
BACKGROUND & AIM: Understanding the real-world effectiveness of all-oral hepatitis C virus (HCV) regimens informs treatment decisions. We evaluated the effectiveness of daclatasvir+sofosbuvir±ribavirin (DCV+SOF±RBV) and velpatasvir/sofosbuvir (VEL/SOF)±RBV in genotype 2 and genotype 3 patients treated in routine practice.

METHODS: Observational, intent-to-treat cohort of genotype 2 and genotype 3 patients initiating DCV+SOF±RBV or VEL/SOF±RBV at any Department of Veterans Affairs facility.

RESULTS: For genotype 2, SVR rates did not differ between DCV+SOF (94.5%, 241/255) and VEL/SOF (94.4%, 2105/2230) (p=0.94) or between DCV+SOF+RBV (88.1%, 37/42) and VEL/SOF+RBV (89.5%, 221/247)(p=1.00). For genotype 3, SVR rates did not differ between DCV+SOF (90.8%, 366/403) and VEL/SOF (92.0%, 1203/1307)(p=0.50) or between DCV+SOF+RBV (88.1%, 430/488) and VEL/SOF+RBV (86.4%, 370/428)(p=0.51). In multivariate models for genotype 2 and 3 patients, treatment regimen was not a significant predictor of odds of SVR. For genotype 3, significant predictors of reduced odds of SVR were prior HCV treatment-experience (odds ratio (OR) 0.51, 95% confidence interval (CI) 0.36-0.72, p<0.001), FIB-4 >3.25 (OR 0.60, 95%CI 0.43-0.84, p=0.002) and a history of decompensated liver disease (OR 0.68, 95%CI 0.47-0.98, p=0.04). For genotype 2 and 3 patients treated with VEL/SOF±RBV, 89% and 85% received 12-week durations, respectively. For DCV+SOF±RBV, 56% and 20% of genotype 2 patients received 12-weeks and 24-weeks, respectively; for genotype 3, 53% and 23% received 12-week and 24-week durations with most direct-acting antiviral experienced patients receiving 24-weeks. CONCLUSIONS: In genotype 2 and 3 HCV-infected patients, DCV+SOF±RBV and VEL/SOF±RBV produced similar SVR rates within genotype, and regimen did not have a significant impact on odds of SVR. For genotype 3 patients, prior treatment-experience and advanced liver disease were significant predictors of reduced odds of SVR regardless of regimen. LAY SUMMARY: In clinical practice, cure rates for genotype 2 HCV were 94% and cure rates for genotype 3 HCV were 90%. The chance of achieving cure was the same whether a person received daclatasvir plus sofosbuvir or
velpatasvir/sofosbuvir. Ribavirin did not affect cure rates. The chance of a cure was lowest in people who had received HCV medication in the past.


**OBJECTIVE:** An estimated 336 per 100,000 people in Russia are infected with hepatitis C virus, including up to 75% with genotype (GT) 1b. In the TURQUOISE-II/III trials, a 12-week regimen of the direct-acting antiviral agents ombitasvir (OBV), paritaprevir (PTV), ritonavir, and dasabuvir (DSV) in GT1b-infected patients with compensated cirrhosis resulted in 12-week sustained virologic response (SVR) rates of 100%. PATIENTS AND METHODS: In TURQUOISE-IV, GT1b-infected patients (n=36) from Russia and Belarus with compensated cirrhosis, who were treatment naive or previously treated with pegylated interferon/ribavirin (RBV), received OBV/PTV/ritonavir+DSV+RBV for 12 weeks. The primary efficacy end point was SVR at 12 weeks. Safety assessments included adverse event (AE) monitoring and laboratory testing.

**RESULTS:** At baseline, patients had Child-Pugh scores of 5 (92%) or 6 (8%). Overall, 69% were treatment experienced (44% prior null responders, 32% relapers, and 16% partial responders). All patients achieved SVR at 12 weeks (36/36; 100%). No patient experienced a serious AE or discontinued treatment prematurely. Treatment-emergent AEs possibly related to study drugs occurring in greater than or equal to 10% of patients were asthenia (19%), anemia (14%), cough (14%), and headache (11%); most events were mild in severity. Clinically significant laboratory abnormalities were infrequent.

**CONCLUSION:** In Russian and Belarusian patients with hepatitis C GT1b infection and compensated cirrhosis, 100% achieved SVR at 12 weeks after 12 weeks' treatment with OBV/PTV/ritonavir+DSV+RBV. The treatment was well tolerated.

**Race and Hepatitis C Care Continuum in an Underserved Birth Cohort.** Kim NJ1,2, Locke CJ1,2, Park H1,2, Magee C2, Bacchetti P3, Khalili M4,5,6. J Gen Intern Med. 2018 Sep 20. doi: 10.1007/s11606-018-4649-6. [Epub ahead of print]

**BACKGROUND:** Birth cohort screening is recommended for hepatitis C virus (HCV) and underserved populations are disproportionally affected by HCV. Little is known about the influence of race on the HCV care continuum in this population. **OBJECTIVE:** To assess the cascade of HCV care in a large racially diverse and underserved birth cohort. **DESIGN:** Retrospective cohort study using electronic medical record data abstracted until August 31, 2017.

**PATIENTS:** 34,810 patients born between 1945 and 1965 engaged in primary care between October 1, 2014, and October 31, 2016, within the safety-net clinics of the San Francisco Health Network. **MAIN MEASURES:** Rate of hepatitis C testing, hepatitis C treatment, and response to therapy. **RESULTS:** Cohort characteristics were as follows: median age 59 years, 57.6% male, 25.5% White (20.6% Black, 17.7% Latino, 33.0% Asian/Pacific Islander (API), 2% other), and 32.6% preferred a non-English language. 99.7% had an HCV test (95.4% HCV antibody, 4.3% HCVRNA alone). Among HCV antibody-positive patients (N = 4587), 22.9% were not tested for confirmatory HCVRNA. Among viremic patients (N = 3673), 20.8% initiated HCV therapy, 90.6% achieved sustained virologic response (SVR) and 8.1% did not have a SVR test. HCV screening and treatment were highest in APIs (98.7 and 34.7% respectively; p < 0.001). Blacks had the highest chronic HCV rate (22.2%; p < 0.001). Latinos had the lowest SVR rate.
(81.3%; p = 0.01). On multivariable analysis, API race (vs White, OR 1.20; p = 0.001), presence of HIV co-infection (OR 1.58; p = 0.02), presence of chronic kidney disease (OR 0.47; p < 0.001), English (vs non-English) as preferred language (OR 0.54; p = 0.002), ALT (OR 0.39 per doubling; p < 0.001), and HCVRNA (OR 0.83 per 10-fold increase; p < 0.001) were associated with HCV treatment. CONCLUSIONS: Despite near-universal screening, gaps in active HCV confirmation, treatment, and verification of cure were identified and influenced by race. Tailored interventions to engage and treat diverse and underserved populations with HCV infection are needed.


**BACKGROUND & AIMS:** Proton pump inhibitors (PPIs) are commonly prescribed to treat acid-related disorders. Some direct-acting antiviral regimens for chronic hepatitis C virus (HCV) infection have reduced efficacy in patients taking concomitant acid-reducing agents, including PPIs, due to interactions between drugs. We analyzed data from 9 multicenter, phase 2 and 3 trials to determine the efficacy and pharmacokinetics of an HCV therapeutic regimen comprising glecaprevir and pibrentasvir (glecaprevir/pibrentasvir) in patients taking concomitant acid-reducing agents. **METHODS:** We analyzed data from 2369 patients infected with HCV genotypes 1-6 and compensated liver disease treated with an all-oral regimen of glecaprevir/pibrentasvir for 8-16 weeks. We compared efficacy and pharmacokinetics among patients receiving at least 1 dose of an acid-reducing agent (a PPI, an H2 blocker, or antacid). High-dose PPI was defined as daily dose greater than 20 mg omeprazole dose equivalent. The objectives were to evaluate rate of sustained virologic response 12 weeks post-treatment (SVR12) and to assess steady-state glecaprevir and pibrentasvir exposures in patients on acid-reducing agents. **RESULTS:** Of the 401 patients (17%) who reported use of acid-reducing agents, 263 took PPIs (11%; 109 patients took a high-dose PPI and 154 patients took a low-dose PPI). Rates of SVR12 were 97.0% among patients who used acid-reducing agents and 97.5% among those not using acid-reducing agents (P = .6). An SVR12 was achieved in 96.3% taking a high-dose PPI and 97.4% taking a low-dose PPI, with no virologic failures in those receiving a high-dose PPI (P = .7). Glecaprevir, but not pibrentasvir, bioavailability was affected; its exposure decreased by 41% in patients taking a high-dose PPI. **CONCLUSIONS:** In an analysis of data from 9 clinical trials, we observed a high rate of SVR12 (approximately 97%) among patients treated with glecaprevir/pibrentasvir for HCV infection—even among patients taking concomitant ARA or high-dose PPI. This was despite decreased glecaprevir exposures in patients when on high-dose PPIs. ClinicalTrials.gov numbers, NCT02243280 (SURVEYOR-I), NCT02243293 (SURVEYOR-II), NCT02604017 (ENDURANCE-I), NCT02640482 (ENDURANCE-2), NCT02640157 (ENDURANCE-3), NCT02636595 (ENDURANCE-4), NCT02642432 (EXPEDITION-1), NCT02651194 (EXPEDITION-4), NCT02446717 (MAGELLAN-I).


**Caring Ambassadors Program Hepatitis C Literature Review © 2018**
BACKGROUND AND OBJECTIVES: Studies evaluating the role of hepatitis C viral (HCV) infection on the progression of CKD are few and conflicting. Therefore, we evaluated the association of untreated HCV on kidney function decline in patients with stage 3-5 CKD.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: This retrospective cohort study included members of Kaiser Permanente Southern California and Kaiser Permanente Mid-Atlantic States aged ≥18 years, with incident HCV and CKD diagnoses from January 1, 2004 to December 31, 2014. We used generalized estimating equations to compare the rate of change in eGFR between those with HCV and CKD versus CKD alone, adjusting for covariates. Cox proportional hazards models compared the risk of 25% decrease in eGFR and ESKD (defined as progression to eGFR<15 ml/min per 1.73 m2 on two or more occasions, at least 90 days apart) in those with HCV and CKD versus CKD alone, adjusting for covariates.

RESULTS: We identified 151,974 patients with CKD only and 1603 patients with HCV and CKD who met the study criteria. The adjusted annual decline of eGFR among patients with HCV and CKD was greater by 0.58 (95% confidence interval [95% CI], 0.31 to 0.84) ml/min per 1.73 m2, compared with that in the CKD-only population (HCV and CKD, -1.61; 95% CI, -1.87 to -1.35 ml/min; CKD only, -1.04; 95% CI, -1.06 to -1.01 ml/min). Adjusted for covariates, the hazard for a 25% decline in eGFR and for ESKD were 1.87 (95% CI, 1.75 to 2.00) and 1.93 (95% CI, 1.64 to 2.27) times higher among those with HCV and CKD, respectively, compared with those with CKD only.

CONCLUSIONS: Untreated HCV infection was associated with greater kidney function decline in patients with stage 3-5 CKD.


BACKGROUND: The benefits of treatment of hepatitis C virus with direct-acting antiviral drugs in patients with decompensated liver cirrhosis (DLC) are still unclear. AIM: To evaluate the degree of improvement in hepatic decompensation events and quality of life (QOL) in treated patients with DLC. PATIENTS AND METHODS: One hundred and fifty patients with hepatitis C virus-related DLC were included; 75 of these patients received treatment (group I) [sofosbuvir (SOF) with either daclatasvir or ledipasvir for 24 weeks without ribavirin (RBV) or for 12 weeks with RBV] and 75 patients did not receive treatment as a comparable group (group II). Patients who achieved a sustained virological response at 12 weeks were assessed in terms of decompensation events, model for end-stage liver disease score, Child-Turcotte-Pugh score, biochemical changes, and QOL (applied on Mcguill QOL questionnaire) before starting treatment and 6 months after end of treatment, and were compared with untreated patients.

RESULTS: Forty-two (56%) patients received SOF/daclatasvir for 24 weeks without RBV and 19 (25.3%) patients received SOF/ledipasvir for 24 weeks without RBV. The model for end-stage liver disease score improved in treated patients (mean change -1.73), but worsened in untreated patients (mean change +11.8) before and after 6 months. Also, the Child-Turcotte-Pugh score improved significantly (P<0.001). Serum albumin, prothrombin time, bilirubin, a-fetoprotein, and alanine aminotransferase improved in treated patients (P<0.001). Health-related QOL improved in treated patients (mean change +17.65) and worsened in untreated ones (mean change -18.68; P<0.001). CONCLUSION: Treated patients with DLC showed an improvement in liver tests and health-related QOL. Longer durations of follow-up for decompensation events are needed.

AIM: Results of recent studies have confirmed the efficacy of an 8-week course of ledipasvir/sofosbuvir (LDV/SOF) in patients who are non-cirrhotics, native to treatment, are infected with hepatitis C (HCV) genotype 1, and have HCV viral load < 6 million IU/mL. However, there are limited data on a shortened treatment course in patients who are over the age of 65. METHODS: A retrospective study was performed to examine the safety, tolerability, and sustained viral response rates (SVR) of the 8-week LDV/SOF therapy compared to the 12-week LDV/SOF therapy among non-cirrhotic, treatment-naïve, genotype 1 HCV patients with viral load < 6 million IU/mL who are 65 years of age or older. RESULTS: A total of 454 patients were identified of which 182 non-cirrhotic, genotype 1 HCV-RNA < 6 million IU/mL patients received the 8-week LDV/SOF treatment and 272 received the 12-week LDV/SOF treatment. Mean [± standard deviation (SD)] aspartate aminotransferase to platelet ratio index score for the entire cohort was 0.45 ± 0.03. The mean (± SD) age for the 8-week treatment was 69.7 (± 7) years, 54.7% male and 45.3% female. The mean (± SD) age of the 12-week treatment was 71.7 (± 3) years, 56.4% male and 43.6% female. Overall, SVR-12 for the 8-week regimen was 93% and SVR-12 for the 12-week regimen was 95%. For the 182 treated with the 8-week LDV/SOF treatment, there were no serious adverse events requiring hospitalization or signs of liver failure requiring transplantation. Overall, the 8-week treatment patient cohort experienced less fatigue, headache, dry mouth, and diarrhea. This finding was statistically significant with a P value < 0.001. CONCLUSION: Eight-week LDV/SOF therapy in treatment-naïve, non-cirrhotic, genotype 1 HCV patients with RNA < 6 million IU/mL was found safe, better tolerated, effective, and required less upfront cost when compared with the 12-week LDV/SOF treatment regimen in properly selected geriatric population.


Real-world data regarding the effectiveness and safety of generic sofosbuvir (SOF)-based interferon-free direct acting antiviral agents (DAAs) for patients with chronic hepatitis C virus (HCV) infection remain limited. A total of 517 chronic HCV-infected patients receiving 12 or 24 weeks of SOF-based therapies were retrospectively enrolled in 4 academic centers in Taiwan. The rate of sustained virologic response at week 12 off-therapy (SVR12) and that of treatment completion were assessed. The baseline characteristics and on-treatment HCV viral kinetics to predict SVR12 were analyzed. By evaluable population (EP) analysis, the SVR12 rate was 95.4% (95% confidence interval [CI]: 93.2-96.9%). The SVR12 was achieved in 29 of 34 patients (85.3%, 95% CI: 69.6-93.6%), 130 of 139 patients (93.5%, 95% CI: 88.2-96.6%), 119 of 124 patients (96.0%, 95% CI: 90.9-98.3%) and 215 of 220 patients (97.7%, 95% CI: 94.8-99.0%) who received SOF in combination with ribavirin (RBV), ledipasvir (LDV), daclatasvir (DCV) and velpatasvir (VEL), respectively. Of 517 patients, 514 (99.4%) completed the scheduled treatment. All 15 patients with true virologic failures were relapers. Two
decompensated cirrhotic patients had on-treatment deaths which were not related to DAAs. All 7 patients who were lost to follow-up had undetectable HCV RNA level at the last visit. The SVR12 rates were comparable in terms of baseline patient characteristics and viral decline at week 4 of treatment. In conclusion, generic SOF-based regimens are well tolerated and provide high SVR12 rates in patients with chronic HCV infection.

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


**BACKGROUND:** More data on resistance of HCV genotype (GT) 3 and 4 to Direct-Acting Antivirals (DAAs) are still needed. We investigated presence of Resistance-Associated Substitutions (RASs) pre- and post-treatment and their emergence under DAAs in HCV GT3 and GT4 infected patients failing DAA regimens by next-generation sequencing (NGS).

**METHODS:** Sanger sequencing and NGS were performed on NS5B and NS5A for plasma samples prior- and post-treatment of 13 patients. Positions implicated in resistance to anti-NS5A and anti-NS5B in literature were analysed. **RESULTS:** No baseline RASs was detected on NS5B but one GT4r virus developed the mutation S282T at failure. On NS5A, we detected pre-existing RASs or polymorphisms in viruses of 6/10 patients (L28M for a GT4a, M28V for a GT4r, L30R for a GT4a, 2 GT4d, and 1 GT4r, T58P for a GT4d) by Sanger sequencing and in viruses of 7/10 patients by NGS. Additional baseline minority substitutions detected by NGS were Y93H in a GT3a, L28M in a GT4a and a GT4d, and L28F in a GT4d virus. At failure, these substitutions were found at frequency of 100%. The Y93H was detected alone at baseline while the L28M and L28F were accompanied by polymorphisms L30R or L30R + T58P.

**CONCLUSIONS:** The use of NGS in patients failing DAAs and infected by HCV GT3 and GT4 revealed the emergence of specific patterns of substitutions on NS5A and NS5B, in particular substitutions at position 28 on NS5A in GT4 virus, highlighting the need to list these substitutions in guidelines for resistance interpretation.


Emerging evidence indicates that long noncoding RNAs (lncRNAs) regulate various biological processes, especially innate and adaptive immunity. However, the relationship between lncRNAs and the interferon (IFN) pathway remains largely unknown. Here, we report that lncRNA ITPRIP-1 (lncITPRIP-1) is involved in viral infection and plays a crucial role in the virus-triggered IFN signaling pathway through the targeting of melanoma differentiation-associated gene 5 (MDA5). LncITPRIP-1 can be induced by viral infection, which is not entirely dependent on the IFN signal. Besides, there is no coding potential found in the lncITPRIP-1 transcript. LncITPRIP-1 binds to the C terminus of MDA5, and it possesses the ability to boost the oligomerization of both the full length and the 2 caspase activation and recruitment domains of MDA5 in a K63-linked polyubiquitination-independent manner. Amazingly, we also found that MDA5 can suppress hepatitis C virus (HCV) replication independently of IFN signaling through...
its C-terminal-deficient domain bound to viral RNA, in which lncITPRIP-1 plays a role as an assistant. In addition, the expression of lncITPRIP-1 is highly consistent with MDA5 expression, indicating that lncITPRIP-1 may function as a cofactor of MDA5. All the data suggest that lncITPRIP-1 enhances the innate immune response to viral infection through the promotion of oligomerization and activation of MDA5. Our study discovers the first lncRNA ITPRIP-1 involved in MDA5 activation.IMPORTANCE Hepatitis C virus infection is a global health issue, and there is still no available vaccine, which makes it urgent to reveal the underlying mechanisms of HCV and host factors. Although RIG-I has been recognized as the leading cytoplasmic sensor against HCV for a long time, recent findings that MDA5 regulates the IFN response to HCV have emerged. Our work validates the significant role of MDA5 in IFN signaling and HCV infection and proposes the first lncRNA inhibiting HCV replication by promoting the activation of MDA5 and mediating the association between MDA5 and HCV RNA, the study of which may shed light on the MDA5 function and treatment for hepatitis C patients. Our suggested model of how lncITPRIP-1 orchestrates signal transduction for IFN production illustrates the essential role of lncRNAs in virus elimination.

Transduction with Lentiviral Vectors Altered the Expression Profile of Host MicroRNAs. Huang H#1, Zhang C#1, Wang B#1, Wang F1, Pei B1, Cheng C1, Yang W1, Zhao Z2,3,4,5. J Virol. 2018 Aug 29;92(18). pii: e00503-18. doi: 10.1128/JVI.00503-18. Print 2018 Sep 15. RNA interference (RNAi) is widely used in gene knockdown analysis and as a tool to screen host genes involved in viral infection. Owing to the limitations of transducing cells with synthetic small interfering RNAs (siRNAs), lentiviral short hairpin RNA (shRNA) vectors are more widely used. However, we found that stable transduction with lentiviral shRNA vectors inhibited hepatitis C virus (HCV) propagation in human hepatoma cells. We found by microRNA (miRNA) microarray analysis that this inhibition was induced by the alteration of host miRNA expression. In addition to one miRNA (miR-196b-5p) previously reported to be involved in HCV infection, other miRNAs (miR-216a-5p, -216b-5p, -217, and -30b-5p) were found to influence HCV infection in this study. Further studies suggested that this effect was independent of the transcription of shRNAs. The lentiviral vector itself and the integration site of the lentiviral vector might determine the change in miRNA expression. Moreover, the upregulation of JUN contributed to the dysregulation of miR-216a-5p, -216b-5p, and -217 in stably transduced cells. Although the changes in miRNA expression were beneficial for inhibiting HCV infection in our study, this off-target effect should be considered when transduction with lentiviral vectors is performed for other purposes, especially in therapy.IMPORTANCE We found that stable transduction with lentiviral shRNA was able to nonspecifically inhibit HCV infection by the dysregulation of host miRNAs. Previous studies showed that the overexpression of shRNAs oversaturated the host miRNA pathways to inhibit HCV infection. In contrast, the miRNA machinery was not affected in our study. Knockout studies suggested that the nonspecific effect was independent of the transcription of shRNAs. The lentiviral vector itself and the integration sites in the host genome determined the changes in miRNAs. Stable transduction with lentiviral vectors was able to increase the expression of JUN, which in turn upregulated miR-216a-5p, miR-216b-5p, and miR-217. miR-216a-5p and miR-216b-5p might inhibit HCV by suppressing the host autophagic machinery. Our study suggested a novel nonspecific effect of lentiviral vectors, and this side effect should be considered when transduction with lentiviral vectors is performed for other purposes, especially in therapy.

Kidney transplant from donors with hepatitis C virus (HCV) antibody has been limited to HCV viremic recipients only, due to concern of the HCV transmission. However, the new antiviral medications provide an opportunity to expand the utilization of these donors. To study the risk of HCV transmission in kidney transplantation, we used discarded donor kidneys and determined HCV RNA levels by quantitative real-time PCR in bilateral (right and left) kidney biopsies and plasma from 14 HCV antibody-positive donors (sensitivity: 15 international unit (IU)/mL plasma; 1.8 IU/50 nL kidney). In three NAT-negative donors, HCV RNA was negative in plasma and kidney. In all 11 NAT-positive donors, HCV RNA was positive in plasma (range: 5807-19 134 177 IU/mL) but negative in six kidneys from four donors with plasma HCV RNA <1.5 million IU/μL. HCV RNA correlated between right and left kidneys (P = 0.75) and between kidney and plasma (r = 0.86). When normalized by volume, HCV RNA median (range) was 49 (0-957) IU/50 nL plasma and 1.0 (0-103) IU/50 nL kidney, significantly lower in kidney (P = 0.005) than in plasma (14-fold). Plasma HCV RNA can be used to predict the kidney HCV load. Future studies are needed if plasma/kidney HCV levels can be used to stratify donors for transmission risk and recipients for post-transplant management in extended utilization of HCV antibody-positive donors.

**HIV/HCV Coinfection**


Since the advent of new direct acting antivirals (DAA), substantial changes in hepatitis C (HCV) treatment guidelines have occurred. However, little is known about how these recommendations have been adopted into clinical practice. We conducted a retrospective review of human immunodeficiency virus (HIV)/HCV coinfected patients treated with DAAs at the Ryan White Clinic of the Jackson Health System in Miami, FL, USA. Our aim was to determine changes in HCV evaluation and treatment patterns in the use of DAAs over a four-year period from January 2014 to December 2017. Data were divided into two periods: period 1 (2014-2015) and period 2 (2016-2017). In comparison with the rest of the cohort, patients in period 2 had a lower frequency of advanced liver disease (24.4% vs. 48.6%, p = 0.026) and underwent more elastography (34.1% vs. 2.7%, p < 0.001) and less ultrasound (78.0% vs. 97.3%, p = 0.011). They were more often treated with ledipasvir/sofosbuvir (85.4% vs. 56.8%, p = 0.005) and less often with simeprevir/sofosbuvir (0% vs. 32.4%, p < 0.001). Gastrointestinal side effects were reported less frequently (2.4% vs. 18.9%, p = 0.017) in this period. In accordance with the updated guidelines, our study demonstrated a growing preference for non-invasive methods to assess fibrosis in recent years. Regarding treatment, there was a clear preference for second generation DAAs in 2016-2017, along with initiation of treatment in the early stages of liver disease.

BACKGROUND: Once-daily glecaprevir coformulated with pibrentasvir (glecaprevir/pibrentasvir) demonstrated high rates of sustained virologic response 12 weeks after treatment (SVR12) in patients with hepatitis C virus (HCV) genotype 1-6 infection. This phase 3 study evaluated the efficacy and safety of glecaprevir/pibrentasvir in patients with chronic HCV genotype 1-6 and human immunodeficiency virus type 1 (HIV-1) coinfection, including patients with compensated cirrhosis. METHODS: EXPEDITION-2 was a phase 3, multicenter, open-label study evaluating glecaprevir/pibrentasvir (300 mg/120 mg) in HCV genotype 1-6/HIV-1-coinfected adults without and with compensated cirrhosis for 8 and 12 weeks, respectively. Patients were either HCV treatment-naive or experienced with sofosbuvir, ribavirin, or interferon, and antiretroviral therapy (ART) naive or on a stable ART regimen. Treatment-experienced genotype 3-infected patients were excluded. The primary endpoint was the SVR12 rate. RESULTS: In total, 153 patients were enrolled, including 16 (10%) with cirrhosis. The SVR12 rate was 98% (n = 150/153; 95% confidence interval, 95.8-100), with no virologic failures in 137 patients treated for 8 weeks. One genotype 3-infected patient with cirrhosis had on-treatment virologic failure. Most adverse events were mild in severity; 4 patients (2.6%) had serious adverse events, all deemed unrelated to glecaprevir/pibrentasvir. Treatment discontinuation was rare (<1%). All patients treated with ART maintained HIV-1 suppression (<200 copies/mL) during treatment. CONCLUSIONS: Glecaprevir/pibrentasvir for 8 weeks in noncirrhotic and 12 weeks in cirrhotic patients is a highly efficacious and well-tolerated treatment for HCV/HIV-1 coinfection, regardless of baseline HCV load or prior treatment with interferon or sofosbuvir.


BACKGROUND: Coinfection with human immunodeficiency virus (HIV) accelerates hepatitis C virus (HCV)-related liver fibrosis. Macrophages are triggered during both viral infections and are critical in liver inflammation/fibrogenesis. Liver fibrosis strongly associates with serum soluble CD163 (sCD163, a macrophage activation marker); comprehensive evaluation in HIV/HCV coinfection is lacking. METHODS: We retrospectively analyzed sCD163 (enzyme-linked immunosorbent assay) and hepatic CD163 (immunofluorescent CD163/CD68 costaining) in patients infected with HIV/HCV, HCV, or HIV, pre- and post-antiviral therapy. RESULTS: sCD163 was significantly higher in HIV/HCV compared to either monoinfection, and decreased following successful antiviral therapy, although did not fully normalize. In HIV/HCV, sCD163 was associated with necroinflammation, Ishak fibrosis scores, and noninvasive fibrosis scores. We observed a novel trend whereby sCD163 levels progressively increase with increasing Ishak fibrosis score, peaking at stage 4, above which levels plateaued. Periportal CD163+ macrophage frequency was also higher with increasing fibrosis score. When stratified by fibrosis stage, sCD163 levels were higher in HIV/HCV than HCV but only in individuals with mild to moderate fibrosis. CONCLUSIONS: In HIV/HCV, increasing sCD163 levels accompanied periportal CD163+ macrophage enrichment in mild to moderate fibrosis, but not in established...
cirrhosis, suggesting that sCD163 is a dynamic biomarker of fibrogenesis rather than accumulated fibrosis. Our findings implicate HIV-related macrophage activation in accelerated fibrosis progression in HIV/HCV coinfection.


BACKGROUND/AIMS: Limited data exist comparing the safety and efficacy of direct-acting antivirals (DAAs) in hepatitis C virus (HCV) monoinfected and HCV/human immunodeficiency virus (HIV) coinfected patients in the real-world clinic practice setting. METHODS: All HCV monoinfected and HCV/HIV coinfected patients treated with DAAs between January 2014 and October 2017 in community clinic settings were retrospectively analyzed. Pretreatment baseline patient characteristics, treatment efficacy, factors affecting sustained virologic response at 12 weeks (SVR12) after treatment, and adverse reactions were compared between the groups. RESULTS: A total of 327 patients were included in the study, of which 253 were HCV monoinfected, and 74 were HCV/HIV coinfected. There was a statistically significant difference observed in SVR12 when comparing HCV monoinfection and HCV/HIV coinfection (94% and 84%, respectively, p=0.005). However, there were no significant factors identified as a predictor of a reduced response. The most common adverse effect was fatigue (27%). No significant drug interaction was observed between DAA and antiretroviral therapy. None of the patients discontinued the treatment due to adverse events. CONCLUSIONS: In a real-world setting, DAA regimens have lower SVR12 in HCV/HIV coinfection than in HCV monoinfection. Further studies involving a higher number of HCV/HIV coinfected patients are needed to identify real predictors of a reduced response.

Effectiveness of 8 weeks of ledipasvir/sofosbuvir for hepatitis C in HCV-HIV-coinfected patients. Vega AD1, Hynicka LM1, Claey K1, Chua JV2, Heil EL1. Antivir Ther. 2018 Sep 7. doi: 10.3851/IMP3263. [Epub ahead of print]

BACKGROUND: Data is limited on the use of 8 weeks of therapy with Ledipasvir/Sofosbuvir (LDV/SOF) for special populations such as HCV/HIV-coinfected patients. The primary objective of this analysis was to compare SVR12 rates among HCV-monoinfected and HCV/HIV-coinfected patients in a real-world clinical setting. Additionally, we compared SVR12 rates among patients receiving 8 versus 12 weeks of therapy. METHODS: This was a single-center, retrospective study of HCV-infected patients prescribed LDV/SOF at ambulatory clinics associated with the University of Maryland Medical Center (UMMC) from May 2015 to May 2016. Data were obtained from UMMC electronic medical record and outpatient pharmacy claims database. Comparisons between groups were made using Chi-squared or Fisher's exact test for categorical variables and Student's t-test or Wilcoxon rank-sum for continuous variables. All analyses were per-protocol; patients missing SVR12 data (25.2%) could not be evaluated for our stated objectives. RESULTS: A total of 274 patients were included. Median age was 58 years; 62.8% were male; 82.5% were black. SVR12 data was available for 65 HCV/HIV-coinfected patients, of which 62 (95.4%) achieved SVR12. There was no difference in SVR12 rate between HCV/HIV-coinfected patients and HCV-monoinfected patients (86/90; 95.6%) (p = 0.959). Additionally, there was no difference in SVR12 attainment between HIV/HCV-coinfected patients who received 8 versus 12 weeks of therapy (p = 0.101). CONCLUSIONS:
Eight weeks of LDV/SOF was effective for treatment-naïve, non-cirrhotic, HCV-genotype 1 patients in this real-world setting, regardless of HIV status. Increased uptake of the 8-week regimen can decrease costs for patients and payers without compromising outcomes.


We assessed the effect of co-infection by hepatitis C virus (HCV) on immunological and virological response at 48 weeks from initiation of antiretroviral therapy (ART). We included patients from the Cohort of Spanish HIV Research Network (CoRIS) starting ART between January 2004 and November 2014, had at least 1 CD4 T-cell count and viral load measurements both in the previous 6 months and at 48 (±12) weeks from ART initiation, and HCV serology before ART initiation. We used linear regression for mean differences in CD4 T-cell count increase from ART initiation and logistic regression to estimate odds ratios for virological response. Of 12,239 patients by November 30, 2015, 5070 met inclusion criteria: 4382 (86.4%) HIV mono-infected and 688 (13.6%) HIV/HCV co-infected. Co-infected patients were more likely to have acquired HIV through injecting drugs use (57.4% vs. 1.1%), to be women, older, and Spanish, have a lower educational level, and having started ART with lower CD4 counts and acquired immunodeficiency syndrome. CD4 T-cell count increase at 48 weeks was 229.7 cell/μL in HIV-monoinfected and 161.9 cell/μL in HIV/HCV-coinfected patients. The percentages of patients achieving a virological response at 48 weeks were 87.0% and 78.3% in mono and coinfected patients, respectively. Multivariable analyses showed that at 48 weeks, coinfected patients increased 44.5 (95% confidence interval [CI]: 24.8-64.3) cells/μL less than monoinfected and had lower probability of virological response (odds ratio: 0.62; 95% CI: 0.44-0.88). HIV/HCV-coinfected patients have lower immunological and virological responses at 48 weeks from ART initiation than monoinfected patients.


Hepatitis C virus (HCV) treatment in HIV/HCV co-infected individuals has renewed relevance given the ongoing opioid crisis and rise of new HIV and HCV infections associated with injection drug use. Patients co-infected with HIV and HCV demonstrate increased rates of hepatic fibrosis, progression to liver failure, and liver-related mortality. HIV co-infection does not impact outcomes of current HCV treatments, and patients should be treated the same as HCV mono-infected persons, though attention to drug:drug interactions is required. In this review, we discuss the mechanisms mediating injury to the liver in HIV mono-infection and HIV/HCV co-infection, and present the landmark trials of HCV treatment in HIV-infected individuals.
hepatic fibrosis, progression to liver failure, and liver-related mortality. HIV co-infection does not impact outcomes of current HCV treatments, and patients should be treated the same as HCV mono-infected persons, though attention to drug:drug interactions is required. In this review, we discuss the mechanisms mediating injury to the liver in HIV mono-infection and HIV/HCV co-infection, and present the landmark trials of HCV treatment in HIV-infected individuals.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Risk factors for hepatitis C virus (HCV) infection vary, and there were an estimated 1.75 million new cases worldwide in 2015. The World Health Organization aims for a 90% reduction in new HCV infections by 2030. An HCV vaccine would prevent transmission, regardless of risk factors, and significantly reduce the global burden of HCV-associated disease. Barriers to development include virus diversity, limited models for testing vaccines, and our incomplete understanding of protective immune responses. Although highly effective vaccines could prevent infection altogether, immune responses that increase the rate of HCV clearance and prevent chronic infection may be sufficient to reduce disease burden. Adjuvant envelope or core protein and virus-vectored non-structural antigen vaccines have been tested in healthy volunteers who are not at risk for HCV infection; viral vectors encoding non-structural proteins are the only vaccine strategy to be tested in at-risk individuals. Despite development challenges, a prophylactic vaccine is necessary for global control of HCV.

Risk factors for hepatitis C virus (HCV) infection vary, and there were an estimated 1.75 million new cases worldwide in 2015. The World Health Organization aims for a 90% reduction in new HCV infections by 2030. An HCV vaccine would prevent transmission, regardless of risk factors, and significantly reduce the global burden of HCV-associated disease. Barriers to development include virus diversity, limited models for testing vaccines, and our incomplete understanding of protective immune responses. Although highly effective vaccines could prevent infection altogether, immune responses that increase the rate of HCV clearance and prevent chronic infection may be sufficient to reduce disease burden. Adjuvant envelope or core protein and virus-vectored non-structural antigen vaccines have been tested in healthy volunteers who are not at risk for HCV infection; viral vectors encoding non-structural proteins are the only vaccine strategy to be tested in at-risk individuals. Despite development challenges, a prophylactic vaccine is necessary for global control of HCV.

OBJECTIVE: Assess hepatitis C virus (HCV) prevalence and incidence among person who began injecting drugs during the opioid epidemic in New York City (NYC) and identify possible new directions for reducing HCV infection among persons who inject drugs. METHODS: 846 persons who began injecting drugs between 2000 and 2017 were recruited from persons entering Mount Sinai Beth Israel substance use treatment programs. A structured interview was administered and HCV antibody testing conducted. Protective effects of non-injecting drug use were examined among persons who "reversed transitioned" to non-injecting drug use and persons who used non-injected heroin in addition to injecting. RESULTS: Participants were 79% male, 41% White, 15% African-American, 40% Latinx, with a mean age of 35. Of those who began injecting in 2000 or later, 97 persons (11%) "reverse transitioned" back to non-injecting drug use. Reverse transitioning was strongly associated with lower HCV seroprevalence (30% versus 47% among those who continued injecting, p < 0.005). Among those who continued injecting, HCV seropositivity was inversely associated with current non-injecting heroin use (AOR = 0.72, 95%CI 0.52-0.99). HCV incidence among persons continuing to inject was estimated as 13/100 person-years. HCV seropositive persons currently injecting cocaine were particularly likely to report behavior likely to transmit HCV. CONCLUSIONS: Similar to other locations in the US, NYC is experiencing high rates of HCV infection among persons who have begun injecting since 2000. New interventions that facilitate substitution of non-injecting for injecting drug use and that reduce transmission behavior among HCV seropositives may provide additional methods for reducing HCV transmission.

Increased HCV Screening Yields Discordant Gains in Diagnoses Among Urban and Rural Veteran Populations in Texas: Results of a Statewide Quality Improvement Initiative.

BACKGROUND: Chronic hepatitis C virus (HCV) infection is a significant health burden among military veterans. Our goals were to increase monthly HCV screenings, diagnoses, and sustained virologic responses (SVR) among 88,652 unscreened birth cohort Veterans in Texas. METHODS: The interventions were enabled within six of the eight healthcare systems (HCSs) that compose Veteran's Integrated Service Network 17. The remaining two HCSs served as controls. The HCSs were separated into two groups: urban and rural; each composed of a control and three interventional HCSs. Decision support programming was embedded within the Computerized Patient Record System that prompted HCV screening among previously unscreened birth cohort patients. Clinical process design and educational efforts were enacted to enhance treatment capacity. RESULTS: Monthly screenings increased 4.89 times (p < 0.001) and 2.97 times (p < 0.001) during the postinterventional period relative to control for urban and rural HCSs, respectively. For urban HCSs, diagnoses increased 1.58 (p < 0.001) times more than the control group during the postinterventional period, but there was no difference in number of diagnoses in the rural HCSs (p = 0.86). Monthly SVR increased 2.69 times more than the control group during the postinterventional period (p < 0.001). CONCLUSION: Decision support improved HCV screening among birth cohort patients in both urban and rural HCSs. Increased screening boosted the monthly number of diagnoses in the urban HCSs, but not in the rural
HCSs; which rebuts the utility of birth cohort screening among rurally residing veterans. These interventions significantly improved the rate of SVR achievement relative to control.

**Australia on track to achieve WHO HCV elimination targets following rapid initial DAA treatment uptake: a modeling study.** Kwon JA1, Dore GJ1, Grebely J1, Hajarizadeh B1, Guy R1, Cunningham EB1, Power C2, Estes C3, Razavi H3, Gray RT1; HCV Estimates and Projections Reference Group. J Viral Hepat. 2018 Sep 29. doi: 10.1111/jvh.13013. [Epub ahead of print]

Subsidized direct-acting antiviral (DAA) treatment recently became available to all adults living with chronic hepatitis C (HCV) in Australia. Based on rapid uptake (32,600 people initiated DAA in 2016) we estimated the impact on HCV epidemiology and mortality in Australia and determined if Australia can meet the WHO HCV elimination targets by 2030. Using a mathematical model, we simulated pessimistic, intermediate, and optimistic DAA treatment scenarios in Australia over 2016-2030. We assumed treatment and testing rates were initially higher for advanced fibrosis and the same across HCV transmission risk level sub-populations. We also assumed constant testing rates after 2016. We compared the results to the 2015 level and a counterfactual (IFN-based) scenario. During 2016-2030, we estimated an intermediate DAA treatment scenario (2016, 32,600 treated; 2017, 21,370 treated; 2018,17,100 treated; 2019 and beyond, 13,680 treated each year) would avert 40,420 new HCV infections, 13,260 liver-related deaths (15,320 in viraemic; -2,060 in cured), and 10,730 HCC cases, equating to a 53%, 63% and 75% reduction respectively, compared to the IFN-based scenario. The model also estimated that Australia will meet the WHO targets of incidence and treatment by 2028. Time to a 65% reduction in liver-related mortality varied considerably between HCV viraemic only cases (2026) and all cases (2047). Based on a feasible DAA treatment scenario incorporating declining uptake, Australia should meet key WHO HCV elimination targets in 10 to 15 years. The pre-DAA escalation in those with advanced liver disease makes the achievement of the liver-related mortality target difficult. This article is protected by copyright. All rights reserved.

**Race and Hepatitis C Care Continuum in an Underserved Birth Cohort** Kim NJ1,2, Locke CJ1,2, Park H1,2, Magee C2, Bacchetti P3, Khalili M4,5,6. Gen Intern Med. 2018 Sep 20. doi: 10.1007/s11606-018-4649-6. [Epub ahead of print]

**BACKGROUND:** Birth cohort screening is recommended for hepatitis C virus (HCV) and underserved populations are disproportionally affected by HCV. Little is known about the influence of race on the HCV care continuum in this population. **OBJECTIVE:** To assess the cascade of HCV care in a large racially diverse and underserved birth cohort. **DESIGN:** Retrospective cohort study using electronic medical record data abstracted until August 31, 2017. **PATIENTS:** 34,810 patients born between 1945 and 1965 engaged in primary care between October 1, 2014, and October 31, 2016, within the safety-net clinics of the San Francisco Health Network. **MAIN MEASURES:** Rate of hepatitis C testing, hepatitis C treatment, and response to therapy. **RESULTS:** Cohort characteristics were as follows: median age 59 years, 57.6% male, 25.5% White (20.6% Black, 17.7% Latino, 33.0% Asian/Pacific Islander (API), 2% other), and 32.6% preferred a non-English language. 99.7% had an HCV test (95.4% HCV antibody, 4.3% HCVRNA alone). Among HCV antibody-positive patients (N = 4587), 22.9% were not tested for confirmatory HCVRNA. Among viremic patients (N = 3673), 20.8% initiated HCV therapy, 90.6% achieved sustained virologic response (SVR) and 8.1% did not have a SVR test. HCV screening and treatment were highest in APIs (98.7 and 34.7% respectively; p < 0.001).
Blacks had the highest chronic HCV rate (22.2%; p < 0.001). Latinos had the lowest SVR rate (81.3%; p = 0.01). On multivariable analysis, API race (vs White, OR 1.20; p = 0.001), presence of HIV co-infection (OR 1.58; p = 0.02), presence of chronic kidney disease (OR 0.47; p < 0.001), English (vs non-English) as preferred language (OR 0.54; p = 0.002), ALT (OR 0.39 per doubling; p < 0.001), and HCVRNA (OR 0.83 per 10-fold increase; p < 0.001) were associated with HCV treatment. **CONCLUSIONS:** Despite near-universal screening, gaps in active HCV confirmation, treatment, and verification of cure were identified and influenced by race. Tailored interventions to engage and treat diverse and underserved populations with HCV infection are needed.


**INTRODUCTION:** Young adults who inject drugs and live in rural communities are at high risk for hepatitis C virus (HCV) infection. Recent changes in HCV treatment must be communicated within these communities to improve access to care and reduce HCV transmission. **METHODS:** Field workers in the ¡VÁLE! Hepatitis Treatment and Integrated Prevention Services study identified frequently asked questions (FAQs) posed by young-adult participants at high risk for HCV during screening and educational sessions. From 2016 to 2018, 183 young adults (44.3% women; 85.8% Latino/a) younger than 30 years who inject drugs and reside in Rio Arriba or Doña Ana counties in New Mexico were enrolled. The research team compiled deidentified questions during field enrollments. **RESULTS:** FAQs were reviewed and categorized into four major domains, including risk/prevention, screening, treatment, and reinfection. FAQs were addressed by a team of medical and public health professionals, using the most current research and recommendations. **CONCLUSIONS:** These FAQs address important gaps in HCV knowledge among young adults who are at high risk for infection. The FAQs also highlight the importance of risk reduction counseling provided by frontline public health providers as well as access to safe and effective HCV treatments for young adults who inject drugs.


The epidemiology of hepatitis C virus (HCV) has changed significantly over the last decade. Once most prevalent among older adults, the current burden has disproportionately affected young adults including women of childbearing age (WOCA). The Society for Maternal-Fetal Medicine recently issued guidelines that made no change in the recommendation to screen pregnant women based on risk factors. The current burden in young adults including WOCA supports a change in strategy away from risk-based screening to universal HCV screening in pregnancy. Universal screening offers several advantages that position us for a future where HCV treatment in pregnancy can happen and offers us progress toward the elimination of HCV.

Recognizing the importance of timely guidance regarding the rapidly evolving field of hepatitis C management, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) developed a web-based process for the expeditious formulation and dissemination of evidence-based recommendations. Launched in 2014, the hepatitis C virus (HCV) guidance website undergoes periodic updates as necessitated by availability of new therapeutic agents and/or research data. A major update was released electronically in September 2017, prompted primarily by approval of new direct-acting antiviral agents and expansion of the guidance's scope. This update summarizes the latest release of the HCV guidance and focuses on new or amended recommendations since the previous September 2015 print publication. The recommendations herein were developed by volunteer hepatology and infectious disease experts representing AASLD and IDSA and have been peer reviewed and approved by each society's governing board.

"Why Me?" Understanding the HCV Care Continuum Among People With Serious Mental Illness. Arnold RM1, Machover H1, Wall ME1, Ahmadizadeh I1, Potts W1, Himelhoch S1. Psychiatr Serv. 2018 Sep 17:appips201700542. doi: 10.1176/appi.ps.201700542. [Epub ahead of print]

OBJECTIVE: Despite possible cure rates of >90% with new treatment, people with serious mental illness are rarely screened for hepatitis C virus (HCV). A colocated approach may help patients navigate the care continuum. METHODS: This study used a mixed-methods approach to increase understanding of the HCV care continuum for people with mental illness (N=170). Quantitative data included laboratory testing, risk assessments, and chart reviews. Qualitative interviews (N=9) were conducted to gain a broader understanding. RESULTS: Thirty-one (18%) patients tested positive for HCV; 13 were cured of HCV, and 10 are still receiving treatment. Qualitative interviews revealed that fear of the diagnosis may be an important treatment barrier. CONCLUSIONS: Those with serious mental illness who were diagnosed as having HCV and received the colocated prevention and treatment program were able to navigate the continuum of care for HCV treatment. Fear of diagnosis may be an important consideration for future efforts.

HEPATOCELLULAR (LIVER) CANCER


BACKGROUND: Hepatocellular carcinoma is a common malignancy in Asia. It is associated with chronic hepatitis B virus or hepatitis C virus infection and alcoholic hepatitis. Commonly, the tumor metastasizes to the lungs, regional lymph nodes, and bone. Recently, the incidence of metastatic spinal cord compression caused by primary hepatocellular carcinoma has been reported more frequently due to improved diagnosis and therapeutic modalities. The presentation of primary hepatocellular carcinoma with spinal cord compression is very rare. To the best of our knowledge, there are only 33 such cases published to date. The majority of cases involve patients of Asian origin and are associated with hepatitis B infection. CASE PRESENTATION: We report consecutive cases of two Native American (American Indian) patients (a 64-year-old man and a 70-year-old man) who presented with symptoms of spinal cord compression due to metastatic spread of hepatocellular carcinoma and were associated with hepatitis C infection. In
one of these cases, the hepatitis C infection had been successfully controlled (hepatitis C titers were undetectable for 1 year before he presented with spinal cord compression). This occurrence in a Native American with a controlled hepatitis C infection has not been reported previously.

CONCLUSIONS: Primary care physicians, oncologists, and gastroenterologists should be cognizant of this unusual presentation of hepatocellular carcinoma in a Native American. Such knowledge may help improve early diagnosis and survival.


**BACKGROUND AND AIMS:** Hepatocellular carcinoma (HCC) risk is high in cirrhosis. We sought to describe differences in HCC risk, predictors and trends over time according to etiology of cirrhosis. **METHODS:** We identified 116,404 patients with cirrhosis diagnosed between 2001-2014 in the VA healthcare system and determined incident HCC cases occurring from the date of cirrhosis diagnosis until 01/31/2017. Patients were divided by cirrhosis etiology into hepatitis C virus (HCV, n = 52,671), alcoholic liver disease (ALD, n = 35,730), nonalcoholic fatty liver disease (NAFLD, n = 17,354), or OTHER (n = 10,649). **RESULTS:** During a mean follow-up of 4.3 years, 10,042 new HCC cases were diagnosed. Patients with HCV had >3 times higher incidence of HCC (3.3 per 100 patient-years) than patients with ALD (0.86/100 patient-years), NAFLD (0.90/100 patient-years) or OTHER (1.0/100 patient-years), an association that persisted after adjusting for baseline characteristics. HCC incidence was 1.6 times higher in patients with cirrhosis diagnosed in 2008-2014 (2.47/100 patient-years) than in 2001-2007 (1.55/100 patient-years). Independent predictors of HCC among all cirrhosis etiologies included: age, male sex, Hispanic ethnicity, high serum alpha fetoprotein, alkaline phosphatase and AST/ALT ratio and low serum albumin and platelet count. Diabetes was associated with HCC in ALD-cirrhosis and NAFLD-cirrhosis, and BMI in ALD-cirrhosis. **CONCLUSIONS:** HCC risk is 3 times greater in cirrhotic patients with HCV than ALD or NAFLD. HCC risk continues to increase over time in analyses extending to 2017 in cirrhosis of all etiologies. Multiple readily available risk factors for HCC were identified that were influenced by cirrhosis etiology and could be used to develop HCC risk estimation models.

**The AP2M1 gene expression is a promising biomarker for predicting survival of patients with hepatocellular carcinoma.** Cho SH1, Pak K2, Jeong DC3, Han ME4, Oh SO4, Kim YH4. J Cell Biochem. 2018 Sep 27. doi: 10.1002/jcb.27699. [Epub ahead of print]

There is a growing need for the discovery of new prognostic factors for cases where the scoring and staging system of hepatocellular carcinoma (HCC) does not result in a clear definition. We analyzed whether AP-2 complex subunit mu (AP2M1) expression could be a new prognostic marker for HCC based on the roles of AP2M1 in influencing hepatocyte growth factor (HGF) promoter regulation and hepatitis C virus (HCV) assembly. Patient data were extracted from cohorts of the Gene Expression Omnibus (GSE10186), International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA). Differential expression value between matched cancer and normal liver was identified using ICGC cohort. Subsequently, we compared AP2M1 expression as a prognostic gene with other well-known prognostic genes for HCC, using the time-dependent area under the curve (AUC) of the Uno's C-index, the AUC value of the receiver operating characteristics at 5 years, Kaplan-Meier survival curve, and multivariate analysis. Particularly, TCGA and GSE10186 patients were divided into subgroups.
based on alcohol intake, hepatitis B, and C viral infections, and analyzed in the same methods. The AP2M1 expression values in patients with cancer were much higher than matched normal liver. The AP2M1 level showed excellent prognosis predictions in comparison with existing markers in the three independent cohorts (n = 647). In particular, it was more predictive of prognosis than other markers in alcohol intake and HCV infections. In conclusion, we were confident that AP2M1 provides sufficient value as a new prognostic marker for HCC especially patients with HCV infection and/or alcohol intake.


Understanding the transcriptional regulatory elements that influence the progression of liver disease in the presence of hepatitis C virus (HCV) infection is critical for the development of diagnostic and therapeutic approaches. Systems biology provides a roadmap by which these elements may be integrated. In this study, a previously published dataset of 124 microarray samples was analyzed in order to determine differentially expressed genes across four tissue types/conditions (normal, cirrhosis, cirrhosis HCC, and HCC). Differentially expressed genes were assessed for their functional clustering and those genes were annotated with their potential transcription factors and miRNAs. Transcriptional regulatory networks were constructed for each pairwise comparison between the 4 tissue types/conditions. Based on our analysis, it is predicted that the disruption in the regulation of transcription factors such as AP-1, PPARγ, and NF-κB could contribute to the liver progression from cirrhosis to steatosis and eventually to HCC. Whereas the condition of the liver digresses, the downregulation of miRNAs' (such as miR-27, Let-7, and miR-106a) expression makes the transition of the liver through each pathological stage more apparent. This preliminary data can be used to guide future experimental work. An understanding of the transcriptional regulatory attributes acts as a road map to help design interference strategies in order to target the key regulators of progression of HCV induced HCC.


**OBJECTIVES:** Wisteria floribunda agglutinin-positive human Mac-2-binding protein (WFA+-M2BP) is a glycomarker. The present community-based long-term follow-up study repeatedly determined the serum WFA+-M2BP level and examined its short- and long-term associations with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). **METHODS:** A total of 921 participants with antibodies against HCV seropositive, but seronegative for hepatitis B surface antigen were enrolled from seven townships in Taiwan during 1991-1992. The participants were regularly followed and their serum WFA+-M2BP levels were measured at baseline and follow-up. HCC was ascertained through active follow-up and computerized data linkage with the National Cancer Registration System until December 31, 2013. Cox proportional hazards and logistic regression models were applied to estimate the magnitude of associations between serum WFA+-M2BP levels and HCC. **RESULTS:** During a median follow-up of 21.7 years, 122 new-onset HCC cases were identified. Elevated serum WFA+-M2BP levels were associated with an increased risk of HCC (p < 0.001). Patients with increasing changes in serum WFA+-M2BP levels, relative to their baseline levels, had a 4.36-fold risk of HCC. The areas under receiver operating curves (AUROCs) of WFA+-M2BP for predicting
HCC showed that the prediction efficacy was significantly higher while closer to HCC diagnosis (p = 0.024). The AUROC was 0.91 for predicting HCC within 1 year by including the predictors of age, sex, alanine aminotransferase, alpha-fetoprotein (AFP) and WFA+-M2BP.  
**CONCLUSIONS:** Serum WFA+-M2BP level may elevate before HCC onset and is a short-term predictor of HCC among patients infected with HCV.