients with sustained virological response (SVR) twelve weeks after completing treatment, frequency and type of adverse events, and NS3/4A protease inhibitor mutations were described. **RESULTS:** Forty-one patients were included: 13 (31.7%) patients were HCV-treatment naïve, 22 (53.7%) had advanced liver fibrosis or cirrhosis (Fibroscan stage F3 and F4); none had decompensated cirrhosis or hepatocellular carcinoma; all were receiving antiretroviral treatment, consisting for most them (83%) in either a nucleoside reverse-transcriptase inhibitor/protease inhibitor or/integrase inhibitor combination; all patients had undetectable HIV-RNA. One patient was lost to follow-up. SVR was achieved by 52.5% of patients. Five patients experienced virological failure during treatment and four relapsed. Seven discontinued treatment due to adverse events. Main adverse events included severe anemia (88%) and rash (25%). NS3/4A protease mutations were analyzed at baseline and at the time of virological failure in the 9 patients experiencing non-response, breakthrough or relapse. No baseline resistance mutation could predict resistance to HCV protease inhibitor-based treatment. **CONCLUSION:** Telaprevir and boceprevir retain their place among potential treatment strategies in HIV-HCV coinfected patients including those with advanced compensated liver disease and who failed previous PegIFN/RBV therapy.

**Dual antiviral therapy for HIV and hepatitis C - drug interactions and side effects,** Esposito I1, Labarga P, Barreiro P, et al. Expert Opin Drug Saf. 2015 Sep;14(9):1421-34. doi: 10.1517/14740338.2015.1073258. Epub 2015 Jul 28. **INTRODUCTION:** Roughly 20% of HIV-positive persons worldwide are coinfected with hepatitis C virus (HCV). The recent advent of direct-acting antivirals (DAA) that cure most hepatitis C patients has attracted much attention. Knowledge on drug interactions between DAA and antiretrovirals (ARV) may allow maximizing antiviral efficacy while minimizing drug-related toxicities. **AREAS COVERED:** We review the most frequent side effects and clinically significant drug interactions between DAA and ARV. We further discuss how they can be prevented and managed in HIV/HCV-coinfected patients. **EXPERT OPINION:** The safety profile of current DAA and the most recently approved ARV is quite favorable. Interactions between DAA and ARV could be frequent in clinical practice. The most common drug interactions affect drug metabolism by inducing or inhibiting the cytochrome P450 system, leading to abnormal drug exposures. Throughout this mechanism HCV and HIV protease inhibitors interact, especially when co-formulated with ritonavir as a pharmacoenhancer, and non-nucleoside HCV and HIV polymerase inhibitors. In contrast, HIV and HCV nucleos(t)ide polymerase inhibitors, and most HCV NS5A inhibitors (i.e., ledipasvir) and HIV integrase inhibitors (i.e., dolutegravir), do not or only marginally affect CYP450, and therefore are free of significant drug interactions. Exposure to HIV and HCV nucleos(t)ide analogues (i.e., tenofovir and sofosbuvir, respectively) is subject to induction/inhibition of drug transporters (i.e., P-glycoprotein).
**Antiviral phytochemicals identification from Azadirachta indica leaves against HCV NS3 protease: an in silico approach.** Ashfaq UA1, Jalil A, Ul Qamar MT. Nat Prod Res. 2015 Aug 14:1-4. [Epub ahead of print]

Hepatitis C virus (HCV) is a major health problem across the world affecting the people of all age groups. It is the main cause of hepatitis and at chronic stage causes liver cirrhosis and hepatocellular carcinoma. Various therapeutics are made against HCV but still there is a need to find out potential therapeutics to combat the virus. The goal of this study is to identify the phytochemicals of Azadirachta indica leaves having antiviral activity against HCV NS3 protease through molecular docking and simulation approach. Results show that the compound 3-Deacetyl-3-cinnamoyl-azadirachtin possesses good binding properties with HCV NS3/4A protease. It can be concluded from this study that Deacetyl-3-cinnamoyl-azadirachtin may serve as a potential inhibitor against NS3/4A protease.


Hepatitis C is a disease caused by hepatitis C virus (HCV) that causes chronic infection, cirrhosis, and hepatocellular carcinoma. The current standard therapy is a combination of pegylated interferon-α plus ribavirin with NS3 protease inhibitors. Addition of NS3 protease inhibitors increases response rates; however, this addition is associated with significant side effects and an increase in the overall cost of the treatment. Therefore, there remains a need to develop safe and inexpensive drugs for the treatment of HCV infections. In this study, we examined the antiviral activity of a crude extract from Dimocarpus longan leaves against HCV (genotype 2a strain JFH1). The D. longan crude extract exhibited anti-HCV activity with a 50% effective concentration (EC50) of 19.4 μg/ml without cytotoxicity. A time-of-addition study demonstrated that the crude extract exerts anti-HCV activity at both the entry and post-entry steps. The crude extract markedly blocked viral entry step through a direct virucidal effect with a marginal inhibition of virion assembly. The co-treatment of the crude extract with cyclosporine A or telaprevir, an NS3 protease inhibitor, had additive and synergistic antiviral effects, respectively. Our findings suggest that the D. longan crude extract may be a candidate of the add-on therapy for HCV infection.

**Epidemiology, Diagnostics, and Miscellaneous Works**

What are some innovative models or approaches to educating and training medical professionals in supporting the HCV patient through care, cure and wellness?


The aim of this study was to determine the impact of education provided by a nurse on quality of life, anxiety, and depression in patients receiving hepatitis C virus (HCV) therapy. The total number of patients receiving HCV treatment was 25 patients (18 females and 7 males). Organized patient lectures addressed transmission routes of HCV, effects of virus on the liver, interferon treatment, treatment complications and care, and psychosocial problems faced by...
patients with HCV and their families. Lectures were followed by interviews in small groups including 3-4 patients each and repeated 3 months after. Data were collected by patient surveys, Hospital Anxiety-Depression Scale, and Short Form (SF)-36 Health Survey (SF-36). There were no significant differences between pre- and posteducation for the SF-36 domains, namely role physical, health perception, social functioning, role emotion, and mental health, whereas there were significant differences between pre- and posteducation for the SF-36 domains, namely physical function, bodily pain, and vitality. Pre-education depression and anxiety scores were higher than posteducation depression and anxiety scores. Specific educational programs provided by nurses improved patients' quality of life and decreased anxiety and depression in patients receiving HCV therapy. These findings support the importance of educational programs provided by nurses for HCV patients.

What advocacy role can military retirees play in the fight for social justice for HCV patients, particularly within the veteran patient population?

Hepatitis C Virus in the US Military Retiree Population: To Screen, or Not to Screen?

BACKGROUND: In 2012, the Centers for Disease Control (CDC) recommended hepatitis C virus (HCV) screening for those born between 1945 and 1965. Prior recommendations endorsed screening based on risk factors (RFs). Because United States (US) military retirees have had at least 20 years of access to free comprehensive health care, mandatory physical fitness tests, periodic health assessments and mandatory drug screening, we hypothesized that the prevalence of HCV amongst military retirees is lower than the national average. Thus the new CDC screening guidelines may not be applicable or cost effective in this particular population.

METHODS: A quality improvement (QI) initiative implemented the new birth-cohort CDC screening guidelines for the internal medicine (IM) clinic of our hospital (QI group). An age-matched group from the same IM clinic, screened based on RFs for HCV infection, served as the comparator (RF group). The prevalence of the anti-HCV antibody and chronic infection was determined and compared with each other and with the national average.

RESULTS: The prevalence of the HCV antibody was 2.1% and 2.3% in the QI and RF groups, respectively (odds ratio (OR): 1.08, 95% CI: 0.37 - 3.21, P = 1.000). The prevalence of chronic infection was 0.4% and 1.8% in the QI and RF groups, respectively (OR: 4.39, 95% CI: 0.80 - 24.13, P = 0.083). When our data were compared with the national average, there were no statistical differences in the prevalence of the HCV antibody; however, there was statistically more viral clearance, and subsequently less chronic infection, in the QI group versus the national average.

CONCLUSIONS: The military retiree population did not have a lower prevalence of the HCV antibody than the American populace whether screened based on age or traditional RFs. Thus, the CDC guidelines are applicable in this population. One interesting finding of this study is the higher rate of viral clearance in military retirees when compared with the national average. It is therefore possible that military retirees may be more likely to have natural viral eradication than the civilian population.

All-cause mortality and progression risks to hepatic decompensation and hepatocellular carcinoma in patients infected with hepatitis C

BACKGROUND: A key question in chronic hepatitis C (HCV) care is beginning treatment immediately versus delaying treatment. Risks of mortality and disease progression in "real-
world" settings are important to assess the implications of delaying HCV treatment.

**METHODS:** A cohort study in HCV patients identified from four integrated health systems in the United States who had liver biopsies during 2001-2012. The probabilities of death and progression to hepatocellular carcinoma, hepatic decompensation (hepatic encephalopathy, esophageal varices, ascites or portal hypertension) or liver transplant were estimated over 1, 2 or 5 years by fibrosis stage (Metavir F0-F4) determined by biopsy at beginning of observation.

**RESULTS:** Among 2,799 HCV mono-infected patients who had a qualifying liver biopsy, the mean age at the time of biopsy was 50.7 years. The majority were male (58.9%) and non-Hispanic white (66.9%). Over a mean observation of 5.0 years, 261 (9.3%) patients died and 34 (1.2%) received liver transplants. At 5 years after biopsy, the estimated progression risks to hepatic decompensation or hepatocellular carcinoma was 37.2% in F4 patients, 19.6% in F3, 4.7% in F2, and 2.3% in F0/F1 patients. Baseline biopsy stage F3 or F4 and platelet count below normal were the strongest predictors of progression to hepatic decompensation or hepatocellular carcinoma. **CONCLUSIONS:** The risks of death and progression to liver failure varied greatly by fibrosis stage. Clinicians and policy makers could use these progression risk data in prioritization and in determining the timing of treatment for patients in early stages of liver disease.

Imagine ways in which liver health services (through the lens of cirrhosis) can be integrated into our medical models and social support services. How can we encourage intergenerational discussions around the cure for HCV or the implications of cirrhosis?


**BACKGROUND AND AIMS:** Liver cirrhosis is an important public health concern in the United States and a significant source of morbidity and mortality. However, the epidemiology of cirrhosis is incompletely understood. The aims of this study were to estimate the prevalence of cirrhosis in the general US population, determine characteristics of affected Americans with a focus on health disparities, and calculate excess mortality attributable to cirrhosis. **METHODS:** National Health And Nutrition Examination Survey data conducted between 1999 and 2010 were used to estimate cirrhosis prevalence and factors associated with cirrhosis. The National Center for Health Statistics-linked death certificate data from the National Death Index were linked to the National Health And Nutrition Examination Survey database for the years 1999 to 2004, and attributable mortality was calculated using propensity score adjustment. Cirrhosis was ascertained by aspartate aminotransferase-to-platelet ratio of >2 and abnormal liver function tests. **RESULTS:** The prevalence of cirrhosis in the United States was approximately 0.27%, corresponding to 633,323 adults. Sixty-nine percent reported that they were unaware of having liver disease. The prevalence was higher in non-Hispanic blacks and Mexican Americans, those living below the poverty level, and those with less than a 12th grade education. Diabetes, alcohol abuse, hepatitis C and B, male sex, and older age were all independently associated with cirrhosis, with a population attributable fraction of 53.5% from viral hepatitis (mostly hepatitis C), diabetes, and alcohol abuse. Mortality was 26.4% per 2-year interval in cirrhosis compared with 8.4% in propensity-matched controls. **CONCLUSIONS:** The prevalence of cirrhosis is higher than previously estimated. Many cases may be undiagnosed, and more than half are potentially preventable by controlling diabetes, alcohol abuse, and viral hepatitis. Public health efforts are needed to reduce this disease burden, particularly among racial/ethnic minorities and individuals at lower socioeconomic status.

AIM: To compare the nutritional status between alcoholic compensated cirrhotic patients and hepatitis C virus (HCV)-related cirrhotic patients with portal hypertension. METHODS: A total of 21 patients with compensated cirrhosis (14 with HCV-related cirrhosis and seven with alcoholic cirrhosis) who had risky esophageal varices were investigated. In addition to physical variables, including the body mass index, triceps skinfold thickness, and arm-muscle circumference, the nutritional status was also assessed using the levels of pre-albumin (pre-ALB), retinol-binding protein (RBP) and non-protein respiratory quotient (NPRQ) measured with an indirect calorimeter. RESULTS: A general assessment for the nutritional status with physical examinations did not show a significant difference between HCV-related cirrhosis and alcoholic cirrhosis. However, the levels of pre-ALB and RBP in alcoholic compensated cirrhotic patients were significantly higher than those in HCV-related compensated cirrhotic patients. In addition, the frequency of having a normal nutritional status (NPRQ ≥ 0.85 and ALB value > 3.5 g/dL) in alcoholic compensated cirrhotic patients was significantly higher than that in HCV-related compensated cirrhotic patients. CONCLUSION: According to our small scale study, alcoholic compensated cirrhotic patients can develop severe portal hypertension even with a relatively well-maintained liver function and nutritional status compared with HCV-related cirrhosis.

In your thoughts, what would an ADAP (AIDS Drug Assistance Program) model for HCV look like in the US, and is this feasible, in your opinion, given today’s financial and political climate? Access to Costly New Hepatitis C Drugs: Medicine, Money, and Advocacy. Trooskin SB1, Reynolds H2, Kostman JR3. Clin Infect Dis. 2015 Aug 12. pii: civ677. [Epub ahead of print] Hepatitis C affects >3 million people in the United States, and often leads to end-stage liver disease or death. In 2014, several new drugs to treat hepaticic C virus received US Food and Drug Administration approval, with remarkable cure rates exceeding 90%. Medicaid, however, is rationing these drugs, and other insurers have restricted coverage due to their exorbitant costs and the large size of the population in need. These access barriers and disparities have resulted in national patient advocacy mobilization, US congressional inquiry, and legal challenges. The US Department of Health and Human Services has been urged to intervene. We propose the establishment of a federal program, analogous to AIDS Drug Assistance Programs, to reduce access barriers and facilitate focused price negotiations. The federal government may further undertake a nonvoluntary acquisition of the pharmaceutical patents pursuant to federal statutory authority and principles of eminent domain. Projections indicate this proposal could lower costs by 90% and eliminate rationing.

What barriers or pushback do you envision a medical system might raise to prevent or postpone the use of and HCV flagging alert within the electronic health record? Improving Hepatitis C Virus Screening Rates in Primary Care: A Targeted Intervention Using the Electronic Health Record. Sidlow R, Msaouel P. J Healthc Qual. 2015 Sep-Oct;37(5):319-23. doi: 10.1097/JHQ.0000000000000010. With the advent of effective treatments for hepatitis C virus (HCV), it has become a public health priority to increase the identification of HCV carriers and link them to systems of care. As a result, in 2012, the Centers for Disease Control and Prevention recommended that all adults
born between 1945 and 1965 should receive one-time testing for HCV. In response to this mandate, we sought an effective nonintrusive means to increase HCV screening rates in our busy primary care practices. **METHODS:** We designed an HCV testing decision support module that was integrated into the electronic health record (EHR) and triggered an automatic test order for eligible patients at the time of visit. Rates of HCV screening for eligible patients were measured before and after implementation. **RESULTS:** Hepatitis C virus screening rates increased by 254% after implementation of this tool. **CONCLUSION:** Incorporating a clinical reminder into the EHR effectively and appropriately increased the hepatitis C testing rates among primary care patients with no previous testing. Such tools can be an effective means to operationalize health system-wide testing efforts.

**New Therapies, Evidence, and Guidance in Hepatitis C Management: Expert Practices and Insights from an Educational Symposium at the AMCP 27th Annual Meeting Expo.**
Terrault N1, Monto A, Stinchon MR, Rusie E, Moreo K. J Manag Care Spec Pharm. 2015 Sep;21(9):S1-S17.
**BACKGROUND:** The 2013-2014 approvals of new direct-acting antiviral (DAA) therapies for hepatitis C virus (HCV) infection have engendered a paradigm shift in HCV treatment and management, offering the potential for a cure at a population level. The availability of the highly effective and relatively safe DAAs prompted revisions to guidance recommendations based on new clinical trial evidence. In the context of this paradigm shift and considerations of the costs associated with the new DAAs, managed care professionals face new questions and challenges regarding HCV treatment and management approaches. To address the continuing education needs of this group, PRIME Education, Inc. (PRIME) conducted a symposium on HCV at the 27th Annual Meeting Expo of the Academy of Managed Care Pharmacy. Moderated by Michael R. Stinchon, Jr., RPh, the program panel featured 2 internationally recognized leaders in hepatitis C treatment and research: Norah Terrault, MD, MPH, and Alex Monto, MD. **OBJECTIVE:** To summarize the educational symposium presentations and discussions. **METHODS:** This article is organized by key questions that the panelists and attendees raised for discussion during the 2-hour symposium. The questions addressed methods for assessing liver fibrosis; comprehensive patient assessment to inform treatment decisions; the influence of viral load on decisions about treatment duration; the role of ribavirin in optimizing treatment efficacy; unmet treatment needs for patients with HCV genotype 3 or advanced liver disease; and managed care strategies for patient education, adherence promotion, and care coordination. In answering attendee questions on these issues, the expert panelists presented established evidence, and recognizing limitations to current evidence and guidance recommendations, they discussed applications of clinical judgment and offered their views and practices regarding individualized care for patients with HCV. **SUMMARY:** In response to questions about the utility of noninvasive methods for assessing liver fibrosis, the expert panel presented a comparative overview of the methodology, accuracy, risks, limitations, and costs of noninvasive tests and liver biopsy. Discussion highlighted the strengths of noninvasive methods for diagnosing advanced disease and cirrhosis and the methods' limitations that pose barriers to ensuring that patients receive necessary antiviral therapy. Based on guidance recommendations, treatment should be prioritized in patients with advanced fibrosis or cirrhosis (Metavir score F3 to F4). While acknowledging the importance of this recommendation, the symposium panelists also argued that making effective decisions about whom, and when, to treat requires a more comprehensive clinical approach to patient assessment and adjusting recommended priorities according to individual patient...
considerations. This approach involves evaluating outcomes such as extrahepatic complications, including those affecting quality of life, functional status, and work productivity. In response to questions regarding decisions about DAA therapy duration based on viral load, the panel engaged the audience in thinking critically about evidence-based cutoff values and natural fluctuations of HCV RNA concentrations. Discussions centered on the importance of clinical judgment to ensure that the treatment duration promotes the highest efficacy and avoids risks of relapse. The panel responded to several audience questions about the role of ribavirin in new DAA regimens. Evidence-based presentations and discussions focused on patient-specific factors that must be considered to inform effective decisions about adding ribavirin. The panel took a similar approach to answering questions about emerging challenges and the difficult-to-treat populations of patients with HCV genotype 3 or advanced liver disease. The symposium concluded with presentation of, and discussion on, managed care strategies for educating patients about appropriate HCV medication use, improving adherence, and coordinating care provided by the interprofessional team. **CONCLUSIONS:** The availability of new DAAs for HCV raises new questions and challenges for managed care professionals, especially regarding prioritizing patients for immediate therapy as well as treatment and management approaches that account for the needs of individual patients and subpopulations. The educational symposium summarized in this article directly addressed key questions and challenges through presentations of evidence, guidance recommendations, and interactive discussions on the views and practices of international leaders in HCV treatment and research.


Hepatitis C virus (HCV) infection continues to disproportionately affect incarcerated populations. New HCV drugs present opportunities and challenges to address HCV in corrections. The goal of this study was to evaluate the impact of the treatment costs for HCV infection in a state correctional population through a budget impact analysis comparing differing treatment strategies. Electronic and paper medical records were reviewed to estimate the prevalence of hepatitis C within the Rhode Island Department of Corrections. Three treatment strategies were evaluated as follows: (1) treating all chronically infected persons, (2) treating only patients with demonstrated fibrosis, and (3) treating only patients with advanced fibrosis. Budget impact was computed as the percentage of pharmacy and overall healthcare expenditures accrued by total drug costs assuming entirely interferon-free therapy. Sensitivity analyses assessed potential variance in costs related to variability in HCV prevalence, genotype, estimated variation in market pricing, length of stay for the sentenced population, and uptake of newly available regimens. Chronic HCV prevalence was estimated at 17 % of the total population. Treating all sentenced inmates with at least 6 months remaining of their sentence would cost about $34 million-13 times the pharmacy budget and almost twice the overall healthcare budget. Treating inmates with advanced fibrosis would cost about $15 million. A hypothetical 50 % reduction in total drug costs for future therapies could cost $17 million to treat all eligible inmates. With immense costs projected with new treatment, it is unlikely that correctional facilities will have the capacity to treat all those afflicted with HCV. Alternative payment strategies in collaboration with outside programs may be necessary to curb this epidemic. In
in order to improve care and treatment delivery, drug costs also need to be seriously reevaluated to be more accessible and equitable now that HCV is more curable.

We know HCV symptoms are quiet and many experts say ‘there are few to no symptoms’. However, patients, particularly post cure, speak of the number of symptoms they experienced but didn’t recognize because they were so habituated to that symptom. What implications do you think it would have on treatment access if symptoms were actually recognized as the symptoms that they are and the impact that they make on patients’ lives? Particularly for those in the earlier stages of disease?


OBJECTIVES: Fatigue is a leading concern of patients with chronic hepatitis C virus (HCV) infection. Despite its clinical significance, fatigue in HCV is poorly understood and therefore invariably under-treated. A cognitive-behavioural approach offers a framework to understand and treat fatigue, but the characteristics of fatigue in chronic HCV infection have not been documented from a cognitive-behavioural perspective. This study captured the common and unique aspects of fatigue from a cognitive-behavioural perspective in individuals with HCV infection and clinically significant fatigue.

DESIGN: Cross-sectional, qualitative using a critical realism approach.

METHODS: Fourteen individuals (64% women; age >18 years) participated in semi-structured interviews. The interviews documented the features, course, and perceived antecedents of fatigue; fatigue-specific cognitions; fatigue management behaviours; and the functional impact of fatigue.

RESULTS: Participants' descriptions included the aspects of fatigue that have been targets of cognitive-behavioural therapy in other medical conditions, including attributing fatigue to the illness; expectation of chronicity; low control; and fatigue-driven coping. There were also components of fatigue experience that appear to be unique characteristics of fatigue related to HCV, including predominantly physical fatigue; high acceptance of fatigue; and liver-protective diet as a fatigue management behaviour.

CONCLUSIONS: This was the first study to document the experience of fatigue in chronic HCV infection in a cognitive-behavioural framework. The findings suggest that the cognitive-behavioural approach can be applied to fatigue in chronic HCV infection. This would open an avenue to alleviate fatigue and thus improve the primary patient-reported outcome of the disease.

Statement of contribution What is already known on this subject? Fatigue is a key patient-reported outcome measure of chronic hepatitis C virus (HCV) infection. Fatigue management is not part of the standard care, because fatigue is poorly characterized in this population. What does this study add? A cognitive-behavioural approach can be applied to understand fatigue in HCV infection. Identified aspects of fatigue (antecedents, consequences, cognitions, behaviours) that can be treatment targets. Cognitive-behavioural therapy would open a new treatment avenue to alleviate fatigue in HCV infection.


OBJECTIVES: The objectives of this study were to identify and quantify the factors driving patient and physician preferences for treatments of genotype 1 hepatitis C virus infection in the UK. METHODS: A web survey was conducted, including 100 patients (50 treatment-naive and 50 treatment-experienced patients) and 50 physicians (gastroenterologists/ hepatologists and
A discrete-choice experiment was conducted to elicit the participants' preferences on the basis of seven attributes with four levels each: efficacy, that is probability of reaching sustained virologic response, treatment duration, treatment convenience (i.e. number of pills and/or injections), gastrointestinal problems, anaemia, dermatological problems and neuropsychological problems. The statistical analysis applied a mixed logit model to estimate preference weights and relative importance scores. **RESULTS:** Results indicated that the sustained virologic response rate was the most important attribute to participants. Physicians placed an even greater weight on the efficacy of treatments with a relative importance score of 9.33 [95% confidence interval: (6.93-11.91)], as compared with 6.16 [95% confidence interval: (4.34-8.15)] for patients. Neuropsychological problems ranked second for patients and physicians, and were more important to treatment-naive patients than to treatment-experienced patients or physicians. Gastrointestinal problems, anaemia and dermatological problems were of minor importance to all participants. These findings may be explained by the improvement in the management of physical adverse reactions over the last few years, thus making treatment easier to tolerate. **CONCLUSIONS:** This study is the first conjoint analysis assessing and comparing the preferences of patients and physicians in hepatitis C virus.

With such a signification percentage of HCV patients developing, or at risk for developing cirrhosis, and the dearth of specialty service providers (hepatologists, gastroenterologists) at the community level, what do you see as practical interventions to bridge the gap to increase accessibility of specialty care providers, who are typically only available in tertiary care centers?

**Facility- and Patient-Level Factors Associated with Esophageal Variceal Screening in the USA.** Flemming JA1, Saxena V2, Shen H2,3, Terrault NA2, Rongey C2,3. Dig Dis Sci. 2015 Sep 12. [Epub ahead of print]

**BACKGROUND AND AIM:** The American Association for the Study of Liver Disease (AASLD) recommends screening for esophageal varices (EV) by esophagoduodenoscopy (EGD) in patients with cirrhosis to guide decisions regarding primary prophylaxis for EV hemorrhage. We aimed to identify patient and facility factors associated with EV screening in veterans with hepatitis C (HCV)-associated cirrhosis. **METHODS:** This was a population-based cohort study. Veterans with HCV and newly diagnosed cirrhosis between 1/1/2004 and 12/31/2005 and followed until 12/31/2011 were included. The primary outcome was receipt of EGD within 1 year of cirrhosis diagnosis. Patient- and facility-level factors associated with EV screening were determined. **RESULTS:** A total of 4230 patients with HCV cirrhosis were identified. During median follow-up of 6.1 years (IQR: 4.0-8.0), 21.5 % developed a decompensating event, and 38.3 % died. Fifty-four percent received an EGD, and 33.8 % had an EGD within guidelines. Median time from cirrhosis diagnosis to EGD was 72 days (IQR: 12-176). Factors independently associated with receipt of EV screening were a decompensation event (OR 1.16, CI 1.01-1.32) and gastroenterology/hepatology clinic access (OR 2.1, CI 1.73-2.46), whereas cardiovascular (OR 0.81, CI 0.69-0.95), mental health (OR 0.79, CI 0.68-0.91), and respiratory (OR 0.85, CI 0.72-0.99) comorbidities were associated with reduced likelihood of EV screening. **CONCLUSION:** EV screening per AASLD guidelines occurs in only one-third of patients. This missed opportunity was strongly associated with access to gastroenterology/hepatology specialty care. Additionally, providers may be relying on clinical cues (i.e., decompensation) to prompt referral for endoscopy suggesting education to improve compliance with guidelines is needed.
Chronic hepatitis C virus (HCV) viral infection is the most common blood-borne viral infection and approximately 2%-3% of the world's population or 170-200 million people are infected. In the United States as many as 3-5 million people may have HCV. Psychiatric and substance use disorders (SUDs) are common co-morbid conditions found in people with HCV and are factors in predisposing people to HCV infection. Also, these co-morbidities are reasons that clinicians exclude people from antiviral therapy in spite of evidence that people with HCV and co-morbid psychiatric and SUD can be safely and effectively treated. Furthermore, the neuropsychiatric side effects of interferon (IFN), until recently the mainstay of antiviral therapy, have necessitated an appreciation and assessment of psychiatric co-morbidities present in people with HCV. The availability of new medications and IFN-free antiviral therapy medication combinations will shorten the duration of treatment and exposure to IFN and thus decrease the risk of neuropsychiatric side effects. This will have the consequence of dramatically altering the clinical landscape of HCV care and will increase the number of eligible treatment candidates as treatment of people with HCV and co-morbid psychiatric and SUDs will become increasingly viable. While economically developed countries will rely on expensive IFN-free antiviral therapy, less developed countries will likely continue to use IFN-based therapies at least until such time as IFN-free antiviral medications become generic. The current manuscript discusses the efficacy and viability of treating HCV in people with psychiatric and SUDs comorbidities, the treatment of the neuropsychiatric side effects of IFN-based therapies and the impact of new medications and new treatment options for HCV that offer the promise of increasing the availability of antiviral therapy in this vulnerable population.

Chronic hepatitis C infection is the leading cause of chronic liver disease, cirrhosis, hepatocellular carcinoma as well as the primary indication for liver transplantation in the United States. Despite recent advances in drugs for the treatment of hepatitis C, predictive models estimate the incidence of cirrhosis due to hepatitis C infection will continue to rise for the next two decades. There is currently an immense interest in the treatment of patients with fibrosis and early-stage cirrhosis as treatment can lead to decrease in the rates of decompensated cirrhosis, hepatocellular carcinoma and need for liver transplantation in these patients. The goal of this paper is to provide clinicians and health care professionals further information about the treatment of patients with hepatitis C infection and cirrhosis. Additionally, the paper focuses on the disease burden, epidemiology, diagnosis and the disease course from infection to treatment. We provide an overview of multiple studies for the treatment of chronic hepatitis C infection that have included patients with cirrhosis. We also discuss the advantages and disadvantages of treatment in cirrhotic patients and focus on the most up to date guidelines available for treatment.

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


Recent advances in the treatment of hepatitis C virus (HCV) infection have led to the availability of both highly efficacious interferon-containing and interferon-sparing regimens. However, the use of such therapies faces restrictions due to high costs. For patients who are medically eligible to receive interferon, the choice between the two will likely be impacted by preferences surrounding interferon, severity of disease, coverage policies and out-of-pocket costs. We developed a decision model to quantify the trade-offs between immediate, interferon-containing therapy and delayed, interferon-free therapy for patients with chronic, genotype 1 HCV infection. We projected the quality-adjusted life expectancy stratified by the presence or absence of cirrhosis for four strategies: (i) no treatment; (ii) immediate, one-time treatment with an interferon-containing regimen; (iii) immediate treatment as above with the opportunity for retreatment in patients who fail to achieve sustained virologic response with interferon-free therapy in 1 year; and (iv) delayed therapy with interferon-free therapy in 1 year. When compared to one-time immediate treatment with the interferon-containing regimen, delayed treatment with the interferon-free regimen in 1 year resulted in longer life expectancy, with a 0.2 quality-adjusted life year (QALY) increase in noncirrhotic patients, and a 1.1 QALY increase in patients with cirrhosis. This superiority in health benefits was lost when wait time for interferon-free therapy was greater than 3-3.2 years. In this modelling analysis, interferon-free therapy resulted in superior health benefits compared to immediate therapy with interferon until wait time exceeded 3-3.2 years. Such data can inform decision-making regarding treatment initiation for HCV as healthcare financing evolves.


_Caring Ambassadors Program Hepatitis C Literature Review © 2015_
The recent advances in hepatitis C virus (HCV) therapeutics have brought combinations of direct acting antiviral medications that offer interferon-free, well-tolerated regimens with sustained virologic response rates greater than 90% in clinical trials for many patient groups. The successes have prompted discussions regarding cure for all patients. These regimens have already demonstrated the ability to cure previously challenging patient groups, including human immunodeficiency virus-HCV coinfection, decompensated cirrhosis, and post-liver transplantation. Limitations exist in the current portfolio of agents, with suboptimal outcomes for genotype 3 and limited data in genotypes 5 and 6. More data are urgently needed in patients with chronic kidney disease and in children. With ongoing developments, highly effective regimens for all these patient groups are within reach. To deliver HCV treatment throughout the world and particularly in low- and middle-income countries, regimens need to be affordable but also pan-genotypic, well-tolerated, and delivered once daily for 4-8 weeks. With such a regimen, cure for all patients would then hinge on the ability to identify patients with HCV infection and deliver treatment within their communities. This review will discuss the strategies that will be necessary to realize this opportunity to cure all persons with HCV infection.

With an expected and projected increase of PWID in a given city, what would be the types and layers of services and targeted interventions that you would integrate to address include infection and the prevention of new infections?


People who inject drugs (PWID) are at high risk for blood-borne pathogens transmitted during the sharing of contaminated injection equipment, particularly hepatitis C virus (HCV). HCV prevalence is influenced by a complex interplay of drug-use behaviors, social networks, and geography, as well as the availability of interventions, such as needle exchange programs. To adequately address this complexity in HCV epidemic forecasting, we have developed a computational model, the Agent-based Pathogen Kinetics model (APK). APK simulates the PWID population in metropolitan Chicago, including the social interactions that result in HCV infection. We used multiple empirical data sources on Chicago PWID to build a spatial distribution of an in silico PWID population and modeled networks among the PWID by considering the geography of the city and its suburbs. APK was validated against 2012 empirical data (the latest available) and shown to agree with network and epidemiological surveys to within 1%. For the period 2010-2020, APK forecasts a decline in HCV prevalence of 0.8% per year from 44(±2)% to 36(±5)%, although some sub-populations would continue to have relatively high prevalence, including Non-Hispanic Blacks, 48(±5)%. The rate of decline will be lowest in Non-Hispanic Whites and we find, in a reversal of historical trends, that incidence among non-Hispanic Whites would exceed incidence among Non-Hispanic Blacks (0.66 per 100 person years vs 0.17 per 100 person years). APK also forecasts an increase in PWID mean age from 35(±1) to 40(±2) with a corresponding increase from 59(±2)% to 80(±6)% in the proportion of the population >30 years old. Our studies highlight the importance of analyzing subpopulations in disease predictions, the utility of computer simulation for analyzing demographic and health trends among PWID and serve as a tool for guiding intervention and prevention strategies in Chicago, and other major cities.
**Beyond cure: preventing and managing the complications of end-stage liver disease.**


**PURPOSE OF REVIEW:** The aim of this review was to define the implication of hepatitis C virus (HCV) eradication in patients with cirrhosis. **RECENT FINDINGS:** Sustained virologic response (SVR) is associated with a favourable outcome in patients with cirrhosis especially in the presence of regression of cirrhosis but also with extrahepatic outcomes regarding health-related quality of life, risk of diabetes, risk of cardiovascular diseases and control of HIV replication by antiretroviral therapy. In patients with decompensated cirrhosis identifying the point of no return where viral eradication is not followed by clinical improvement is extremely relevant. A strict follow-up is needed in order to early diagnose HCC and signs of liver dysfunction, even after SVR, not only in patients with histological diagnosis of cirrhosis but also in those with advanced disease identified by liver stiffness measurements or by noninvasive methods. **SUMMARY:** Eradication of HCV is associated with regression or ‘freezing’ of cirrhosis even if it is still unknown the point of no return where this has no benefit for the patient. Nevertheless, in patients with cirrhosis, follow-up should be pursued after eradication of HCV. In addition, HCV eradication has several extrahepatic benefits.


**OBJECTIVES:** Although effective, direct acting antiviral (DAA) therapies for genotype 1 (GT 1) hepatitis C virus (HCV) have been associated with compliance challenges. Additionally, treatment at predominantly community-based centers has been associated with low retention of patients on treatment and higher dropout rates. The OPTIMAL Phase IV interventional trial (ClinicalTrials.gov Identifier: NCT01405027) was designed to evaluate the impact of an education program for community investigator (CI) sites participating in a Chronic Liver Disease Foundation study treating chronic GT 1 HCV patients. **METHODS:** This physician educational program was administered by 22 Hepatology Centers of Educational Expertise (HCEE) academic sites to 33 CI sites asked to participate from December 2011 to July 2012. The HCEE mentors from DAA-experienced academic sites educated those at CI sites on therapeutic management, practice, and patient outcomes through a series of four standardized educational sequence visits regarding the use of first generation HCV protease inhibitors and the overall treatment of HCV. **RESULTS:** Treatment duration compliance rates for patients treated at CI sites versus those treated at HCEE academic sites were evaluable in 77 of 84 HCEE academic site patients, 102 of 113 patients treated at CI sites, and 179 of 197 overall patients. The treatment duration compliance rates for patients treated at HCEE academic sites, CI sites and overall were 85.4 ± 25.39%, 83.8 ± 27.37%, and 84.5 ± 26.48%, respectively, and did not differ statistically between the groups (p = 0.49). Almost half (47%) of the patients in the study achieved a sustained virological response for 24 weeks (SVR24) regardless of the type of site (p = 0.64). Safety profiles were similar at both HCEE and CI sites. **CONCLUSIONS:** These results demonstrated that education of CI sites unfamiliar with DAAs resulted in patient outcomes consistent with those observed at DAA-experienced academic sites.

**AIM:** To assess serum cartilage oligomeric matrix protein (COMP) as a marker of cirrhosis and risk of progression to hepatocellular carcinoma (HCC). **METHODS:** A COMP enzyme-linked immunosorbent assay was used to test 187 patients with chronic liver diseases at the time point of first evaluation. The selected patients included 72 with chronic hepatitis B infection, 75 with chronic hepatitis C infection, 22 with primary biliary cirrhosis, 7 with autoimmune hepatitis type 1, and 11 with alcoholic liver disease. Demographic, biochemical, histological and clinical characteristics of the patients were recorded at the first evaluation. One hundred and forty-seven patients were followed for a median [interquartile range (IQR)] duration of 96.5 (102) mo. The clinical, biochemical and histological data, as well as the development of cirrhosis, HCC according to internationally accepted criteria and in case of death, a liver-related cause during the follow-up period, were recorded at the electronic database of our clinic. COMP determination was also performed in 43 healthy individuals who served as the control study group. **RESULTS:** COMP positivity (> 15 U/L) was detected in 22%-36% among chronic liver disease groups. Strikingly, almost 83% of COMP-positive patients were cirrhotic at baseline, independently of cause of liver disease. Among the patients who developed HCC during follow-up, 73.7% (14/19) were COMP positive at baseline. COMP positivity was significantly associated with older age (P < 0.001), advanced fibrosis (P = 0.001) and necroinflammatory activity (P = 0.001), higher aspartate aminotransferase (P < 0.001), alanine aminotransferase (P < 0.02), γ-glutamyl transpeptidase (P = 0.003), alkaline phosphatase (P = 0.001), bilirubin (P < 0.05), international normalized ratio (P = 0.002) and alpha-fetoprotein levels (P < 0.02), and lower albumin (P < 0.001), and platelet count (P = 0.008). COMP levels [median (IQR)] were significantly higher in cirrhotics compared to non-cirrhotics [13.8 (7.9) U/L vs 9.8 (4.6) U/L, respectively; P < 0.001]. On multivariate logistic regression analysis, COMP-positivity was independently associated only with cirrhosis (OR = 4.40, 95%CI: 1.33-14.69, P = 0.015). Kaplan-Meier analysis showed that COMP positivity was significantly associated with HCC development (P = 0.007) and higher incidence of liver-related death (P < 0.001). **CONCLUSION:** Elevated COMP levels are strongly associated with cirrhosis and HCC progression. Serum COMP is a new promising non-invasive biomarker for HCC risk assessment in surveillance programs.


**BACKGROUND:** Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world. Having a very poor prognosis, it currently ranks as the third most common cause of cancer-related deaths. MiRNAs are a set of small, single-stranded, non-coding RNA molecules that negatively regulate gene expression at the post-transcriptional level. Several miRNAs were found to be frequently deregulated in HCC. **OBJECTIVE:** To investigate whether miRNA-122, miRNA-199a, and miRNA-16 are altered in sera of hepatitis C virus (HCV)-induced HCC patients compared with chronic HCV patients without HCC, and to assess their diagnostic value.
to differentiate between HCC and chronic HCV in order to develop a non-invasive diagnostic and prognostic tool for HCC. **METHODS:** We analysed the expression of mature miRNA-122, miRNA-199a, and miRNA-16 in serum by a singleplex TaqMan two-step stem loop quantitative real-time reverse-transcription PCR (qRT-PCR) in 40 newly diagnosed HCC patients and 40 chronic HCV liver cirrhosis patients, as well as 20 apparently healthy individuals as a control group, using RNU48 as a normalisation control. **RESULTS:** Serum miR-16 was significantly lower in HCC than in HCV patients (P = 0.033). The serum level of miR-199a in chronic HCV patients was significantly lower than in healthy controls (P = 0.001). Receiver operating curve (ROC) analysis for serum miRNA-16 for discriminating HCC from HCV patients showed that at the cut-off value of 0.904, the sensitivity and specificity for this marker were 57.5 and 70 %, respectively. The combination of serum miR-16 with serum alpha fetoprotein (AFP) resulted in improved sensitivity to 85% and increased diagnostic accuracy to 87.5 %. Serum miR-199a and miR-16 were significantly associated with several parameters of HCC such as tumour size and number. **CONCLUSION:** The combination of serum miR-16 and serum AFP is a significant improvement on the current best practice of serum AFP for HCC in HCV-positive patients. Serum miR-199a and miR-16 could be used as potential indicators of the progress of HCC.

**Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment.** Kamachi S1, Mizuta T2, Otsuka T1, et al. Hepatol Res. 2015 Jul 29. doi: 10.1111/hepr.12562. [Epub ahead of print]

**BACKGROUND AND AIM:** Sarcopenia, initially proposed as decreased of muscle mass and strength, is associated with aging and malignant diseases. The aim of the present study was to determine whether there is a correlation between sarcopenia and the recurrence of hepatocellular carcinoma (HCC) after curative treatment. **METHODS:** We conducted a retrospective analysis of consecutive naive patients with HCC who underwent curative resection or radiofrequency ablation. To eliminate the influence of cause or the severity of liver damage, subjects were limited to those with HCC with hepatitis C-related cirrhosis and Child-Pugh class A liver function. Patients were assessed using computed tomographic measurement of muscle mass at the level of the third lumbar (L3) vertebrae, the L3 skeletal muscle index (L3 SMI). Sarcopenia was defined by using previously published, sex-specific cut-off value. **RESULTS:** Sarcopenia was present in 61/92 patients. Patients' median age was 71.5 years (range 47 - 84 years), and the baseline characteristics of patients were comparable between patients with and without sarcopenia except for gender, serum albumin level, prothrombin time, diabetes mellitus and body mass index. Recurrence rates at 1, 3 and 5 years were 39.1%,77.1%,81.7% for patients with sarcopenia and 23.5%,59.5% and 75.7% for patients without sarcopenia, respectively (P = 0.03). Multivariate Cox analysis revealed that sarcopenia and preoperative α-fetoprotein > 40 ng/mL were significant independent factors for recurrence. **CONCLUSIONS:** Sarcopenia is a risk factor for recurrence in patients with HCC who were treated with curative treatment.

**Liver-infiltrating CD8+ lymphocytes as prognostic factor for tumour recurrence in hepatitis C virus-related hepatocellular carcinoma.** Ramzan M1,2, Sturm N1,2,3, et al. Liver Int. 2015 Jul 28. doi: 10.1111/liv.12927. [Epub ahead of print]

**BACKGROUND:** Chronic liver inflammation and immune/inflammatory response promote hepatocellular carcinoma. The aim of this study was to characterize the immune status of HCV-related cirrhosis in patients with hepatocellular carcinoma (HCV-HCC) as compared to HCV patients without hepatocellular carcinoma. **METHOD:** Immune markers (CD3, CD4, CD8,
CD20, CD56, TCRγδ, FoxP3) and gene expression profiles (CD8α, CD8β, FoxP3, IL-6, IFN-γ, perforin, RANTES) were analysed in a test cohort by immunohistochemistry and quantitative RT-PCR analysis on serial non-tumorous and tumorous tissues. **RESULTS:** Immune microenvironment was more inflammatory in HCV-HCC than HCV cirrhotic livers. The number of CD3+, CD4+, CD8+ and CD20+ liver-infiltrating lymphocytes was significantly higher, whereas the number of CD56+ cells was significantly lower in HCV-HCC compared to HCV cirrhotic parenchyma. These differences were restricted to fibrous septa for CD4+ and CD20+ cells and to nodular parenchyma for CD8+ cells. Gene expressions of CD8α, FoxP3 and RANTES were also significantly higher in HCV-HCC than in HCV cirrhosis. Interestingly, in a large cohort of 63 HCV-HCC patients. The number of CD8+ cells ≥100/field was associated with significant higher tumour recurrence (P = 0.003) and lower overall survival (P = 0.05) at 5 years. **CONCLUSION:** High densities of liver-infiltrating lymphocytes in HCV-HCC cirrhotic parenchyma prevail inflammatory conditions and could contribute to tumorigenesis and tumour recurrence. These results could contribute towards better clinical evaluation of patients susceptible for HCC recurrence after curative surgery.

What types of liver health information would you integrate into the general population (and where) about the serious issue of NAFLD/fatty liver disease? What about the increase in diabetes and other metabolic issues related to an ‘unwell’ society?


**BACKGROUND & AIMS:** Hepatocellular carcinoma (HCC) can develop in individuals without cirrhosis. We investigated risk factors for development of HCC in the absence of cirrhosis in a U.S. population. **METHODS:** We identified a national cohort of 1500 patients with verified HCC during 2005 to 2010 in the U.S. Veterans Administration (VA) and reviewed their full VA medical records for evidence of cirrhosis and risk factors for HCC. Patients without cirrhosis were assigned to categories of level 1 evidence for no cirrhosis (very high probability) or level 2 evidence for no cirrhosis (high probability), which were based on findings from histologic analyses, laboratory test results, markers of fibrosis from noninvasive tests, and imaging features. **RESULTS:** A total of 43 of the 1500 patients with HCC (2.9%) had level 1 evidence for no cirrhosis, and 151 (10.1%) had level 2 evidence for no cirrhosis; the remaining 1203 patients (80.1%) had confirmed cirrhosis. Compared with patients with HCC in presence of cirrhosis, greater proportions of patients with HCC without evidence of cirrhosis had metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), or no identifiable risk factors. Patients with HCC without evidence of cirrhosis were less likely to have abused alcohol or have hepatitis C virus infection than patients with cirrhosis. Patients with HCC and NAFLD (unadjusted odds ratio, 5.4; 95% confidence interval, 3.4-8.5) or metabolic syndrome (unadjusted odds ratio, 5.0; 95% confidence interval, 3.1-7.8) had more than 5-fold risk of having HCC in the absence of cirrhosis, compared with patients with HCC-related HCC. **CONCLUSIONS:** Approximately 13% of patients with HCC in the VA system do not appear to have cirrhosis. NAFLD and metabolic syndrome are the main risk factors for HCC in the absence of cirrhosis.

**Long-Term Maintenance of Complete Response after Sorafenib Treatment for Multiple Lung Metastases from Hepatocellular Carcinoma.** Katafuchi E1, Takami Y1, Wada Y1,
Sorafenib is an effective treatment for unresectable hepatocellular carcinoma (HCC) characterized by disease stabilization. However, the response rates are very low (<9%), and a complete response is rarely achieved. We report an extremely rare case of a HCC patient with multiple lung metastases treated with sorafenib who achieved a complete response for a long period. A 77-year-old woman was diagnosed with chronic hepatitis C in 1990. In 2007, a HCC detected in the liver was treated with percutaneous ethanol injection therapy. Subsequently, recurrence of HCC in the liver was treated with microwave coaguloncrotic therapy in 2010. In April 2011, a computed tomography (CT) scan revealed innumerable multiple metastases spread diffusely in both lungs. Tumor marker levels were extremely high [α-fetoprotein (AFP) 76,170 ng/ml, lens culinaris agglutinin-reactive fraction of AFP 7.5%, des-γ-carboxyprothrombin (DCP) 63,400 mAU/ml]. Sorafenib was administered at a reduced dose of 400 mg/day because of old age. Four months after sorafenib treatment, AFP and DCP had decreased to within normal levels, and the multiple lung metastases had disappeared. Currently, sorafenib is administered at a reduced dose of 400 mg/day, and the complete response has been maintained for 48 months.


**BACKGROUND:** Hepatitis C virus (HCV) infection is an established cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC); however, it is unclear if the virus plays a direct role in the development of HCC. Hepatocyte nuclear factor 4α (HNF4α) is a critical determinant of epithelial architecture and hepatic development; depletion of HNF4α is correlated with oncogenic transformation. We explored the viral role in the inhibition of HNF4α expression, and consequent induction of tumor-promoting genes in HCV infection-associated HCC.

**METHODS:** Western blot analysis was used to monitor the changes in expression levels of oncogenic proteins in liver tissues from HCV-infected humanized mice. The mechanism of HNF4α depletion was studied in HCV-infected human hepatocyte cultures in vitro. Targeting of HNF4α expression by viral non-coding RNA was examined by inhibition of Luciferase HNF4α 3’-UTR reporter. Modulation of invasive properties of HCV-infected cells was examined by Matrigel cell migration assay. **RESULTS:** Results show inhibition of HNF4α expression by targeting of HNF4α 3’-UTR by HCV-derived small non-coding RNA, vmr11. Vmr11 enhances the invasive properties of HCV-infected cells. Loss of HNF4α in HCV-infected liver tumors of humanized mice correlates with the induction of epithelial to mesenchymal transition (EMT) genes. **CONCLUSIONS:** We show depletion of HNF4α in liver tumors of HCV-infected humanized mice by HCV derived small non-coding RNA (vmr11) and resultant induction of EMT genes, which are critical determinants of tumor progression. These results suggest a direct viral role in the development of hepatocellular carcinoma.


**AIM:** To investigate factors that accurately predict hepatocellular carcinoma (HCC) development after antiviral therapy in chronic hepatitis C (CHC) patients. **METHODS:** CHC patients who received pegylated interferon and ribavirin were enrolled in this cohort study that
investigated the ability of alpha-fetoprotein (AFP) to predict HCC development after interferon (IFN) therapy. **RESULTS:** Of 1255 patients enrolled, 665 developed sustained virological response (SVR) during mean follow-up period of 5.4 years. HCC was occurred in 89 patients, and 20 SVR patients were included. Proportional hazard models showed that HCC occurred in SVR patients showing AFP ≥ 5 ng/mL before therapy and in non-SVR patients showing AFP ≥ 5 ng/mL before and 1 year after therapy besides older age, and low platelet counts. SVR patients showing AFP ≥ 5 ng/mL before therapy and no decrease in AFP to < 5 ng/mL 1 year after therapy had significantly higher HCC incidence than non-SVR patients showing AFP ≥ 5 ng/mL before therapy and decreased AFP (P = 0.043). AFP ≥ 5 ng/mL before therapy was significantly associated with low platelet counts and high values of alanine aminotransferase (ALT) in stepwise logistic regression analysis. After age, gender, platelet count, and ALT was matched by propensity score, significantly lower HCC incidence was shown in SVR patients showing AFP < 5 ng/mL before therapy than in those showing AFP ≥ 5 ng/mL. **CONCLUSION:** The criteria of AFP < 5 ng/mL before and 1 year after IFN therapy is a beneficial predictor for HCC development in CHC patients.

What are good tools and venues to increase patient literacy and the engagement of patients in the prevention of further disease progression when vital information is often not readily accessible and may not be in terms patients understand?


**BACKGROUND AND AIMS:** Hepatocellular carcinoma (HCC) has limited treatment options when diagnosed at advanced stages; therefore early detection is critical to reduce mortality. There is disagreement about the value of α-Fetoprotein (AFP) in HCC surveillance. We aim to improve the sensitivity of AFP in HCC surveillance using an algorithm that incorporates screening history to define patient-specific thresholds for positive screen. **METHODS:** De-identified data from the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial, which enrolled 1050 patients with hepatitis C and advanced fibrosis or cirrhosis prospectively followed every 3-6 months, were analyzed. AFP was assayed at each visit and ultrasonography was performed every 6-12 months. A panel adjudicated the diagnosis of HCC. A parametric empirical Bayes (PEB) screening algorithm, which incorporates screening history, was compared to a single threshold (ST) approach for interpreting AFP results. **RESULTS:** During a median follow-up of 80 months, 88 patients (48/427 with cirrhosis and 40/621 with advanced fibrosis) were diagnosed with HCC. PEB improved the sensitivity of AFP for detecting all HCC from 60.4% to 77.1% (p-value<0.0005) in patients with cirrhosis and from 72.5% to 87.5% (p-value=0.0015) in patients with advanced fibrosis, when the false positive rate among all screenings was set at 10%. PEB algorithm detected HCC 1.7-1.9 years earlier in the cirrhosis group and 1.4-1.7 years earlier in the advanced fibrosis group, compared to ST approach. **CONCLUSIONS:** PEB increases the sensitivity of AFP testing and detects HCC earlier among hepatitis C patients with advanced fibrosis or cirrhosis. These data should prompt a re-evaluation of how AFP is used in combination with ultrasound in HCC surveillance.

GOALS: To evaluate hepatocellular carcinoma (HCC) surveillance rates among commercially insured patients, and evaluate factors associated with compliance with surveillance recommendations. BACKGROUND: Most HCC occurs in patients with cirrhosis. American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines each recommend biannual HCC surveillance for cirrhotic patients to diagnose HCC at an early, curable stage. However, compliance with these guidelines in commercially insured patients is unknown. STUDY: We used the Truven Health Analytics databases from 2006 to 2010, using January 1, 2006 as the anchor date for evaluating outcomes. The primary outcome was continuous surveillance measure, defined as the proportion of time "up-to-date" with surveillance (PTUDS), with the 6-month interval immediately following each ultrasound categorized as "up-to-date." RESULTS: During a median follow-up of 22.9 (interquartile range, 16.3 to 33.9) months among 8916 cirrhotic patients, the mean PTUDS was 0.34 (SD, 0.29), and the median was 0.31 (interquartile range, 0.03 to 0.52). These values increased only modestly with inclusion of serum alpha-fetoprotein testing, contrast-enhanced abdominal computed tomographic scans or magnetic resonance imagings, and/or extension of up-to-date time to 12 months. Being diagnosed by a nongastroenterology provider and increasing age were significantly associated with decreased HCC surveillance (P<0.05), whereas a history of a hepatic decompensation event, presence of any component of the metabolic syndrome, and diagnosis of hepatitis B or hepatitis C were significantly associated with increased surveillance (P<0.05). However, even among patients with the most favorable characteristics, surveillance rates remained low. CONCLUSIONS: HCC surveillance rates in commercially insured at-risk patients remain poor despite formalized guidelines, highlighting the need to develop interventions to improve surveillance rates.

Inflammatory and oncogenic roles of a tumor stem cell marker doublecortin-like kinase (DCLK1) in virus-induced chronic liver diseases. Ali N1,2,3, Chandrakesan P1, Nguyen CB1, et al. Oncotarget. 2015 Aug 21;6(24):20327-44. Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide. We previously showed that a tumor/cancer stem cell (CSC) marker, doublecortin-like kinase (DCLK1) positively regulates hepatitis C virus (HCV) replication, and promotes tumor growth in colon and pancreas. Here, we employed transcriptome analysis, RNA interference, tumor xenografts, patient's liver tissues and hepatospheroids to investigate DCLK1-regulated inflammation and tumorigenesis in the liver. Our studies unveiled novel DCLK1-controlled feed-forward signaling cascades involving calprotectin subunit S100A9 and NFκB activation as a driver of inflammation. Validation of transcriptome data suggests that DCLK1 coreexpression with HCV induces BRM/SMARCA2 of SW1/SNF1 chromatin remodeling complexes. Frequently observed lymphoid aggregates including hepatic epithelial and stromal cells of intermodular septa extensively express DCLK1 and S100A9. The DCLK1 overexpression also correlates with increased levels of S100A9, c-Myc, and BRM levels in HCV/HBV-positive patients with cirrhosis and HCC. DCLK1 silencing inhibits S100A9 expression and hepatoma cell migration. Normal human hepatocytes (NHH)-derived spheroids exhibit CSC properties. These results provide new insights into the molecular mechanism of the hepatitis B/C-virus induced liver inflammation and tumorigenesis via DCLK1-controlled networks. Thus, DCLK1 appears to be a novel therapeutic target for the treatment of inflammatory diseases and HCC.
What types of liver health information would you integrate into the general population (and where) about the serious issue of NAFLD/fatty liver disease? What about the increase in diabetes and other metabolic issues related to an ‘unwell’ society?


**BACKGROUND:**
The impact of diabetes for hepatocellular carcinoma (HCC) development in chronic hepatitis C (CHC) patients remains controversial. **AIM:** To investigate the risk of HCC in CHC patients who develop new onset diabetes. **METHODS:** We conducted a nation-wide cohort study by using Taiwanese National Health Insurance Research Database, which comprised of data from >99% of entire population. Among randomly sampled one million enrollees, 6251 adult CHC patients were identified from 1997 to 2009. Diabetes was defined as new onset in the patient who was given the diagnosis in the years 1999-2009 but not in 1997-1998. The cohorts of CHC with new onset diabetes (n = 1100) and 1:1 ratio age-, gender-, and inception point (onset date of diabetes) matched nondiabetes (n = 1087) were followed up from the inception point until the development of HCC, withdrawal from insurance, or December 2009. **RESULTS:** After adjustment for competing mortality, patients with new onset diabetes had a significantly higher cumulative incidence of HCC (Relative Risk = 1.544, 95% CI = 1.000-2.387, modified log-rank test, P = 0.047) as compared to those without. After adjustment for age, gender, cirrhosis, hyperlipidaemia, CHC treatment, diabetes treatment, comorbidity index, obesity and statins therapy by Cox proportional hazard model, diabetes was still an independent predictor for HCC (hazard ratio (HR) = 1.906, 95% CI = 1.102-3.295, P = 0.021). The risk for HCC was increased in those who were 40-59 years old, independent of other variables (HR = 3.086, 95% CI = 1.045-9.112, P = 0.041), and after adjustment for competing mortality (modified log-rank test, P = 0.009). **CONCLUSION:** Chronic hepatitis C patients who develop diabetes are at an increased risk of hepatocellular carcinoma over time.