The availability of Fibroscan screening, while limited in most areas across the country, is becoming more available, particularly for research purposes. This noninvasive tool is a viable option for alternatives to invasive biopsies and procedures. Given the lack of availability of the Fibroscan machine, particularly at the community level, what are way to maintain engagement with high risk patients to ensure ongoing, lifelong imaging to prevent the development of complications related to cirrhosis?


**BACKGROUND/AIM:** Transient elastography is a relatively new, noninvasive method of measuring liver stiffness. This study aimed to evaluate the diagnostic accuracy of transient elastography and other noninvasive methods for the diagnosis of esophageal varices (EV) in patients with cirrhosis. **METHODS:** This cross-sectional study graded EV according to size in 145 consecutive patients with cirrhosis who underwent endoscopy, Fibroscan, and other noninvasive diagnostic methods. The accuracy of these diagnostic methods in diagnosing EV was evaluated on the basis of area under receiver operating characteristic (AUROC) curves. **RESULTS:** Elastography was successful in 123 patients. Of these, 54.5% had hepatitis C and 10.6% had hepatitis B. EV were absent in 39.8%, small EV was present in 24.4%, and large EV was present in 35.8% of patients. Fibroscan, aspartate aminotransferase-to-platelet ratio index, and international normalized ratio showed low accuracy in diagnosing EV in non-viral-related cirrhosis patients (AUROCs 0.66, 0.68, and 0.67, respectively). Fibroscan and aspartate aminotransferase-to-platelet ratio index were more accurate in measuring EV with a viral etiology (AUROCs 0.704 and 0.703, respectively). A cutoff value of 16.9 kPa was 83.8% sensitive in diagnosing EV in non-viral-cirrhotic patients, whereas a cutoff value of 19.9 kPa was 83.4% sensitive in diagnosing EV in patients with viral hepatitis. Fibroscan was moderately accurate in diagnosing grade I EV and less accurate in diagnosing grades II and III EV in all cirrhotic patients, irrespective of the underlying etiology. **CONCLUSION:** Fibroscan might be useful in predicting the presence of EV in patients with cirrhosis with a viral etiology. However, endoscopy remains the gold standard for EV screening.
IMPORTANCE: Novel treatments for hepatitis C virus (HCV) infection are highly efficacious but costly. Thus, many insurers cover therapy only in advanced fibrosis stages. The added health benefits and costs of early treatment are unknown. OBJECTIVE: To assess the cost-effectiveness of (1) treating all patients with HCV vs only those with advanced fibrosis and (2) treating each stage of fibrosis. DESIGN, SETTING, AND PARTICIPANTS: This study used a decision-analytic model for the treatment of HCV genotype 1. The model used a lifetime horizon and societal perspective and was representative of all US patients with HCV genotype 1 who had not received previous treatment. Comparisons in the model included antiviral treatment of all fibrosis stages (METAVIR [Meta-analysis of Histological Data in Virial Hepatitis] stages F0 [no fibrosis] to F4 [cirrhosis]) vs treatment of stages F3 (numerous septa without cirrhosis) and F4 only and by specific fibrosis stage. Data were collected from March 1 to September 1, 2014, and analyzed from September 1, 2014, to June 30, 2015. INTERVENTIONS: Six HCV therapy options (particularly combined sofosbuvir and ledipasvir therapy) or no treatment. MAIN OUTCOMES AND MEASURES: Cost and health outcomes were measured using total medical costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs), calculated as the difference in costs between strategies divided by the difference in QALYs. RESULTS: We simulated 1000 individuals, but present the results normalized to a single HCV-infected person. In the base-case analysis, among patients receiving 8 or 12 weeks of sofosbuvir-ledipasvir treatment, treating all fibrosis stages compared with treating stages F3 and F4 adds 0.73 QALYs and $28 899, for an ICER of $39 475 per QALY gained. Treating at stage F2 (portal fibrosis with rare septa) costs $19 833 per QALY gained vs waiting until stage F3; treating at stage F1 (portal fibrosis without septa), $81 165 per QALY gained compared with waiting until stage F2; and treating at stage F0, $187 065 per QALY gained compared with waiting until stage F1. Results for other regimens show a similar pattern. At base-case drug prices, treating 50% of all eligible US patients with HCV genotype 1 would cost $53 billion. In sensitivity analyses, the ICER for treating all stages vs treating stages F3 and F4 was most sensitive to cohort age, drug costs, utility values in stages F1 and F2, and percentage of patients eligible for 8-week therapy. Except for patients aged 70 years, the ICER remains less than $100 000 per QALY gained. A 46% reduction in cost of sofosbuvir-ledipasvir therapy decreases the ICER for treating at all fibrosis stages by 48%. CONCLUSIONS AND RELEVANCE: In this simulated model, treating HCV infection at early stages of fibrosis appeared to improve health outcomes and to be cost-effective but incurred substantial aggregate costs. The findings may have implications for health care coverage policies and clinical decision making.
the NS5A inhibitor velpatasvir in a once-daily, fixed-dose combination tablet or matching placebo for 12 weeks. Because of the low prevalence of genotype 5 in the study regions, patients with genotype 5 did not undergo randomization but were assigned to the sofosbuvir-velpatasvir group. The primary end point was a sustained virologic response at 12 weeks after the end of therapy. **RESULTS:** Of the 624 patients who received treatment with sofosbuvir-velpatasvir, 34% had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. A total of 8% of patients were black, 19% had cirrhosis, and 32% had been previously treated for HCV. The rate of sustained virologic response among patients receiving sofosbuvir-velpatasvir was 99% (95% confidence interval, 98 to >99). Two patients receiving sofosbuvir-velpatasvir, both with HCV genotype 1, had a virologic relapse. None of the 116 patients receiving placebo had a sustained virologic response. Serious adverse events were reported in 15 patients (2%) in the sofosbuvir-velpatasvir group and none in the placebo group. **CONCLUSIONS:** Once-daily sofosbuvir-velpatasvir for 12 weeks provided high rates of sustained virologic response among both previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5, or 6, including those with compensated cirrhosis.


**BACKGROUND:** As the population that is infected with the hepatitis C virus (HCV) ages, the number of patients with decompensated cirrhosis is expected to increase. **METHODS:** We conducted a phase 3, open-label study involving both previously treated and previously untreated patients infected with HCV genotypes 1 through 6 who had decompensated cirrhosis (classified as Child-Pugh-Turcotte class B). Patients were randomly assigned in a 1:1:1 ratio to receive the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir once daily for 12 weeks, sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or sofosbuvir-velpatasvir for 24 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy. **RESULTS:** Of the 267 patients who received treatment, 78% had HCV genotype 1, 4% genotype 2, 15% genotype 3, 3% genotype 4, and less than 1% genotype 6; no patients had genotype 5. Overall rates of sustained virologic response were 83% (95% confidence interval [CI], 74 to 90) among patients who received 12 weeks of sofosbuvir-velpatasvir, 94% (95% CI, 87 to 98) among those who received 12 weeks of sofosbuvir-velpatasvir plus ribavirin, and 86% (95% CI, 77 to 92) among those who received 24 weeks of sofosbuvir-velpatasvir. Post hoc analysis did not detect any significant differences in rates of sustained virologic response among the three study groups. Serious adverse events occurred in 19% of patients who received 12 weeks of sofosbuvir-velpatasvir, 16% of those who received 12 weeks of sofosbuvir-velpatasvir plus ribavirin, and 18% of those who received 24 weeks of sofosbuvir-velpatasvir. The most common adverse events were fatigue (29%), nausea (23%), and headache (22%) in all patients and anemia (31%) in the patients receiving ribavirin. **CONCLUSIONS:** Treatment with sofosbuvir-velpatasvir with or without ribavirin for 12 weeks and with sofosbuvir-velpatasvir for 24 weeks resulted in high rates of sustained virologic response in patients with HCV infection and decompensated cirrhosis.

**BACKGROUND**: There is an unmet need for interferon- and ribavirin-free treatment for chronic hepatitis C virus (HCV) infection in patients with comorbidities including cardiovascular disease (CVD). The aim of this study was to evaluate the rates of sustained virologic response (SVR) and adverse events in a cohort of patients with nosocomially-acquired HCV genotype 1b following 12-weeks of therapy with fixed-dose combination (FDC) ledipasvir/sofosbuvir (LDV/SOF).

**METHODS**: This is a prospective, single-center, open-label study of 5 non-cirrhotic patients with HCV genotype 1b and significant comorbid cardiovascular disease (CVD), conducted at the Massachusetts General Hospital. All patients were prescribed FDC tablet (ledipasvir 90mg /sofosbuvir 400mg) once daily for 12 weeks. Serial measurements of safety parameters, virology, host immune correlates, and adherence were performed. The primary outcome was the proportion of patients with SVR (plasma HCV RNA level <25 IU/mL), 12 weeks after treatment completion (SVR12).

**RESULTS**: All five patients (100%) achieved SVR12, with no episodes of on- or post-treatment relapse. The most commonly reported adverse events were gastrointestinal illness and upper respiratory viral-type illness. There were no serious adverse events or discontinuations of medication attributable to the study drug. Deep sequencing analysis revealed no baseline NS3, NS5A or NS5B resistance-associated variants (RAVs).

**CONCLUSIONS**: In this open-label, uncontrolled, pilot study enrolling patients with HCV genotype 1b and significant CVD, administration of a fixed-dose, oral combination of ledipasvir and sofosbuvir for 12 weeks was associated with high rates of SVR and minimal adverse events. Larger prospective studies that also include patients with cirrhosis and prior treatment non-responders are necessary.


**BACKGROUND & AIMS**: Statins decrease portal pressure in patients with cirrhosis and increase survival times of those who have bled from varices. However, statins can be hepatotoxic. It is important to determine whether long-term statin use will be beneficial or detrimental for patients with cirrhosis because physicians are reluctant to prescribe statins to patients with liver disease. We investigated effects of statins on decompensation and survival times in patients with compensated cirrhosis.

**METHODS**: We performed a retrospective cohort using the Veteran Affairs Clinical Case Registry, which contains nationwide data from veterans infected with the hepatitis C virus (HCV). We identified patients with compensated cirrhosis from January 1996 through December 2009. Statin use was according to filled prescriptions. Cirrhosis and decompensation were determined from ICD9 codes, using a validated algorithm.

**RESULTS**: Among 40,512 patients with HCV compensated cirrhosis (98% male, median age of 56 years), 2802 statin users were identified. We developed a propensity score model using variables associated with statin prescription, and new statin users were matched with up to 5 non-users; 685 statin users were matched with 2062 non-users. Discrimination of the propensity score model was 0.92. Statin users had lower risk of decompensation (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.39-0.77) and death (HR, 0.56; 95% CI, 0.46-0.69), compared with non-users. Findings persisted after adjustment for age, FIB-4 index score, serum level of albumin, model for end-stage liver disease and Child scores (HR for decompensation, 0.55; 95% CI, 0.39-0.78) and HR for death, 0.55; 95% CI, 0.45-0.68).

**CONCLUSIONS**: Based on data from the Veteran Affairs Clinical Case Registry, statin use among patients with HCV and
compensated cirrhosis is associated with over 40% lower risk of cirrhosis decompensation and death. Although statins cannot yet be widely recommended for these patients, their use should not be avoided.


**BACKGROUND:** Patients with chronic hepatitis C virus (HCV) infection and cirrhosis have higher risk for liver-related complications and have historically been more difficult to cure than patients without cirrhosis. We evaluated the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir, without ribavirin, for 12 weeks in patients with HCV GT1b infection and compensated cirrhosis. **METHODS:** Treatment-naïve and peginterferon/ribavirin treatment-experienced patients received 12 weeks of ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily). Key inclusion criteria were hemoglobin $\geq 10$ g/dL, albumin $\geq 2.8$ g/dL, platelet count $\geq 25$ x 109/L, creatinine clearance $\geq 30$ ml/min, and Child-Pugh score $\leq 6$. Efficacy was assessed by the percentage of patients achieving SVR (HCV RNA <25 IU/mL) 12 weeks post-treatment (SVR12). Efficacy and safety were assessed in all patients receiving study drug. **RESULTS:** Sixty patients with HCV GT1b infection and cirrhosis received treatment. The study population comprised 62% male, 55% treatment-experienced, 83% with IL28B non-CC genotype, 22% with platelet count <90 x 109/L, and 17% with albumin <3.5 g/dL. All 60 patients completed treatment, and SVR12 was achieved in 100% (95% CI, 94.0 - 100%) of patients. The most common adverse events were fatigue (22%), diarrhea (20%), and headache (18%). Only one patient (1.7%) experienced a serious adverse event. Laboratory abnormalities were infrequently observed and not clinically significant. **CONCLUSIONS:** The HCV regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks achieved 100% SVR12 and was well tolerated in HCV GT1b-infected patients with cirrhosis, suggesting that this 12-week ribavirin-free regimen is sufficient in this population.


**OBJECTIVES:** Triple therapy using peg-interferon, ribavirin and simeprevir (PEG-IFN/RBV/SMV) has reportedly resulted in high-sustained virological response (SVR) rates in patients with chronic hepatitis C (CHC), especially in naïve cases and relapers to prior PEG-IFN/RBV therapy. Here, we retrospectively analyzed the antiviral response associated with a triple regimen, in the context of early reduction of viral load during treatment. **METHODS:** Forty-six CHC patients with HCV genotype 1b were treated with PEG-IFN/RBV/SMV triple therapy: 20 were naïve cases, 12 were relapers and 14 were non-responders to prior PEG-IFN/RBV therapy. We evaluated rapid virological response (RVR), complete early virological response (EVR), viral clearance at the end of the treatment (EOT) and at 12 weeks after the EOT (SVR12). In addition, we quantified the serum HCV-RNA on the 1st day and the 7th day after initiating treatment. **RESULTS:** Multivariate analysis revealed that response to prior treatment was identified as an independent factor for achieving SVR12 after triple therapy (p = 0.0005).
The achievement of serum HCV-RNA <2 log10 IU/ml on day 7, RVR, EVR and EOT were associated with SVR12 (p = 0.0050, p = 0.0002, p = 0.0009 and p = 0.0002, respectively).

CONCLUSIONS: Rapid decline of HCV is a predictive factor for the achievement of SVR12, even in antiviral triple therapy with PEG-IFN/RBV/SMV. An extended treatment period should be applied for patients who show detectable serum HCV-RNA at week 4.


BACKGROUND & AIMS: The interferon-free regimen of simeprevir plus sofosbuvir was recommended by professional guidelines for certain patients with hepatitis C virus (HCV) genotype 1 infection based on the findings of a phase 2 trial. We aimed to evaluate the safety and efficacy of this regimen in clinical practice settings in North America. METHODS: We collected demographic, clinical, and virologic data, as well as reports of adverse outcomes, from sequential participants in HCV-TARGET—a prospective, observational cohort study of patients undergoing HCV treatment in routine clinical care settings. From January through October 2014, 836 patients with HCV genotype 1 infection began 12 weeks of treatment with simeprevir plus sofosbuvir (treatment duration of up to 16 weeks); 169 of these patients received ribavirin. Most patients were male (61%), Caucasian (76%), or black (13%); 59% had cirrhosis. Most had failed prior treatment with peginterferon and ribavirin without (46%) or with telaprevir or boceprevir (12%). The primary outcome was sustained virologic response (SVR), defined as level of HCV RNA below quantification at least 64 days after the end of treatment (beginning of week 12 after treatment—a 2 week window). Logistic regression models with inverse probability weights were constructed to adjust for baseline covariates and potential selection bias. RESULTS: The overall rate of SVR rate was 84% (675/802 patients, 95% CI: 81-87%). Model-adjusted estimates indicate patients with cirrhosis, prior decompensation, and previous protease inhibitor treatments were less likely to achieve an SVR. The addition of ribavirin had no detectable effects on SVR. The most common adverse events were fatigue, headache, nausea, rash, and insomnia. Serious adverse events and treatment discontinuation occurred in only 5% and 3% of participants, respectively. CONCLUSIONS: In a large, prospective observational cohort study, a 12 week regimen of simeprevir plus sofosbuvir was associated with high rates of SVR and infrequent treatment discontinuation.


BACKGROUND: Treatment of genotype 1 hepatitis C virus (HCV) infection with combination directly acting antivirals (DAA) for 8-24 weeks is associated with high rates of sustained virologic response (SVR). We previously demonstrated that adding a third DAA to ledipasvir and sofosbuvir (LDV/SOF) can result in high SVR rates in patients without cirrhosis. In this study, we investigated whether a similar regimen would yield equivalent rates of cure in patients with advanced liver fibrosis. METHODS: Fifty patients were enrolled at the Clinical Research Center of the National Institutes of Health and associated healthcare centers. Enrollment and follow-up data from April 2014 to June 2015 are reported here. Eligible participants were aged ≥18 years, had chronic HCV genotype 1 infection (serum HCV RNA ≥2000 IU/mL), and stage
3-4 liver fibrosis. HCV RNA was measured using a reverse-transcription polymerase chain reaction assay. **RESULTS:** Of patients treated with LDV, SOF, and the NS3/4A protease inhibitor GS-9451 for 6 weeks, 76% (38 of 50; 95% confidence interval, 60%-85%) had SVR achieved 12 weeks after the end of treatment. There was no statistically significant difference in treatment efficacy between treatment-naïve patients (72%, 18 of 25) and those with treatment experience (80%; 20 of 25) (P = .51). Overall, 11 patients (22%) experienced virologic relapse, and 1 (2%) was lost to follow-up at 4 weeks after treatment. No serious adverse events, discontinuations, or deaths were associated with this regimen. **CONCLUSIONS:** Adding a third DAA to LDV/SOF may result in a moderate SVR rate, lower than that observed in patients without cirrhosis. Significant liver fibrosis remains an impediment to achieving SVR with short-duration DAA therapy.


**OBJECTIVES:** The optimal treatment of hepatitis C virus (HCV) genotype 6 is unclear owing to its limited geographic distribution. Because of a high predictive value of rapid virological response (RVR) for sustained virological response (SVR), we conducted an open-label randomized controlled trial to compare 24- and 48-week peginterferon/ribavirin combination therapy for patients with HCV genotype 6 in Southern China who achieved an RVR.

**METHODS AND FINDINGS:** Treatment-naïve, non-cirrhotic patients with chronic hepatitis C genotype 6 were treated with pegylated interferon α-2a (180 μg/week) and ribavirin (800-1,200 mg, according to weight) for 4 weeks. Patients who achieved an RVR, which was defined as HCV RNA negativity at week 4 (<50 IU), were randomized to receive either an additional 20 or 44 weeks of treatment (24- and 48-week treatment groups, respectively). The primary outcome measure was SVR. From January 2011 to June 2014, 152 (152/210, 72.4%) patients with HCV genotype 6a and RVR were randomized 1:1 to the 24- or 48-week treatment group. The SVR rates in the 24- and 48-week groups in the intention-to-treat analysis were 90.8% (69/76) and 88.2% (67/76), respectively; those in the per-protocol analysis were 95.7% (67/70) and 97.0% (64/66), respectively. More patients in the 48-week group had anemia (46.1% vs. 28.9%, P = 0.03), but other adverse events were comparable between the groups. The limitation of the present study was that only patients from Southern China were enrolled which may inhibit the extensive application of the findings. **CONCLUSION:** Twenty-four weeks of peginterferon/ribavirin combination therapy was non-inferior to 48 weeks in patients with HCV genotype 6a in Southern China who achieved an RVR.


**BACKGROUND:** The optimal retreatment strategy for chronic hepatitis C virus (HCV) patients who fail directly-acting antiviral agent (DAA)-based treatment is unknown. In this study, we assessed the efficacy and safety of ledipasvir (LDV) and sofosbuvir (SOF) for 12 weeks in HCV genotype-1 (GT-1) patients who failed LDV/SOF-containing therapy. **METHODS:** In this single-center, open-label, phase 2a trial, 34 participants with HCV (GT-1) and early-stage liver
fibrosis who previously failed 4-6 weeks of LDV/SOF with GS-9669 and/or GS-9451 received LDV/SOF for 12 weeks. The primary endpoint was HCV viral load below the lower limit of quantification 12 weeks after completion of therapy (sustained virological response [SVR]12). Deep sequencing of the NS3, NS5A, and NS5B regions were performed at baseline, at initial relapse, prior to retreatment, and at second relapse with Illumina next-generation sequencing technology. RESULTS: Thirty-two of 34 enrolled participants completed therapy. Two patients withdrew after day 0. Participants were predominantly male and black, with median baseline HCV viral load of $1.3 \times 10^6$ IU/mL and Metavir fibrosis stage 1 and genotype-1a. Median time from relapse to retreatment was 22 weeks. Prior to retreatment, 29 patients (85%) had NS5A-resistant variants. The SVR12 rate was 91% (31/34; intention to treat, ITT) after retreatment. One patient relapsed. CONCLUSIONS: In patients who previously failed short-course combination DAA therapy, we demonstrate a high SVR rate in response to 12 weeks of LDV/SOF, even for patients with NS5A resistance-associated variants.


**INTRODUCTION:** Clinical trials have demonstrated the efficacy of all-oral direct-acting antiviral (DAA) regimens in the treatment of patients infected with hepatitis C virus (HCV). This study assessed real-world effectiveness of two recently approved regimens; paritaprevir/ritonavir/ombitasvir; dasabuvir (3D), and sofosbuvir/ledipasvir (SOF/LDV) in patients with HCV genotype 1. **METHODS:** A retrospective analysis of administrative claims data (IMS Health Patient-Centric Data Warehouse/Medivo database) from October 1, 2013 to August 14, 2015 was conducted. Patients ≥19 years of age with a HCV genotype 1 infection, a prescription fill for 3D or SOF/LDV, and ≥1 HCV viral load (VL) assessment from weeks 4-30 post-treatment were selected for analysis. Percentages of patients achieving sustained virologic response (SVR; defined as HCV RNA ≤43 IU/mL) were determined. Unadjusted SVR rates were compared between treatment groups using Fisher's exact tests. SVR rates were also assessed using multivariate regression with adjustment for age group, sex, and treatment history. Analyses were repeated for a subset of patients with VL assessment from 12 to 30 weeks post-treatment. **RESULTS:** A total of 1707 (44 3D and 1663 SOF/LDV) patients were included. The majority (60%) were male, 49% were aged 55-64 years, and 97% were treatment-naïve 1 year prior to index. The unadjusted relative risk (RR) for achieving SVR in patients treated with SOF/LDV compared with 3D was 0.98%, 95% confidence interval (CI): 0.93-1.02. After adjusting for the baseline covariates, the RR was 0.98%, 95% CI: 0.94-1.03. **CONCLUSIONS:** In this early view of real-world data, effectiveness of all-oral DAA regimens in HCV genotype 1 patients was concordant with results from registration trials. SVR rates were similar for the two regimens. Further studies are needed to confirm these results.


**BACKGROUND:** Effective, pangenotypic treatments for hepatitis C virus (HCV) infection are needed. **OBJECTIVE:** To assess the safety and efficacy of sofosbuvir with velpatasvir in patients infected with HCV genotypes 1 to 6. **DESIGN:** Randomized, phase 2, open-label study. (ClinicalTrials.gov: NCT01858766). **SETTING:** 48 U.S. sites. **PATIENTS:** 377 treatment-
naive noncirrhotic patients. In part A, patients infected with HCV genotypes 1 to 6 were randomly assigned to sofosbuvir, 400 mg, with velpatasvir, 25 or 100 mg, for 12 weeks. In part B, patients with genotype 1 or 2 HCV infection were randomly assigned to sofosbuvir, 400 mg, and velpatasvir, 25 or 100 mg, with or without ribavirin for 8 weeks. **MEASUREMENTS:** Sustained virologic response at 12 weeks (SVR12). **RESULTS:** In part A, SVR12 rates were 96% (26 of 27) with velpatasvir, 25 mg, and 100% (28 of 28) with velpatasvir, 100 mg, for genotype 1; 93% (25 of 27) in both groups for genotype 3; and 96% (22 of 23) with velpatasvir, 25 mg, and 95% (21 of 22) with velpatasvir, 100 mg, for genotypes 2, 4, 5, and 6. In part B, for genotype 1, SVR12 rates were 87% (26 of 30) with velpatasvir, 25 mg; 83% (25 of 30) with velpatasvir, 25 mg, plus ribavirin; 90% (26 of 29) with velpatasvir, 100 mg; and 81% (25 of 31) with velpatasvir, 100 mg, plus ribavirin. For genotype 2, SVR12 rates were 77% (20 of 26) with velpatasvir, 25 mg; 88% (22 of 25) with velpatasvir, 25 mg, plus ribavirin; 88% (23 of 26) with velpatasvir, 100 mg; and 88% (23 of 26) with velpatasvir, 100 mg, plus ribavirin. Adverse events included fatigue (21%), headache (20%), and nausea (12%). One patient committed suicide. **LIMITATION:** The study was Open-label, no inferential statistics were planned, and sample sizes were small. **CONCLUSION:** Twelve weeks of sofosbuvir, 400 mg, and velpatasvir, 100 mg, was well-tolerated and resulted in high SVR in patients infected with HCV genotypes 1 to 6.

Despite many societal misperceptions that patients with mental health or substance use diagnoses should not access HCV treatment because of their inability to adhere to HCV therapies, this research suggests that adherence rates, particularly with shorter treatment duration, are excellent in this population. How can this real-world data be leveraged when combating harsh treatment and medically unsupported restrictions?

**High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study.** Petersen T1, Townsend K2, Gordon LA3,4, et al. Hepatol Int. 2015 Nov 26. [Epub ahead of print]

**BACKGROUND:** As treatment for chronic hepatitis C (HCV) virus has evolved to all-oral, interferon-free directly acting antiviral (DAA) therapy, the impact of these improvements on patient adherence has not been described. **METHODS:** Medication adherence was measured in 60 HCV, genotype-1, treatment-naïve participants enrolled in a phase 2a clinical trial at the National Institutes of Health and community clinics. Participants received either ledipasvir/sofosbuvir (LDV/SOF) (90 mg/400 mg) (one pill) daily for 12 weeks, LDV/SOF + GS-9451 (80 mg/day) (two pills) daily for 6 weeks, or LDV/SOF + GS-9669 (500 mg twice daily; three pills, two in the morning, one in the evening) for 6 weeks. Adherence was measured using medication event monitoring system (MEMS) caps, pill counts and patient report. **RESULTS:** Overall adherence to DAAs was high. Adherence declined over the course of the 12-week treatment (p = 0.04). While controlled psychiatric disease or symptoms of depression did not influence adherence, recent drug use was a risk factor for non-adherence to 12-week (p = 0.01), but not 6-week regimens. Adherence as measured by MEMS was lower than by patient report. **CONCLUSIONS:** Adherence to short courses of DAA therapy with 1-3 pills a day was excellent in an urban population with multiple risk factors for non-adherence.

**Basic and Applied Science, Pre-Clinical Studies**

**Expression of Interferon Lambda 4 Is Associated with Reduced Proliferation and Increased Cell Death in Human Hepatic Cells.**
Interferon lambda 4 (IFN-λ4) is a novel type-III interferon that can be generated only in individuals carrying a ΔG frame-shift allele of an exonic genetic variant (rs368234815-ΔG/TT). The rs368234815-ΔG allele is strongly associated with decreased clearance of hepatitis C virus (HCV) infection. Here, we further explored the biological function of IFN-λ4 expressed in human hepatic cells—a hepatoma cell line HepG2 and fresh primary human hepatocytes (PHHs). We performed live confocal imaging, cell death and proliferation assays, mRNA expression profiling, protein detection, and antibody blocking assays using transient and inducible stable in vitro systems. Not only did we observe significant intracellular retention of IFN-λ4 but also detected secreted IFN-λ4 in the culture media of expressing cells. Secreted IFN-λ4 induced strong activation of the interferon-stimulated genes (ISGs) in IFN-λ4-expressing and surrounding cells in transwell assays. Specifically, in PHHs, secreted IFN-λ4 induced expression of the CXCL10 transcript and a corresponding pro-inflammatory chemokine, IP-10. In IFN-λ4-expressing HepG2 cells, we also observed decreased proliferation and increased cell death. All IFN-λ4-induced phenotypes—activation of ISGs, decreased proliferation, and increased cell death—could be inhibited by an anti-IFN-λ4-specific antibody. Our study offers new insights into biology of IFN-λ4 and its possible role in HCV clearance.

Construction of bacterial ghosts for transfer and expression of a chimeric hepatitis C virus gene in macrophages. Miri MR1, Behzad-Behbahani A2, Fardaei M3, et al. J Microbiol Methods. 2015 Dec;119:228-32. doi: 10.1016/j.mimet.2015.11.009. Epub 2015 Nov 11. The bacterial ghost (BG) production is a field of biotechnology for applications in vaccine and drug delivery. We assessed the capacity of BG for delivery of a recombinant gene encoded for both cell mediated and antibody dependent epitopes of hepatitis C virus (HCV) into murine macrophages. Escherichia coli (E. coli) cells were transformed with the lysis plasmid (pHH43). To produce chimeric gene, NS3 (non-structural protein 3) and core regions of HCV genome were fused together by splicing by overlap extension (SOEing) PCR and were cloned into plasmid pEGFP-C1. Bacterial ghosts were loaded with recombinant pEGFP-C1 and then were transferred to murine macrophages (RAW 264.7). To investigate plasmid transfection and chimeric mRNA transcription, fluorescent microscopy and RT-PCR were used. In vitro studies indicated that bacterial ghosts loaded with pEGFP-C1 plasmid were efficiently taken up by murine macrophages and indicated a high transfection rate (62%), as shown by fluorescent microscopy. RT-PCR from extracted intracellular mRNAs for chimeric Core-NS3 gene showed a specific 607bp fragment of the gene. The sequence analysis of purified PCR products demonstrated the expected unique mRNA sequence. We constructed a chimeric HCV gene containing both cell mediated and antibody dependent epitopes with a significant expression in murine macrophages delivered by bacterial ghost.

What do you see as potential implications of naturally occurring mutations in patients whose ideal treatment is 12 weeks, but insurance only approves 8 weeks of treatment, thereby putting them at risk for non-responsive treatment, potential resistance, and potential lack of insurance coverage for future therapy?

BACKGROUND: The detection of baseline resistance mutations to new direct-acting antivirals (DAAs) in HCV chronically infected treatment-naïve patients could be important for their management and outcome prevision. In this study, we investigated the presence of mutations, which have been previously reported to be associated with resistance to DAAs in HCV polymerase (NS5B) and HCV protease (NS3) regions, in sera of treatment-naïve patients.

FINDINGS: HCV RNA from 152 naïve patients (84 % Italian and 16 % immigrants from various countries) infected with different HCV genotypes (21, 1a; 21, 1b; 2, 2a; 60, 2c; 22, 3a; 25, 4d and 1, 4k) was evaluated for sequence analysis. Amplification and sequencing of fragments in the NS5B (nt 8256-8640) and NS3 (nt 3420-3960) regions of HCV genome were carried out for 152 and 28 patients, respectively. The polymorphism C316N/H in NS5B region, associated with resistance to sofosbuvir, was detected in 9 of the 21 (43 %) analysed sequences from genotype 1b-infected patients. Naturally occurring mutations V36L, and M175L in the NS3 protease region were observed in 100 % of patients infected with subtype 2c and 4.

CONCLUSION: A relevant proportion of treatment naïve genotype 1b infected patients evaluated in this study harboured N316 polymorphism and might poorly respond to sofosbuvir treatment. As sofosbuvir has been approved for treatment of HCV chronic infection in USA and Europe including Italy, pre-treatment testing for N316 polymorphism on genotype 1b naïve patients should be considered for this drug.

HIV/HCV COINFECTION


OBJECTIVE: To assess the impact of illicit drug use on health-related quality of life (health utility) among opioid-dependent HIV-infected patients. DESIGN: Secondary analyses of data from the Buprenorphine-HIV Evaluation and Support cohort of HIV-infected patients with opioid dependence in 9 US HIV clinics between 2004 and 2009. Health status [short form-12 (SF-12)], combination antiretroviral treatment (ART) status, CD4 cell count, hepatitis C virus antibody status, current drug use, and demographics were assessed at the initial visit and quarterly follow-up visits until 1 year. The SF-6D health utility scores were derived from the SF-12. Multivariate mixed-effects regression models were used to assess the impact of illicit drug use on health utility controlling for demographic, clinical, and social characteristics. RESULTS: Health utility was assessed among 307 participants, 67% male, with a median age of 46 years at 1089 quarterly assessments. In multivariate analyses, illicit opioid use, nonopioid illicit drug use, not being on ART, and being on ART with poor adherence were associated with lower health utility. The observed decrement in health utility associated with illicit opioid use was larger for those on ART with good adherence (beta = -0.067; P < 0.01) or poor adherence (-0.049; P < 0.01) than for those not on ART. CONCLUSIONS: Illicit opioid and nonopioid drug use are negatively associated with health utility in patients with HIV; however, the relative effect of illicit opioid use is smaller than that of not being on ART. Postponing ART until initiation of opioid substitution therapy or abstinence may have limited benefits from the perspective of maximizing health utility.
The need for increased screening is vital and can be used in both laboratory and point-of-care settings. Besides test kits, what additional resources and ‘peoplepower’ would be needed for an effective integration of a rapid point-of-care test in an emergency department, an addiction treatment facility, an FQHC, or any other system?

In this randomized, controlled trial among 957 English- or Spanish-speaking drug misusing adult emergency department (ED) patients, we determined if a tailored brief intervention (BI) increased uptake of rapid HIV/HCV screening, and identified factors associated with greater screening uptake. Rapid HIV/HCV screening uptake was greater in the control than the BI arm (45 vs. 38 %; p < 0.04). Screening uptake depended on elapsed study time and which research staff member offered testing. In the control arm, uptake was lowest for those spending <30 or ≥90 min in the study. In the BI arm, screening uptake generally increased over time. Tailored BI content specifically addressing participant HIV/HCV knowledge, HIV/HCV risk behaviors, or need for HIV/HCV screening was not associated with greater screening uptake. These study findings suggested factors that should be considered when designing future ED-based screening initiatives, such as elapsed study time, who offers testing, and the content of interventions.

OBJECTIVES: INSIGHT (ClinicalTrials.gov NCT01513941) evaluated the efficacy, safety and pharmacokinetics of telaprevir-based therapy and specific antiretroviral agents in hepatitis C virus genotype 1 (HCV-1)/HIV-1-coinfected patients.

PATIENTS AND METHODS: Open-label, Phase IIIb, multicentre study of telaprevir with pegylated-IFN (Peg-IFN) α2a and ribavirin in treatment-naive or -experienced HCV-1/HIV-1-coinfected patients on stable HIV HAART comprising efavirenz, atazanavir/ritonavir, darunavir/ritonavir, raltegravir, etravirine or rilpivirine with two nucleos(t)ide analogues. Patients received 750 mg telaprevir (1125 mg, if on efavirenz) every 8 h plus 180 μg/week Peg-IFNα2a and 800 mg/day ribavirin for 12 weeks, followed by Peg-IFNα2a and ribavirin alone for 12 weeks (HCV treatment naive and relapers without cirrhosis, with extended rapid virological response) or 36 weeks (all others).

RESULTS: Overall, 162 patients (median age of 46 years, 78% male, 92% Caucasian and mean CD4 count of 687 cells/mm3) were treated; 13% had cirrhosis. One-hundred-and-thirty-two patients (81%) completed telaprevir; 14 (9%) discontinued due to an adverse event (AE). Sustained virological response (SVR) 12 rates (<25 IU/mL HCV RNA 12 weeks after the last planned treatment dose) in treatment-naive patients, relapers and non-responders were 64% (41 of 64), 62% (18 of 29) and 49% (34 of 69), respectively. SVR12 rates ranged from 51% (33 of 65) (patients receiving efavirenz) to 77% (13 of 17) (patients receiving raltegravir). Most frequently reported AEs during telaprevir treatment were pruritus (43%) and rash (34%) special search categories. Anaemia special search category occurred in 15% of patients; 6% of patients reported a serious AE. CONCLUSIONS: In treatment-naive/-experienced HCV-1/HIV-1 patients there were significantly higher SVR rates with telaprevir-based therapy compared with pre-specified historical controls, and safety comparable to that in HCV-monoinfected patients.

**OBJECTIVE:** Co-infection with hepatitis C (HCV) is a major cause of morbidity and mortality among individuals with human immunodeficiency virus (HIV). Our objective was to assess the prognostic performance of non-invasive measures of liver fibrosis in predicting all cause mortality in women with HIV/HCV coinfection. **DESIGN:** We studied HCV/HIV coinfected women enrolled in the prospective, multicenter Women's Interagency HIV Study. APRI and FIB-4 were used to identify women without fibrosis at all visits and women who progressed to severe fibrosis. **METHODS:** Enhanced Liver Fibrosis (ELF), which utilizes direct measures of fibrosis, Hyaluronic Acid, Procollagen III aminoterminal peptide and Tissue Inhibitor of Matrix metalloproteinase was performed. **RESULTS:** Included were 381 women with 2296 ELF measurements, with mean follow up 8.3±3.3y. There were 134 deaths (60% with severe liver fibrosis). Receiver operator characteristic curves at fixed time windows prior to death or at end of follow-up showed that ELF was best at predicting mortality when tested within a year of death (Area under the curve for ELF 0.85 vs. APRI 0.69, p<0.0001 and vs FIB-4 0.75, p=0.0036); and 1-3 years prior (ELF 0.71 vs. APRI 0.61, p=0.005 and vs FIB-4 0.65, p=0.06). Use of all three measures did not improve on ELF alone. In multivariate logistic regression models controlling for CD4 count, HIV viral load, antiretroviral use and age, ELF continued to perform better than APRI and FIB-4. **CONCLUSIONS:** ELF predicted all cause mortality and was superior to APRI and FIB-4 in HIV/HCV co-infected women.


Toll-like receptor 8 (TLR8) polymorphisms have been related to hepatitis C virus (HCV) infection. The aim was to estimate the association of TLR8 polymorphisms with HCV-related outcomes in HIV/HCV coinfected patients. We performed a cross-sectional study of 220 patients who underwent a liver biopsy. TLR8 polymorphisms were genotyped using GoldenGate® assay. The outcome variables were non-fibrosis (F0), mild-inflammation (A0/A1), and non-steatosis [fatty hepatocytes (FH) <10%]. Logistic regression analysis was used to compare the outcome variables according to TLR8 polymorphisms. Four polymorphisms were analyzed (rs1013151, rs5744069, rs17256081 and rs3764880). Female patients had higher frequency of TLR8 major alleles at rs17256081 and rs3764880/rs1013151. Female patients had higher frequency of TLR8 major alleles at rs17256081 and rs101315, and minor alleles at rs3764880 and rs5744069. Male patients had higher frequency of TLR8 minor alleles except for rs3764880, where major alleles were higher (p<0.01). Two TLR8 polymorphisms (rs1013151 and rs5744069) were significantly associated with non-fibrosis (F0) [adjusted odds ratio (aOR)=4.42 (95% of confidence interval (95%CI)=1.54; 12.68) (p=0.006) and aOR=4.76 (95%CI=1.69; 13.37) (p=0.003); respectively]. When data were stratified by gender, rs1013151 and rs5744069 polymorphisms remained significant for male patients [adjusted odds ratio (aOR)=4.49 (95%CI=1.08; 18.62) (p=0.039) and aOR=6.17 (95%CI=1.45; 26.20) (p=0.014); respectively]. When data were stratified by major HCV genotypes, patients infected with HCV genotype 1 (GT1) had significant values for both rs1013151 and rs5744069 polymorphisms [aOR=5.79 (95%CI=1.44; 23.32) (p=0.013) and aOR=8.01 (95%CI=2.16; 35.65) (p=0.005); respectively]. Finally, none of the TLR8 polymorphisms were significantly associated with mild-inflammation.
or non-steatosis. In conclusion, TLR8 polymorphisms seem to be related to non-progression of liver fibrosis in HIV/HCV coinfected patients, particularly in males and those patients infected with GT1.

What type of health literate materials and patient tools can be utilized or developed for co-infected patients experiencing drug-drug interactions? How can we promote medication adherence and patient engagement through the process of changing HIV regimens in preparation for HCV treatment?


**OBJECTIVES:** Development of direct acting antivirals (DAA) offers new benefits for patients with chronic hepatitis C. The combination of these drugs with antiretroviral treatment (cART) is a real challenge in HIV/HCV coinfected patients. The aim of this study was to describe potential drug-drug interactions between DAAs and antiretroviral drugs in a cohort of HIV/HCV coinfected patients. **METHODS:** Cross-sectional study of all HIV/HCV coinfected patients attending at least one visit in 2012 in the multicenter French Dat'AIDS cohort. A simulation of drug-drug interactions between antiretroviral treatment and DAAs available in 2015 was performed. **RESULTS:** Of 16,634 HIV-infected patients, 2,511 had detectable anti-HCV antibodies, of whom 1,196 had a detectable HCV-RNA and were not receiving HCV treatment at the time of analysis. 97.1% of these patients were receiving cART and 81.2% had a plasma HIV RNA <50 copies/mL. cART included combinations of nucleoside reverse transcriptase inhibitors with a boosted protease inhibitor in 43.6%, a non-nucleoside reverse transcriptase inhibitor in 17.3%, an integrase inhibitor in 15.4% and various combinations or antiretroviral drugs in 23.7% of patients. A previous treatment against HCV had been administered in 64.4% of patients. Contraindicated associations/potential interactions were expected between cART and respectively sofosbuvir (0.2%/0%), sofosbuvir/ledipasvir (0.2%/67.6%), daclatasvir (0%/49.4%), ombitasvir/boosted paritaprevir (with or without dasabuvir) (34.4%/52.2%) and simeprevir (78.8%/0%). **CONCLUSIONS:** Significant potential drug-drug interactions are expected between cART and the currently available DAAs in the majority of HIV/HCV coinfected patients. Sofosbuvir/ledipasvir and sofosbuvir/daclatasvir with or without ribavirin appeared the most suitable combinations in our population. A close collaboration between hepatologists and HIV/AIDS specialists appears necessary for the management of HCV treatment concomitantly to cART.

Imagine that the nurses involved in this study received ‘pre-counseling’ sessions to discuss their comfort, or discomfort, with the topics relevant in an HIV and HCV testing session. Within that ‘pre-counseling’ session they practiced ways to ask intimate and seemingly invasive questions regarding HIV/HCV risk and developed their own familiarity and language with the topic. How do you imagine the results would have changed in this study had the nurses engaged in a ‘pre-counseling’ session?

Nontargeted human immunodeficiency virus (HIV) screening and targeted hepatitis C virus (HCV) screening for selected high-risk patients (those born between 1945 and 1965 and those who report injection drug use) was integrated into our ED triage process and carried out by nurses. Determining whether emergency nurses accurately perceive what patients experience is important to know because staff misperceptions may pose a barrier to program adherence and sustainability. **METHODS:** We performed a cross-sectional survey study of emergency nurses and patients to assess the accuracy of emergency nurses' perception of patient experience with the HIV/HCV screening program. Respondents evaluated their level of agreement using a 5-item Likert scale for 9 statements across 4 domains related to the patient experience with the screening process (satisfaction, sense of autonomy, sense of privacy, and comfort level). **RESULTS:** Surveys were completed by 65 of the 153 eligible emergency nurses (42%). Of the 1040 patients approached, 610 (59%) were eligible, and 491 of the 610 eligible patients (80%) completed surveys. Across all domains, statistically significant differences were found between emergency nurse perception and patient report, P < .001. Emergency nurses perceived patients to be less satisfied with the screening program, more uncomfortable with being asked screening questions, more concerned about privacy issues, and less likely to feel that the decision to decline screening was autonomous than were patients. **DISCUSSION:** Emergency nurses not only frequently misperceive how patients experience ED-based HIV/HCV screening, but these misperceptions are skewed toward the negative, representing a type of staff bias. Further research is recommended to determine if such misperceptions adversely affect implementation of screening.

**Higher Activation in CD4+ T Cells But Similar Viral Control Among HIV/Hepatitis C Virus-Coinfected Patients on a Simplification Monotherapy.**


The aim of this study was to assess whether hepatitis C virus (HCV) coinfection would affect the clinical and immunological outcome of HIV-infected patients following a simplification strategy. A prospective cohort of HIV-infected patients starting a ritonavir boosted darunavir monotherapy (mtDRV/rtv) was followed for 24 months. HCV infection was evaluated by HCV viremia and hepatic fibrosis. Immune activation was studied as HLA-DR CD38 coexpression on CD4+ and CD8+ T cells and also the quantification of plasma sCD14 levels. Microbial translocation was studied by the plasma levels of 16S rDNA and lipopolysaccharide (LPS). A total of 150 HIV-infected patients were enrolled in this study, including 46 individuals also infected with HCV (30.6%). HIV/HCV coinfection did not decrease mtDRV/rtv efficacy, since similar rates of HIV-1 intermittent viremia (HCV: 26.6% vs. no-HCV: 34.7%) and episodes of virological failure (HCV: 22.2% vs. no-HCV: 11.2%, p-value = 0.381) were found. No major differences were found between both groups at baseline, although higher HLA-DR+CD38+CD4+ T cell counts were found in the coinfected group (HCV: 6.65% vs. no-HCV: 4.55%, p-value = 0.032); this difference was maintained in the 24 months of follow-up. After the 24-month follow-up, both groups, HIV-monoinfected patients and HIV/HCV-coinfected patients, presented similar immune activation and microbial translocation profiles. In conclusion, the use of a simplified mtDRV/rtv strategy compromises neither HIV nor HCV viremic control in coinfected patients, although a higher immune activation of CD4+ T cells was found.

HIV/hepatitis C virus (HCV) patients have a 3-fold increased fracture incidence compared to uninfected patients. The impact of HCV therapy on bone health is unclear. We evaluated bone turnover markers (BTM) in well-controlled (HIV RNA <50 copies/ml) HIV/HCV-coinfected patients who received pegylated interferon-α and ribavirin (PEG-IFN/RBV) in ACTG trial A5178. Early virologic responders (EVR: ≥2 log HCV RNA drop at week 12) continued PEG-IFN/RBV and non-EVRs were randomized to continuation of PEG-IFN alone or observation. We assessed changes in C-terminal telopeptide of type 1 collagen (CTX; bone resorption marker) and procollagen type I intact N-terminal propeptide (P1NP; bone formation marker), and whether BTM changes were associated with EVR, complete early virologic response (cEVR: HCV RNA <600 IU/ml at week 12), or PEG-IFN treatment. A total of 192 subjects were included. After 12 weeks of PEG-IFN/RBV, CTX and P1NP decreased: -120 pg/ml and -8.48 μg/liter, respectively (both p < 0.0001). CTX declines were greater in cEVR (N = 91; vs. non-cEVR (N = 101; p = 0.003). From week 12 to 24, CTX declines were sustained among EVR patients who continued PEG-IFN/RBV (p = 0.027 vs. non-EVR) and among non-EVR patients who continued PEG-IFN alone (p = 0.022 vs. Observation). Median decreases of P1NP in EVR vs. non-EVR were similar at weeks 12 and 24. PEG-IFN-based therapy for chronic HCV markedly reduces bone turnover. It is unclear whether this is a direct IFN effect or a result of HCV viral clearance, or whether they will result in improved bone mineral density. Further studies with IFN-free regimens should explore these questions.


**BACKGROUND:** Co-infection with human immunodeficiency virus (HIV) and Hepatitis-C virus (HCV) poses a significant threat to personal and public health. Substance use among co-infected persons leads to increased morbidity and mortality. The purpose of this study is to examine the continued substance use of people living with HIV-HCV co-infection and receiving antiretroviral therapy (ART). **METHODS:** Individuals living with HIV infection in Atlanta, GA and currently receiving ART (N = 678) completed audio-computer-assisted self-interviews for demographic, health, and behavior characteristics; unannounced pill counts to assess ART adherence over one month; finger-stick blood specimens collected for HCV antibody testing and urine specimens for drug use screening; and obtained HIV viral load and CD4 cell counts from their medical provider. We performed cross-sectional analyses for behavioral and biological markers of health, health behaviors, and substance use. **RESULTS:** Among participants, 131 (19%) were HIV-HCV co-infected; 53% were HIV-mono-infected, and 60% of HIV-HCV co-infected participants tested positive for use of at least one non-alcohol drug: tetrahydrocannabinol (THC) and cocaine were most prevalent. HIV-HCV co-infected individuals were older, with no other significant differences. Within the HIV-HCV co-infected participants, drug users (N = 87) did not differ from non-drug users (N = 53) in terms of ART adherence. However, drug users were significantly more likely to have uncontrolled HIV (17%) compared with those who did not test drug positive (4%). **CONCLUSIONS:** Substance use is prevalent in persons with HIV-HCV co-infection and may interfere with ART. Research with a larger and more representative sample is needed to replicate and confirm these results.

BACKGROUND AND AIM: Previous studies have demonstrated that coffee consumption may be inversely correlated with hepatic fibrosis and cirrhosis. However, the reported results have been inconsistent. To summarize previous evidences quantitatively, a meta-analysis was performed. METHODS: The Medline, Web of Science, and Embase databases (from inception to June 2015) were searched to identify relevant trials that evaluated the effects of coffee consumption on hepatic fibrosis or cirrhosis. Odds ratios (ORs) of advanced hepatic fibrosis or cirrhosis for low or moderate, high, and any coffee consumption versus no consumption were pooled. Two cups per day was used as the cut-off level between low or moderate and high consumption. RESULTS: Sixteen studies were included, involving 3034 coffee consumers and 132076 people who do not consume coffee. The pooled results of the meta-analysis indicated that coffee consumers were less likely to develop cirrhosis compared with those who do not consume coffee, with a summary OR of 0.61 (95%CI: 0.45-0.84). For low or moderate coffee consumption versus no consumption, the pooled OR of hepatic cirrhosis was 0.66 (95%CI: 0.47-0.92). High coffee consumption could also significantly reduce the risk for hepatic cirrhosis when compared with no coffee consumption (OR = 0.53, 95%CI: 0.42-0.68). The effect of coffee consumption on hepatic fibrosis was summarized as well. The pooled OR of advanced hepatic fibrosis for coffee consumption versus no consumption was 0.73 (95%CI: 0.58-0.92). The protective effect of coffee on hepatic fibrosis and cirrhosis was also identified in subgroup meta-analyses of patients with alcoholic liver disease and chronic hepatitis C virus (HCV) infection. CONCLUSION: Coffee consumption can significantly reduce the risk for hepatic fibrosis and cirrhosis.

Association of Baseline Sleep Quality With Trajectories of Depressive Symptoms in Patients Undergoing Interferon Treatment.

OBJECTIVE: Some patients with hepatitis C starting interferon-α (IFN-α) therapy experience depression, although many patients do not develop depressive symptoms. We have found that poor sleep is associated with increased depressive symptoms on average. It is unknown whether this association holds generally or is driven by a specific, distinct subgroup. This investigation first determined whether patterns of change in depressive symptoms form clinically meaningful, distinct subgroups and then tested the extent to which sleep disturbances are associated with a less favorable depression trajectory. METHOD: Group-based trajectory modeling was used on 124 patients with hepatitis C who started IFN-α therapy. The Pittsburgh Sleep Quality Index (PSQI) assessed pretreatment sleep, the Beck Depression Inventory minus the sleep question assessed depression over time, and the Structured Clinical Interview for DSM-IV provided categorical diagnoses. RESULTS: Three distinct subgroups were found, where each subgroup shared similar patterns of depressive symptoms over time. The groups were characterized as
"nondepressed," "slow increase," and "rapid increase." The nondepressed subgroup (44.4%) experienced low depressive symptoms with little change over time. In comparison, all rapid increasers (11.3%) were diagnosed as having a mood disorder by 12 weeks of treatment. The PSQI was strongly associated with group membership, where the odds of developing a rapid increase was elevated 39% for every unit-score increase in the PSQI compared with individuals who remained nondepressed (odds ratio = 1.39, 95% confidence interval = 1.07-1.80, adjusted for depression at baseline). CONCLUSIONS: Only a distinct subpopulation of people is notably vulnerable to a developing a rapid increase in depression symptoms during IFN-α therapy. This group may be identifiable by their markedly poor sleep before IFN-α therapy.

How can leverage the existing grassroots endeavors within the criminal justice communities to better activate prisoners to become liver health advocates?


BACKGROUND: The prevalence of hepatitis C virus (HCV) in U.S. prisoners is high; however, HCV testing and treatment are rare. Infected inmates released back into society contribute to the spread of HCV in the general population. Routine hepatitis screening of inmates followed by new therapies may reduce ongoing HCV transmission. OBJECTIVE: To evaluate the health and economic effect of HCV screening and treatment in prisons on the HCV epidemic in society. DESIGN: Agent-based microsimulation model of HCV transmission and progression of HCV disease. DATA SOURCES: Published literature. TARGET POPULATION: Population in U.S. prisons and general community. TIME HORIZON: 30 years. PERSPECTIVE: Societal. INTERVENTIONS: Risk-based and universal opt-out hepatitis C screening in prisons, followed by treatment in a portion of patients. OUTCOME MEASURES: Prevention of HCV transmission and associated disease in prisons and society, costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), and total prison budget. RESULTS OF BASE-CASE ANALYSIS: Implementing risk-based and opt-out screening could diagnose 41 900 to 122 700 new HCV cases in prisons in the next 30 years. Compared with no screening, these scenarios could prevent 5500 to 12 700 new HCV infections caused by releasees, wherein about 90% of averted infections would have occurred outside of prisons. HCV screening could also prevent 4200 to 11 700 liver-related deaths. The ICERs of screening scenarios were $19 600 to $29 200/QALY, and the respective first-year prison budget was $900 to $1150 million. Prisons would require an additional 12.4% of their current health care budget to implement such interventions. RESULTS OF SENSITIVITY ANALYSIS: Results were sensitive to the time horizon, and ICERs otherwise remained less than $50 000 per QALY. LIMITATION: Data on transmission network, reinfection rate, and opt-out HCV screening rate are lacking. CONCLUSIONS: Universal opt-out HCV screening in prisons is highly cost-effective and would reduce HCV transmission and HCV-associated diseases primarily in the outside community. Investing in U.S. prisons to manage hepatitis C is a strategic approach to address the current epidemic.

transmission and reinfection. Recent innovations have produced breakthrough therapies that are effective in more than 90 percent of patients. These treatments could dramatically reduce the virus's prevalence but are costly. To quantify the benefit of these treatments to society, including the value of reduced transmission, we estimated the effects of several hepatitis C treatment strategies on cost and population health. Treating patients at all disease stages could generate $610-$1,221 billion in additional quality-adjusted life-years, plus an additional $139 billion in saved medical expenditures over fifty years, and minimize the disease burden, but up-front treatment costs would exceed $150 billion. An intermediate scenario—treating 5 percent of the infected population annually, regardless of patients' disease stages—would also return substantial benefits and would be much more affordable under current financing schemes.


**BACKGROUND:** Many people who inject drugs (PWID) use syringes with detachable needles, which have high dead space (HDS). Contaminated HDS blood may substantially contribute to the transmission of HIV, hepatitis C (HCV), and other blood-borne viruses within this population. Newly designed low dead space (LDS) syringe-needle combinations seek to reduce blood-borne virus transmission among PWID. We evaluated the infectivity of HCV-contaminated residual volumes recovered from two LDS syringe-needle combinations.

**METHODS:** We tested two different design approaches to reducing the dead space. One added a piston to the plunger; the other reduced the dead space within the needle. The two approaches cannot be combined. Recovery of genotype-2a reporter HCV from LDS syringe-needle combinations was compared to recovery from insulin syringes with fixed needles and standard HDS syringe-needle combinations. Recovery of HCV from syringes was determined immediately following their contamination with HCV-spiked plasma, after storage at 22°C for up to 1 week, or after rinsing with water. **RESULTS:** Insulin syringes with fixed needles had the lowest proportion of HCV-positive syringes before and after storage. HCV recovery after immediate use ranged from 47%±4% HCV-positive 1 mL insulin syringes with 27-gauge ½ inch needles to 98%±1% HCV-positive LDS syringe-needle combinations yielded recoveries ranging from 65%±5% to 93%±3%. Recovery was lower in combinations containing LDS needles than LDS syringes. After 3 days of storage, as much as 6-fold differences in virus recovery was observed, with HCV recovery being lower in combinations containing LDS needles. Most combinations with detachable needles required multiple rinses to reduce HCV infectivity to undetectable levels whereas a single rinse of insulin syringes was sufficient. **CONCLUSIONS:** Our study, the first to assess the infectivity of HCV in residual volumes of LDS syringes and needles available to PWID, demonstrates that LDS syringe-needle combination still has the greater potential for HCV transmission than insulin syringes with fixed needles. Improved LDS designs may be able to further reduce HCV recovery, but based on the designed tested, LDS needles and syringes remain intermediate between fixed-needle syringes and HDS combinations in reducing exposure to HCV.

OBJECTIVES: In 2010 only 30.9%, of the Puy-de-Dome prison detainees were screened for human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). Our goal was then to promote these assessments, as well as to identify addictive behaviour using FAGERSTROM, Cannabis Abuse Screening Test and CAGE tests, diagnose fibrosis by means of Fibrometer or Fibroscan in hepatic virus carriers and heavy drinkers, and perform HBV vaccinations. 

SETTING: This prospective study of adult detainees in the prisons of Puy-de-Dome, France, took place from June 2012 to December 2013. 

RESULTS: Of the 702 incarcerated individuals, 396(56.4%) were screened and 357(50.9%) enrolled. HIV prevalence was 0.3%, HCV 4.7% and HBV 0.6%. While 234/294(79.6%) smokers and 115/145(79.3%) cannabis users were screened for dependence, excessive alcohol consumption was tested for in 91/179(50.8%) cases. Fibrosis was screened for in 75/80(93.7%) individuals selected with 16.0% presenting with moderate to severe fibrosis, 4/9(44.4%) HCV carriers and 8/65(12.3%) excessive alcohol consumers. HBV vaccination was given to 81/149(54.4%) individuals with no serological markers. A total of nine HIV tests were conducted at the 57 discharge consultations, involving 215 detainees being released, all of which were negative. 

CONCLUSION: The promotion of these evaluations proved beneficial, although viral screening could be achieved for only approaching half of the detainees, as could alcohol consumption assessment and HBV vaccination for those concerned. Fibrosis screening revealed lesions in HCV carriers yet also in heavy drinkers, who are typically less likely to be assessed. Consultations and HIV screening on release were found to be rarely possible.

What preemptive measures can we take to mitigate the inevitable onslaught of alcohol-related cirrhosis facing the United States? What key messages you would include today or what legislation, if any, might be effective in addressing the future burden?


BACKGROUND: Identifying changes in the epidemiology of liver disease is critical for establishing healthcare priorities and allocating resources to develop therapies. The projected contribution of different etiologies toward development of cirrhosis in the United States was estimated based on current publications on epidemiological data and advances in therapy. Given the heterogeneity of published reports and the different perceptions that are not always reconcilable, a critical overview rather than a formal meta-analysis of the existing data and projections for the next decade was performed. 

METHODS: Data from the World Health Organization Global Status Report on Alcohol and Health of 2014, Scientific Registry of Transplant Recipients from 1999 to 2012, National Institute on Alcohol Abuse and Alcoholism, and the Centers for Disease Control and Prevention were inquired to determine future changes in the epidemiology of liver disease. 

RESULTS: Alcohol consumption has increased over the past 60 years. In 2010, transplant-related costs for liver recipients were the highest for hepatitis C (~$124 million) followed by alcohol-related cirrhosis (~$86 million). We anticipate a significant reduction in incidence cirrhosis due to causes other than alcohol because of the availability of high efficiency antiviral agents for hepatitis C, universal and effective vaccination for hepatitis B, relative stabilization of the obesity trends in the United States, and novel, potentially effective therapies for nonalcoholic steatohepatitis. The proportion of alcohol-related liver disease is therefore likely to increase in both the population as a whole and the liver transplant wait list. 

CONCLUSIONS: Alcohol-related cirrhosis and alcohol-related liver disorders will be the major...
cause of liver disease in the coming decades. There is an urgent need to allocate resources aimed toward understanding the pathogenesis of the disease and its complications so that effective therapies can be developed.


**BACKGROUND:** Orthopaedic surgeons are at a high risk of sustaining a percutaneous or mucocutaneous exposure to blood and body fluids. The Center for Disease Control and Prevention recommends a wash with soap and water and notification of the concerned hospital authorities after any percutaneous/mucocutaneous exposure, but a systematic amenability with these guidelines is not always seen. This cross-sectional study was undertaken to determine current knowledge and practices of orthopaedic surgeons in case of a percutaneous sharp injury exposure, emphasizes the immediate first aid steps taken after an exposure, the degree of reporting, and to explore the reasons for noncompliance. Finally, we sought to create awareness about the prevailing Center for Disease Control and Prevention guidelines after any exposure to blood or body fluids. **MATERIALS AND METHODS:** We conducted a cross-sectional survey using an anonymous prepared questionnaire. The study population included exclusively orthopaedic surgeons, including residents, fellows, and attending physicians at 4 US institutions. The questionnaire was also available online on the OTA Web site as a part of survey monkey. The questionnaire comprised 9 multiple choice questions, and more than 1 response could be given for some questions. The questions addressed previous needle stick/sharp injury exposure, number of times that had happened, whether reported to the hospital administration, reason for nonreporting, and risk perception for transmission of blood-borne pathogens (human immunodeficiency virus, HBsAg, and hepatitis C virus). The questions were also asked based on what should be done in four different clinical settings based on respondents risk perception.

**RESULTS:** Of fifty eight attendings, 7 fellows, 45 residents, and 7 respondents who did not indicate their position participated in the survey for a total of 117 respondents. Out of 99, 24 had sustained it once, 18 twice, 11 three times, and 35 at least 4 times. When questioned about informing the incident to the hospital administration, 38% had always reported the incident, 33% had never reported the incident, and the remaining 29% had not reported it every time. Of note, 87% gave the correct response about the risk of transmission of human immunodeficiency virus after an exposure. On questioning about the risk of hepatitis B transmission, from an HBsAg- and HBeAg-positive source, 13% gave the correct response, whereas from HBsAg-positive and HBeAg-negative source, 30% gave the correct response. Regarding transmission of hepatitis C virus from a positive source, 36% responded correctly. The surgeons seemingly attempted to risk stratify their exposure, and they were more likely to report their exposure in the higher risk scenarios. **CONCLUSIONS:** This study demonstrates that orthopaedic surgeons of all levels of training are at high risk of occupational exposure to blood-borne pathogens. Moreover, despite the level of training, the majority of surgeons do not follow the recommended steps, although we do not know the reasons for such behavior. Also, there is a low awareness of the significant risk of hepatitis transmission among orthopaedic surgeons treating a population with a high prevalence of undiagnosed hepatitis.

Recently approved, interferon-free medication regimens for treating hepatitis C are highly effective but extremely costly. We aimed to identify cost-effective strategies for managing treatment-naïve US Veterans with new hepatitis C medication regimens. We developed a Markov model with 1-year cycle length for a cohort of 60-year old Veterans with untreated genotype 1 hepatitis C seeking treatment in a typical year. We compared using sofosbuvir/ledipasvir or ombitasvir/ritonavir/paritaprevir/dasabuvir to treat: (1) any patient seeking treatment, (2) only patients with advanced fibrosis or cirrhosis, or (3) patients with advanced disease first and healthier patients one year later. The previous standard of care, sofosbuvir/simeprevir or sofosbuvir/pegylated interferon/ribavirin, was included for comparison. Patients could develop progressive fibrosis, cirrhosis, or hepatocellular carcinoma, undergo transplantation, or die. Complications were less likely after sustained virologic response. We calculated the incremental cost per quality-adjusted life year (QALY) and varied model inputs in one-way and probabilistic sensitivity analyses. We used the Veterans Health Administration perspective with a lifetime time horizon and 3% annual discounting. Treating any patient with ombitasvir-based therapy was the preferred strategy ($35,560; 14.0 QALYs). All other strategies were dominated (greater costs/QALY gained than more effective strategies). Varying treatment efficacy, price and/or duration changed the preferred strategy. In probabilistic sensitivity analysis, treating any patient with ombitasvir-based therapy was cost-effective in 70% of iterations at a $50,000/QALY threshold and 65% of iterations at a $100,000/QALY threshold.

CONCLUSION: Managing any treatment-naïve genotype 1 hepatitis C patient with ombitasvir-based therapy is the most economically efficient strategy, although price and efficacy can impact cost-effectiveness. It is economically unfavorable to restrict treatment to patients with advanced disease or use a staged treatment strategy. This article is protected by copyright. All rights reserved.

The cascade of care has been useful in creating a nationwide goal to reduce HIV transmission and increase linkage and retention to care. What can we learn from the HIV movement about how to utilize and implement the cascade of HCV care within US health systems and program models?

Cascade of Care for Hepatitis C Virus Infection Within the US Veterans Health Administration. Maier MM1, Ross DB1, Chartier M1, Belperio PS1, Backus LI1. Am J Public Health. 2015 Nov 12:e1-e6. [Epub ahead of print]

OBJECTIVES: We measured the quality of HCV care using a cascade of HCV care model.

METHODS: We estimated the number of patients diagnosed with chronic HCV, linked to HCV care, treated with HCV antivirals, and having achieved a sustained virologic response (SVR) in the electronic medical record data from the Veterans Health Administration's Corporate Data Warehouse and the HCV Clinical Case Registry in 2013. RESULTS: Of the estimated 233,898 patients with chronic HCV, 77% (181,168) were diagnosed, 69% (160,794) were linked to HCV care, 17% (39,388) were treated with HCV antivirals, and 7% (15,983) had achieved SVR.

CONCLUSIONS: This Cascade of HCV Care provides a clinically relevant model to measure the quality of HCV care within a health care system and to compare HCV care across health systems.
OBJECTIVES: Vulnerable, urban populations with a history of substance use disorders have a high prevalence of hepatitis C virus (HCV). Primary care-based treatment has been proposed to improve access to care. In this study, we present outcomes from our urban, primary care-based HCV treatment program in patients treated with telaprevir or boceprevir in combination with pegylated-interferon and ribavirin ("triple therapy"). METHODS: We collected data from 126 consecutive patients with genotype 1 HCV monoinfection seen in our treatment program (2011-2013). Among the 40 who initiated treatment, we analyzed factors associated with achieving a sustained viral response (SVR). RESULTS: During the study period, 40 patients initiated triple therapy (32%), 80% with recent or past substance use disorders. Patients initiating treatment were younger than untreated patients (P=0.002), but otherwise did not differ demographically, or in the severity of their liver fibrosis (P>0.05). An SVR was achieved in 18 patients (45%) and was less likely in patients with recent or past substance use disorders or psychiatric illness (both P<0.01). CONCLUSIONS: Nearly one third of patients initiated triple therapy with SVR rates comparable to other HCV treatment settings, despite a significant burden of mental illness and substance dependence. Our experience demonstrates that a primary care-based practice can successfully deliver HCV care to a vulnerable population. Additional interventions may be needed to improve outcomes in patients with recent or past substance use disorders or psychiatric illness.

Risk environments facing potential users of a supervised injection site in Ottawa, Canada.


BACKGROUND: Supervised injection sites (SISs) have been effective in reducing health risks among people who inject drugs (PWID), including those who face issues of homelessness, mental health illness, interactions with local policing practices, and HIV infection. We investigate the risk behaviours and risk environments currently faced by potential users of an SIS in Ottawa to establish the need for such a service and to contribute to the design of an SIS that can address current health risks and reduce harm. METHODS: The PROUD cohort is a community-based participatory research (CBPR) project that examines the HIV risk environment among people who use drugs in Ottawa. From March to October 2013, 593 people who reported using injection drugs or smoking crack cocaine were enrolled through street-based recruitment in the ByWard Market neighbourhood, an area of the city with a high concentration of public drug use and homelessness. Participants completed a demographic, behavioural, and risk environment questionnaire and were offered HIV point-of-care testing. We undertook descriptive and univariate analyses to estimate potential use of an SIS by PWID in Ottawa and to explore risk behaviours and features of the risk environment faced by potential users of the service.

RESULTS: Of those participants who reported injecting drugs in the previous 12 months (n = 270), 75.2 % (203) reported a willingness to use an SIS in Ottawa. Among potential SIS users, 24.6 % had recently injected with a used needle, 19.0 % had trouble accessing new needles, 60.6 % were unstably housed, 49.8 % had been redzoned by the police, and 12.8 % were HIV positive. Participants willing to use an SIS more frequently injected in public (OR = 1.98, 95 % CI = 1.06-3.70), required assistance to inject (OR = 1.84, 95 % CI = 1.00-3.38), were
hepatitis C positive (OR = 2.13, 95 % CI = 1.16-3.91), had overdosed in the previous year (OR = 2.00, 95 % CI = 1.02-3.92), and identified as LGBTQ (OR = 5.61, 95 % CI = 1.30-24.19).

**CONCLUSION:** An SIS in Ottawa would be well-positioned to reach its target group of highly marginalized PWID and reduce drug-related harms. The application of CBPR methods to a large-scale quantitative survey supported the mobilization of communities of PWID to identify and advocate for their own service needs, creating an enabling environment for harm reduction action.

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**LIVER CANCER**


A mass spectrometry-based methodology has been developed to screen for changes in site-specific core-fucosylation (CF) of serum proteins in early stage HCC with different etiologies. The methods involve depletion of high-abundance proteins, trypsin digestion of medium-to-low-abundance proteins into peptides, iTRAQ labeling, and Lens culinaris Agglutinin (LCA) enrichment of CF peptides, followed by endoglycosidase F3 digestion before mass spectrometry analysis. 1300 CF peptides from 613 CF proteins were identified from patients sera, where 20 CF peptides were differentially expressed in alcohol (ALC)-related HCC samples compared with ALC-related cirrhosis samples and 26 CF peptides changed in hepatitis C virus (HCV)-related HCC samples compared with HCV-related cirrhosis samples. Among these, we found three CF peptides from fibronectin upregulated in ALC-related HCC samples compared with ALC-related cirrhosis samples with an AUC (area under the curve) value of 0.89 at site 1007 with a specificity of 85.7% at a sensitivity of 92.9% (generated with 10-fold cross-validation). When combined with the AFP index, the AUC value reached to 0.92 with a specificity of 92.9% at a sensitivity of 100%, significantly improved compared to that with AFP alone (LR test p < 0.001). In HCV-related samples, the CF level of cadherin-5 at site 61 showed the best AUC value of 0.75 but was not as promising as that of fibronectin site 1007 for ALC-related samples. The CF peptides of fibronectin may serve as potential biomarkers for early stage HCC screening in ALC-related cirrhosis patients.

**Comprehensive analyses of mutations and hepatitis B virus integration in hepatocellular carcinoma with clinicopathological features.** Kawai-Kitahata F1, Asahina Y2,3, Tanaka S4, et al. J Gastroenterol. 2015 Nov 9. [Epub ahead of print]

**BACKGROUND AND AIMS:** Genetic alterations in specific genes are critical events in carcinogenesis and hepatocellular carcinoma (HCC) progression. However, the genetic alterations responsible for HCC development, progression, and survival are unclear.

**METHODS:** We investigated the essential difference in genetic alterations between HCC and adjacent non-HCC tissues using next-generation sequencing technology. **RESULTS:** We found recurrent mutations in several genes such as telomerase reverse transcriptase (TERT; 65 % of the total 104 HCCs), TP53 (38 %), CTNNB1 (30 %), AXIN1 (2 %), PTEN (2 %), and CDKN2A (2 %). TERT promoter mutations were associated with older age (p = 0.005), presence of hepatitis C virus (HCV) infection (p = 0.003), and absence of hepatitis B virus (HBV) infection (p < 0.0001). In hepatitis B surface antigen (HBs Ag)-positive HCC without TERT promoter
mutations, HBV integration into TERT locus was found in 47% patients and was mutually exclusive to TERT promoter mutations. Most (89%) HBV integrants were in the HBx region. TP53 mutations were associated with HBV infection (p = 0.0001) and absence of HCV infection (p = 0.002). CTNNB1 mutations were associated with absence of HBV infection (p = 0.010). Moreover, TERT promoter mutation was significantly associated with shorter disease-free survival (p = 0.005) and poor overall survival (p = 0.024). CONCLUSIONS: Gene alterations in TERT promoter, TP53, CTNNB1, and HBV integration were closely associated with HCC development, and mutations in TERT promoter are related to poor prognosis. These results are useful for understanding the underlying mechanism of hepatocarcinogenesis, diagnosis, and predicting outcomes of patients with HCC.


BACKGROUND: Multiple staging systems have been proposed for hepatocellular carcinoma (HCC). However there is no consensus regarding which system provides the best prognostic accuracy. We aimed to investigate the performance of 11 currently used HCC staging systems. METHODS: Between 2002 and 2013, a large prospective dataset of 3,182 HCC patients were enrolled. The baseline characteristics and staging information were collected. Independent predictors of survival were identified. Homogeneity and corrected Akaike information criterion (AICc) were compared between each system. RESULTS: The median follow-up duration was 17 months. Independent predictors of adverse outcome were serum albumin < 3.5 g/dL, bilirubin ≥ 1 mg/dL, creatinine ≥ 1 mg/dL, alpha-fetoprotein ≥ 20 ng/mL, alkaline phosphatase ≥ 200 IU/L, presence of ascites, multiple tumor nodules, maximal tumor size > 5 cm, presence of vascular invasion, presence of extrahepatic metastasis, and poor performance status (all p<0.001). Significant differences in survival were found across all stages of the 11 systems except between Hong Kong Liver Cancer stage IV and V, Japan Integrated Staging score 4 and 5, and Tokyo score 5 through 8. The Cancer of the Liver Italian Program (CLIP) score was associated with the highest homogeneity and lowest AICc value in the entire cohort. In subgroup analysis, the CLIP score was also superior in patients with hepatitis B- or hepatitis C-related HCC and in patients receiving curative or non-curative treatments. CONCLUSIONS: The CLIP staging system is stable and consistently the best prognostic model in all patients and in patients with different etiology and treatment strategy.


Recently, long non-coding RNAs (lncRNAs) were found to be implicated in cancer progression. However, the contributions of lncRNAs to Hepatitis C virus-related hepatocellular carcinoma (HCC) remain largely unknown. Here, we characterized lncRNA expression in 73 tissue samples from several different developmental stages of HCV-related hepatocarcinogenesis by repurposing microarray data sets. We found that the expression of 7 lncRNAs in preneoplastic lesions and HCC was significantly different. Among these significantly differently expressed lncRNAs, the lncRNA LINC01419 transcripts were expressed at higher levels in early stage HCC compared to dysplasia and as compared with early stage HCC, lncRNA AK021443 level
increase in advanced stage HCC while lncRNA AF070632 level decrease in advanced stage HCC. Using quantitative real-time reverse-transcription PCR, we validated that LINC01419 was significantly overexpressed in HBV-related and HCV-related HCC when compared with matched non-tumor liver tissues. Moreover, functional predictions suggested that LINC01419 and AK021443 regulate cell cycle genes, whereas AF070632 is associated with cofactor binding, oxidation-reduction and carboxylic acid catabolic process. These findings provide the first large-scale survey of lncRNAs associated with the development of hepatocarcinogenesis and may offer new diagnostic biomarkers and therapeutic targets for HCV-related HCC.


Most hepatocellular carcinoma (HCC) patients worldwide do not receive curative treatments. Alternative treatments for most HCC patients include palliative treatments, such as transarterial chemoembolization (TACE), chemotherapy, and radiotherapy. Although statins may be a chemopreventive treatment option for reducing hepatitis B virus (HBV)- and hepatitis C virus (HCV)-related HCC risks, their therapeutic effects are unknown. This study evaluated the effects of statin on HCC patients receiving palliative treatment. Data from the National Health Insurance claims database and cancer registry databases of The Collaboration Center of Health Information Application, Taiwan, were analyzed. We included HCC patients who were treated between January 1, 2001, and December 31, 2010, and followed them from the index date to December 31, 2012. The inclusion criteria were presence of HBV carrier-related HCC, age >20 years, and having received TACE, radiotherapy, or chemotherapy as palliative treatment. The exclusion criteria were cancer diagnosis before HCC was confirmed, surgery, liver transplantation, radiofrequency ablation, or percutaneous ethanol injection as curative treatment, missing sex-related information, HCC diagnosis before HBV, and age <20 years. We enrolled 20,200 HCC patients. The median follow-up duration was 1.66 years (interquartile range, 0.81). In total, 1988 and 18,212 patients received palliative treatment with and without statin use, respectively. HCC patients who received palliative treatment with statin use had lower HCC-specific deaths in all stages than those who received palliative treatment without statin use (P=0.0001, 0.0002, 0.0012, and 0.0002, and relative risk (RR)=0.763, 0.775, 0.839, and 0.718, for stages I-IV, respectively). In all-cause and HCC-specific deaths, decreasing trends (P for trend <0.0001) of adjusted hazard ratios (aHRs) were observed in all stages with no treatment, statin use only, palliative treatment only, and palliative treatment plus statin use. The aHRs of all-cause and HCC-specific deaths increased with the progress in cancer stage and reduced with the use of advanced therapeutic modalities (P for trend <0.0001). Differences in HBV- and non-HBV-related HCC were solely due to statin use. Statin use alone reduced HCC-specific deaths by 36% in non-HBV-related HCC in stage I and 50% in HBV-related HCC in stages II and III. With a relatively substantial reduction in mortality, the therapeutic effects of statin use were stronger in HBV-related HCC than in non-HBV-related HCC. Palliative treatments are critical for HCC patients. Multiple therapeutic methods with statin use reduced the mortality risk. Statins prolong the survival of patients with advanced HCC receiving palliative treatment, thus demonstrating its therapeutic value as an adjuvant treatment. Furthermore, statin-based palliative treatment in early stage HCC remarkably reduced the number of deaths. For patients who cannot tolerate palliative treatments, statin use only might possibly reduce mortality, particularly in HBV-related early stage HCC patients (>50% reduction in HCC deaths).

AIM: To assess the use of mitochondrial DNA (mtDNA) content as a noninvasive molecular biomarker in hepatitis C virus-related hepatocellular carcinoma (HCV-HCC).

MATERIALS AND METHODS: A total of 135 participants were enrolled in the study. Equal numbers of subjects were enrolled in each of three clinically defined groups: those with HCV-related cirrhosis (HCV-cirrhosis), those with HCV-HCC, and a control group of age- and sex-matched healthy volunteers with no evidence of liver disease. mtDNA concentrations were determined using a quantitative real-time polymerase chain reaction (PCR) technique.

RESULTS: mtDNA content was lowest among the HCV-HCC cases. No statistically significant difference was observed between the group of HCV-cirrhosis and the control group as regards mtDNA level. HCC patients with multicentric hepatic lesions had significantly lower mtDNA content than HCC patients with less advanced disease. When a receiver operating characteristic curve analysis was used, a cutoff of 34 was assigned for mtDNA content to distinguish between HCV-HCC cases. No statistically significant difference was observed between the group of HCV-cirrhosis and the control group as regards mtDNA level. HCC patients with multicentric hepatic lesions had significantly lower mtDNA content than HCC patients with less advanced disease. When a receiver operating characteristic curve analysis was used, a cutoff of 34 was assigned for mtDNA content to distinguish between HCV-HCC cases and HCV-cirrhosis patients who are not yet complicated by malignancy. Lower mtDNA content was associated with HCC risk when using either or both healthy controls and HCV-cirrhosis groups for reference.

CONCLUSIONS: mtDNA content analysis could serve as a noninvasive molecular biomarker that reflects tumor burden in HCV-HCC cases and could be used as a predictor of HCC risk in patients of HCV-cirrhosis. In addition, the nonsignificant difference of mtDNA level between HCV-cirrhosis patients and healthy controls could eliminate the gray zone created by the use of alpha-fetoprotein in some cirrhotic patients.


Chronic liver disease has become a global health problem as a result of the increasing incidence of viral hepatitis, obesity and alcohol misuse. Over the past three decades, in the United Kingdom alone, deaths from chronic liver disease have increased both in men and in women. Currently, 2.5% of deaths worldwide are attributed to liver disease and projected figures suggest a doubling in hospitalisation and associated mortality by 2020. Chronic liver diseases vary for clinical manifestations and natural history, with some individuals having relatively indolent disease and others with a rapidly progressive course. About 30% of patients affected by hepatitis C has a progressive disease and develop cirrhosis over a 20 years period from the infection, usually 5-10 years after initial medical presentation. The aim of the current therapeutic strategies is preventing the progression from hepatitis to fibrosis and subsequently, cirrhosis. Hepatic steatosis is a risk factor for chronic liver disease and is affecting about the half of patients who abuse alcohol. Moreover non-alcoholic fatty liver disease is part of the metabolic syndrome, associated with obesity, hypertension, type II diabetes mellitus and dyslipidaemia, and a subgroup of patients develops non-alcoholic steatohepatitis and fibrosis with subsequent cirrhosis. The strengths and pitfalls of liver biopsy are discussed and a variety of new techniques to assess liver damage from transient elastography to experimental techniques, such as in vitro urinary nuclear magnetic resonance spectroscopy. Some of the techniques and tests described are already suitable for more widespread clinical application, as is the case with ultrasound-based
liver diagnostics, but others, such as urinary metabonomics, requires a period of critical
evaluation or development to take them from the research arena to clinical practice.

**Impact of more detailed categorization of shrinkage or progression ratio at initial imaging
response after sorafenib treatment in advanced hepatocellular carcinoma patients.** Wada
Y1, Takami Y1, Tateishi M1, Ryu T1, Mikagi K1, Saitsu H1. Onco Targets Ther. 2015 Nov
2;8:3193-3202.

**BACKGROUND:** Sorafenib therapy improves survival in unresectable hepatocellular
carcinoma (HCC) patients without an objective response. The present study investigated whether
the initial imaging response might be a prognostic indicator after administration of sorafenib
treatment in HCC patients. **PATIENTS AND METHODS:** This retrospective study reviewed
unresectable HCC patients undergoing sorafenib therapy. Patients evaluated without complete
response, partial response (PR), or progressive disease (PD) at the initial imaging response
evaluation by modified Response Evaluation Criteria in Solid Tumors were divided into three
groups according to more detailed categorization of the shrinkage/progression ratio in initial
imaging response. A comparison of progression-free and overall survival among these groups
was performed. **RESULTS:** Of the 43 non-PR non-PD patients with target lesions, ten (23.3%)
exhibited mild response (MR; -30% to -5%), 14 (32.6%) exhibited no change (NC; -5% to +5%),
and 19 (44.2%) exhibited mild-PD (MPD; +5% to +20%). There was no statistical difference in
progression-free or overall survival between MR and NC patients. The median progression-free
survivals in NC+MR and mild-PD patients were 15.0 and 5.3 months, respectively (P<0.01), and
the median survival times were 31.9 and 17.1 months, respectively (P<0.001). In multivariate
analysis, etiology (hepatitis C virus) and initial imaging response (MR+NC) was identified as an
independently good prognostic factor. **CONCLUSION:** More detailed categorization of
shrinkage or progression at the initial imaging response evaluation may be a useful marker for
predicting sorafenib treatment outcomes in HCC patients. If the initial imaging response is not
progression but stability, sorafenib may have a survival benefit.

Understanding that patients with an HCV cure are still at risk for the development of HCC, what
additional tools (i.e. EMR alerts/flags, patient tools, etc.) can we integrate into the medical model to
ensure ongoing wellness, and that patients are surveyed in a timely manner for the prevention of
other comorbidities.

**Development of hepatocellular carcinoma in patients with hepatitis C virus infection who
achieved sustained virological response following interferon therapy: A large-scale, long-
term cohort study.** Nagaoki Y1, Aikata H1, Nakano N1, et al. J Gastroenterol Hepatol. 2015

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


Natural killer (NK) cells are involved in the pathogenesis of hepatitis C viral (HCV) infection and hepatocellular carcinoma (HCC). Recent immunological progresses have revealed the molecular mechanisms of activation or inhibition of NK cells. In patients infected with HCV, the percentages of NK cells are decreased and the NK receptor expression and function of NK cells including cytotoxicity and cytokines production are altered. These alterations in NK cells are associated with persistent infection with HCV, liver injury, liver fibrosis and liver carcinogenesis. In HCV treatment, NK cells play a role in the eradication of HCV in both interferon (IFN)-based therapy and IFN-free therapy using direct-acting antivirals (DAA). In HCC patients, the exhaustion of NK cells that represents lower cytotoxicity and impaired cytokine production might contribute to the progression of HCC. Several immunotherapies targeting NK cells have been reported. NK cell transfer and NK activating gene therapy have been demonstrated to be effective in mouse liver cancer models and several clinical trials are ongoing. Recently the role of MHC class I-related chain A (MICA), a human ligand of NKG2D, has attracted attention in the development of HCC. The expression of MICA could be controlled by anti-HCC drugs including sorafenib. A new chemo-immunotherapy might be expected in the treatment of HCC. In this review, we summarize the impact of NK cells in chronic hepatitis C and HCC.