Effects of Hypercholesterolemia and Statin Exposure on Survival in a Large National Cohort of Patients With Cirrhosis.

BACKGROUND & AIMS: Concerns related to hepatotoxicity frequently lead to discontinuation or non-initiation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase therapy in patients with cirrhosis despite data supporting statin use. We investigated the independent effects of hyperlipidemia and statin exposure on mortality, hepatic decompensation, and hepatocellular carcinoma development in a large national cohort of patients with cirrhosis.

METHODS: We performed a retrospective cohort study of patients with newly diagnosed cirrhosis from January 1, 2008 through June 30, 2016 in the Veterans Health Administration. Subjects were divided into 2 cohorts: 21,921 patients with prior statin exposure (existing users) and 51,023 statin-naïve individuals, of whom 8794 subsequently initiated statin therapy (new initiators) and 44,269 did not (non-initiators). Multivariable Cox proportional hazard models with inverse probability weighting were constructed to assess the effects of time-updating lipid profiles and cumulative exposure to statins on survival and hepatic decompensation. Statin-naïve new initiators were propensity matched with non-initiators to simulate a randomized controlled trial of statin use in cirrhosis.

RESULTS: In statin-naïve subjects, every 10-mg/dL increase in baseline total cholesterol was associated with a 3.6% decrease in mortality. In existing users, each year of continued statin exposure was associated with a hazard ratio of 0.920 (95% confidence interval 0.0.897-0.943) for mortality. After risk-set matching, each year of statin exposure among new initiators was associated with a hazard ratio of 0.913 (95% confidence interval 0.890-0.937) for mortality.

CONCLUSIONS: In a retrospective cohort study of veterans with a new diagnosis of cirrhosis, we associated hypercholesterolemia with well-preserved hepatic function and decreased mortality. Nonetheless, each cumulative year of statin exposure was associated with an independent 8.0%-8.7% decrease of mortality of patients with cirrhosis of Child-Turcotte-Pugh classes A and B.

Liver stiffness measurements in chronic hepatitis C: Treatment evaluation and risk assessment

BACKGROUND AND AIM: Liver stiffness (LS), measured by transient elastography, has been validated as a non-invasive surrogate for liver fibrosis. METHODS: We investigated the long-term predictive ability of LS for hepatocellular carcinoma (HCC) development and overall
survival in 1146 patients with chronic hepatitis C by using LS value at enrollment. We also investigated chronological changes in LS based on antiviral therapy and its outcome in 752 patients. **RESULTS:** During the mean follow-up period of 6.6 years, 190 patients developed HCC. Cumulative HCC incidence rates at 5 years were clearly stratified as 1.7% in the ≤ 5 kPa, 3.3% in 5.1-10 kPa, 16.7% in 10.1-15 kPa, 24.4% in 15.1-20 kPa, 36.3% in 20.1-25 kPa, and 43.7% in > 25 kPa subgroups (P < 0.001). Overall survival was also stratified: 10-year survival rates were 99.3% in the ≤ 5 kPa, 95.4% in 5.1-10 kPa, 81.4% in 10.1-15 kPa, 79.5% in 15.1-20 kPa, 66.1% in 20.1-25 kPa, and 49.1% in > 25 kPa subgroups (P < 0.001). LS decreased at a rate of 8.1% per year in those who achieved sustained virological responses, but increased at 0.1% per year in those who could not achieve sustained virological response instead of antiviral therapy, and increased at 3.7% per year in those who did not undergo antiviral therapy. **CONCLUSIONS:** Liver stiffness measurements can be useful in the prediction of HCC development and overall survival and in the evaluation of chronological changes in liver fibrosis grade during and after antiviral therapy.

**Maintenance interferon therapy in chronic hepatitis C patients who failed initial antiviral therapy: A meta-analysis.**

**OBJECTIVES:** To evaluate the effect of pegylated interferon maintenance therapy in patients with chronic hepatitis C who failed initial antiviral therapy. **METHODS:** This is a meta-analysis of 6 randomized controlled trials that met the eligibility criteria. In all, 2438 chronic hepatitis C patients who failed to achieve sustained virologic response after initial treatment with pegylated interferon and ribavirin (antiviral therapy nonresponders or relapers) were enrolled; 1237 patients received maintenance therapy (Maintenance group) and 1201 received no treatment (Observation group). **RESULTS:** The pooled analyses found that patients in the Maintenance group had a significantly higher rate of normal alanine aminotransferase than did patients in the Observation group (pooled odds ratio [OR] 4.436, 95% confidence interval [CI] 1.225-16.064, P=.023), but there was no significant difference between the 2 groups in the incidence of hepatocellular carcinoma (pooled OR 0.872, 95% CI 0.501-1.519, P=.630), or the mortality rate (pooled OR 1.564, 95% CI 0.807-3.032, P=.185). **CONCLUSIONS:** Interferon-based maintenance therapy in patients with chronic hepatitis C who failed initial antiviral therapy improved liver inflammation as indicated by blood chemistry (alanine aminotransferase).

**Real-world study of hepatitis C treatment with direct-acting antivirals in patients with drug abuse and opioid agonist therapy.**

**Background:** Limited data exist evaluating the treatment outcomes with direct-acting antivirals (DAAs) in patients with drug use in the community setting. We aim to assess the treatment response of DAAs in this subset of patients with or without the opioid agonist therapy (OAT). **Methods:** All the hepatitis C virus (HCV) infected patients treated with DAAs were retrospectively analyzed. Patients were stratified into two groups by the presence or absence of abusing alcohol, cocaine and heroin. All the patients who were assigned to the abuser group had positive urine toxicology with one of the drugs during the DAA treatment. The primary assessment was the sustained virologic response (SVR12) at 12 weeks post-treatment (SVR12). **Results:** Among the 314 patients, 152, 128 and 58 were patients with drug use, non-drug use and receiving OAT. Among the patients with injectable or non-injectable drug use treatment, completion rate was 99% (151/152) and SVR12 was 93.4%. Among the patients with no drug use treatment, completion rate was 95% (122/128) and SVR12 was 88.3%. Among patients
receiving OAT alone, SVR12 was 100%, and in patients with OAT + other drug use, SVR12 was 96.5%. None of the patients included in this study discontinued the treatment due to adverse events associated with treatment medications. **Conclusions:** In this community-based study, DAAs are safe, effective with high overall SVR12 in patients with active drug use (injectable and non-injectable) and OAT enrolled patients. These results support the removal of drug use as a barrier to DAA therapy.

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

**Maintenance interferon therapy in chronic hepatitis C patients who failed initial antiviral therapy: A meta-analysis.**

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**Clinicopathological features of HCV-positive splenic diffuse large B cell lymphoma**

The hepatitis C virus (HCV) is a single-stranded RNA virus which is thought to be involved in the onset of B cell lymphoma. HCV-positive diffuse large B cell lymphoma (DLBCL) has been reported to clinically manifest in extranodal lesions (e.g., in the liver, spleen, and stomach). Here, we investigated HCV-positive and -negative primary splenic DLBCL (p-spDLBCL) and non-primary splenic DLBCL (ordinary DLBCL). Furthermore, to examine HCV lymphomagenesis, RNA in situ hybridization (ISH), RT-PCR (reverse-transcription polymerase chain reaction), and NS3 immunostaining of HCV viral nonstructural proteins were performed. HCV-positive p-spDLBCL patients presented fewer B symptoms (asymptomatic) and better performance status, with elevated presence of splenic macronodular lesions and more germinal center B cell (GCB) sub-group cases than HCV-negative p-spDLBCL patients. However, HCV-positive ordinary DLBCL patients were found to have more non-GCB sub-group cases than HCV-negative ordinary DLBCL patients. HCV-positive DLBCL patients showed 20.6% (7/34) NS3 positivity, 16.7% (1/6) HCV-RNA in situ positivity, and 22.2% (2/9) detection of HCV-RNA in tumor tissue by RT-PCR. Splenic samples were found to have a higher frequency of HCV detection than lymph node samples, thus suggesting that HCV may be closely related to lymphomagenesis, especially in splenic lymphoma.
Use of Hepatitis C-Positive Liver Grafts in Hepatitis C-Negative Recipients.
As the demand for liver transplantation continues to rise, the scarcity of liver donor grafts has led to the use of extended criteria grafts for liver transplantation in select group of patients. Hepatitis C-seropositive liver grafts have been used primarily in hepatitis C-positive recipients, with studies showing non-inferior outcomes when compared to hepatitis C-negative grafts. Studies suggest that hepatitis C serology status of the donor liver does not influence the patient or graft outcomes in the recipient. These results advocate for offering hepatitis C-positive grafts to all patients awaiting liver transplantation regardless of their hepatitis C status. However, some concerns persist regarding the ethics of potentially introducing a new infection into a patient that could progress to chronic liver disease following liver transplantation. The recent approval of direct-acting antiviral therapy offers a solution to this dilemma, as it has changed the landscape of hepatitis C management by making it a curable disease. In this review, we shall discuss the current evidence regarding the use of hepatitis C-seropositive donor grafts in hepatitis C-positive and hepatitis C-negative patients.

Effects of oral hygiene programme and home phone counselling for hepatitis C patients receiving antiviral treatment.
To explore the effectiveness of an oral hygiene programme combined with home phone counselling on hepatitis C patients during antiviral treatment. BACKGROUND: Hepatitis C virus infection is the leading cause of liver diseases. Evidence indicates that the antiviral treatment for hepatitis C virus infection has been successful, albeit its many side effects, such as discomfort symptoms of oral ulcers, which, in turn, leads to discontinued treatment. Inappropriate oral hygiene may worsen the side effects and increase the risk of dropping out of the treatment. DESIGN: A quasi-experimental pre-post-test design was used. METHODS: The oral hygiene programme was based on a standardized protocol of oral health care combined with home phone counselling. The participants were recruited from an outpatient clinic between August 2016 and July 2017. The generalized estimating equation was used for repeated measures of oral health behaviour, oral health status and discomfort symptoms. FINDINGS: Thirty-four participants completed this study. The findings indicated that the oral hygiene programme significantly improved tooth brushing, use of dental floss and oral comfort. The result showed that the participants' oral health status significantly improved in 3 months. CONCLUSIONS: This pilot study supports the finding that an oral hygiene programme can reduce oral discomfort, improve oral hygiene behaviour, and enhance the oral health status of hepatitis C patients receiving treatment. This is a simple and low-cost programme, which can be performed at home easily and boosts the completion of antiviral treatment.

HIV/HCV Coinfection

Hepatitis C treatment uptake and response among human immunodeficiency virus/hepatitis C virus-coinfected patients in a large integrated healthcare system.
U.S. guidelines recommend that patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) be prioritized for HCV treatment with direct-acting antiviral agents (DAAs), but the high cost of DAAs may contribute to disparities in treatment uptake and outcomes. We evaluated DAA initiation and effectiveness in HIV/HCV-coinfected patients in a U.S.-based healthcare system during October 2014-December 2017. Of 462 HIV/HCV-coinfected patients, 276 initiated DAAs (70% cumulative proportion treated over three years).
Lower likelihood of DAA initiation was observed among patients with Medicare (government-sponsored insurance) versus commercial insurance (adjusted rate ratio [aRR] = 0.62, 95% CI = 0.46-0.84), patients with drug abuse diagnoses (aRR = 0.72, 95% CI = 0.54-0.97), patients with CD4 cell count <200 cells/µl versus ≥500 (aRR = 0.45, 95% CI = 0.23-0.91), and patients without prior HCV treatment (aRR = 0.68, 95% CI = 0.48-0.97). There were no significant differences in DAA initiation by age, gender, race/ethnicity, socioeconomic status, HIV transmission risk, alcohol use, smoking, fibrosis level, HIV RNA levels, antiretroviral therapy use, hepatitis B infection, or number of outpatient visits. Ninety-five percent of patients achieved sustained virologic response (SVR). We found little evidence of sociodemographic disparities in DAA initiation among HIV/HCV-coinfected patients, and SVR rates were high. Efforts are needed to increase DAA uptake among coinfected Medicare enrollees, patients with drug abuse diagnoses, patients with low CD4 cell count, and patients receiving first-time HCV treatment.

**Higher relapse rate among HIV/HCV-coinfected patients receiving sofosbuvir/ledipasvir for 8 vs 12 weeks.**

**OBJECTIVES:** To compare the efficacy of sofosbuvir/ledipasvir (SOF/LDV) for 8 weeks (SL8) versus a 12-week course of SOF/LDV (SL12) among HIV/HCV-coinfected patients in clinical practice. In addition we compared sustained virological response (SVR) rates achieved with SL8 in HCV-monoinfected and HIV/HCV-coinfected patients in a real life setting.

**METHODS:** HCV-infected patients were retrospectively selected from the HEPAVIR-DAA and GEHEP-MONO real-life prospective cohorts if they fulfilled the following criteria: 1) Infected with genotype 1; 2) Treatment with SL8 or SL12; 3) Treatment naïve prior to receiving SL8 or SL12; 4) Absence of cirrhosis; 5) Baseline HCV RNA <6 × 106 IU/mL; 6) Reached the scheduled time-point for SVR (SVR12) assessment. SVR12 and relapse rates of HCV-monoinfected and HIV/HCV-coinfected patients were compared on an intention to treat basis. The responses with SL8 and SL12 were also compared. **RESULTS:** In the SL8 group, 107 (51%) HCV-monoinfected and 102 (49%) HIV/HCV-coinfected patients were included. One hundred and sixty-four (43%) HCV-monoinfected subjects and 220 (57%) HIV/HCV-coinfected patients received SL12. SVR12 rates for HIV/HCV-coinfected patients treated with SL8 vs SL12 were SVR12 92.2% vs. 97.3% (p = 0.044) and the respective relapse rates were 4.9% vs. 0.5% (p = 0.013). SVR12 rates for SL8 among HCV-monoinfected and HIV/HCV-coinfected patients were: 96.3% vs. 92.2% (p = 0.243), respectively. The corresponding relapse rates were 0.9% vs. 4.9% (p = 0.112). **CONCLUSION:** HIV/HCV-coinfected patients reach high rates of SVR12 with SL8, although lower than with SL12, mainly due to a higher probability of relapse. SVR12 rates with SL8 are numerically lower and the proportion of relapses higher in HIV/HCV-coinfected patients than in HCV-monoinfected subjects.

**Immunological recovery in T-cell activation after sustained virologic response among HIV positive and HIV negative chronic Hepatitis C patients.**

**BACKGROUND:** Rapid decreases in activated CD4+ and CD8+ (HLA-DR+ and CD38+ co-expressed) T-lymphocytes have been described within 1-2 weeks of initiating direct-acting antiviral (DAA) therapy among chronic Hepatitis C (CHC) patients. However, it is not known whether these changes are maintained past sustained virologic response (SVR), particularly in those who are HIV/HCV-coinfected. **METHODS:** We investigated the changes in immune parameters of T-lymphocytes from pre-DAA therapy to post-SVR among HIV negative and HIV positive patients with CHC. Repeated measurements of activated CD4+ and CD8+ T cells were
analyzed by flow cytometry at pre-DAA therapy, DAA therapy, end of treatment, SVR, and post-SVR. A general linear model for repeated measurements was used to estimate the mean outcome at each timepoint and change between timepoints. **RESULTS:** HCV-monoinfected (n = 161) and HIV/HCV-coinfected (n = 59) patients who achieved SVR with DAA therapy were predominately middle aged, male, black, and non-cirrhotic. At pre-DAA therapy, HCV-monoinfected patients had significantly higher CD4+ T cells and CD4+:CD8+ T-cell ratio, while significantly lower CD8+ and activated CD4+ and CD8+ T cells compared to HIV/HCV-coinfected patients (p < 0.0001). HCV-monoinfected and HIV/HCV-coinfected patients had a significant mean decrease from pre-DAA therapy to post-SVR year 1 for activated CD4+ (HCV-monoinfected: 4.8-3.9%, p < 0.0001; HIV/HCV-coinfected: 6.6-4.5%, p < 0.0001) and activated CD8+ T cells (HCV-monoinfected V: 13.8-11.8%, p = 0.0002; HIV/HCV-coinfected: 18.0-12.4%, p < 0.0001). **CONCLUSION:** This longitudinal study showed CHC patients treated with DAA therapy had continued decrease of T-lymphocytes from start of DAA therapy to after achievement of SVR suggesting improvement as HCV clearance normalizes activated T-cell phenotype.

**Clinical outcomes in HIV+/HCV+ coinfect ed kidney transplant recipients in the pre- and post-direct-acting antiviral therapy eras: 10-Year single center experience.**

**BACKGROUND:** Previous studies have demonstrated inferior patient and graft survival following kidney transplant (KT) in HIV+/HCV+ coinfected patients compared to HIV+/HCV-recipients. However, these studies were conducted prior to the availability of direct-acting antiviral (DAA) agents and data in the modern era are lacking. **METHODS:** Single center retrospective study of HIV+/HCV+ coinfect ed KT recipients (2007-2017). Outcomes were assessed for the pre-DAA and post-DAA (ie, after December 2013) eras including 1-year patient survival, death-censored graft survival, and acute rejection; and serious infections (defined as infections requiring admission to the intensive care unit during initial transplant hospitalization or re-admission to the hospital after discharge) within the first 6 months post-transplant.

**RESULTS:** A total of 13 consecutive HIV+/HCV+ recipients were identified. Median time of post-transplant follow-up was 722 days. Seven patients were transplanted in the DAA era; five of them had anti-HCV Ab+ donors, with two donors being HCV NAT positive; all received DAA therapy, six of them post-transplant (median time from KT to DAA: 83 days; IQR, 54-300). All the patients in the pre-DAA era were on a protease inhibitor-containing ART regimen. One-year patient and death-censored graft survivals were 83% and 67%, respectively, for the patients transplanted in the pre-DAA era, and 100% for both outcomes in the subgroup of patients transplanted in the post-DAA era (P > 0.05). Compared to patients in the post-DAA era, those in the pre-DAA era had higher incidence of serious infections (0 vs 67%; P = 0.02). Acute rejection exclusively occurred in the pre-DAA group (n = 1; 17%). **CONCLUSIONS:** Outcomes of HIV+/HCV+ KT recipients, including HIV-/HCV+ to HIV+/HCV+ transplants, in the DAA era were excellent in this small cohort. Larger studies are needed.
Outcomes of treatment for hepatitis C in prisoners using a nurse-led, statewide model of care

BACKGROUND & AIMS: Treatment programs for people who inject drugs (PWID), including prisoners, are important for achieving hepatitis C elimination targets. There are multiple barriers to treatment of hepatitis C in prisons, including access to specialist physicians, testing and antiviral therapy, short prison sentences, and frequent inter-prison transfer. We aimed to assess the effectiveness of a nurse-led model of care for the treatment of prisoners with hepatitis C.

METHODS: A statewide program for assessment and management of hepatitis C was developed in Victoria, Australia to improve access to care for prisoners. This nurse-led model of care is supported by telemedicine to provide decentralized care within all prisons in the state. We prospectively evaluated the feasibility and efficacy of this nurse-led model of care for hepatitis C within the 14 adult prisons over a 13-month period. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12) using per protocol analysis.

RESULTS: There were 416 prisoners included in the analysis. The median age was 41 years, 90% were male, 50% had genotype 3 and 44% genotype 1 hepatitis C and 21% had cirrhosis. Injecting drug use was reported by 68% in the month prior to prison entry, 54% were receiving opioid substitution therapy, and 86% reported never previously engaging with specialist HCV care. Treatment duration was 8 weeks in 24%, 12 weeks in 59%, and 24 weeks in 17% of treatment courses. The SVR12 rate was 96% (301/313) per protocol. Inter-prison transfer occurred during 26% of treatment courses but was not associated with lower SVR12 rates. No treatment-related serious adverse events occurred.

CONCLUSION: Hepatitis C treatment using a decentralized, nurse-led model of care is highly effective and can reach large numbers of prisoners. Large scale prison treatment programs should be considered to support hepatitis C elimination efforts.

LAY SUMMARY: There is a high burden of hepatitis C infection among prisoners worldwide. Prisoners who continue to inject drugs are also at risk of developing new infections. For this reason, the prison setting provides an opportunity to treat those people at greatest risk of infection and to stop transmission to others. We developed a new method of providing hepatitis C treatment to prisoners, in which nurses rather than doctors assessed prisoners locally at each prison site. Treatment was safe and most prisoners were cured. Such programs will contribute greatly to achieving the World Health Organization's hepatitis C elimination goals.

Barriers and facilitators of hepatitis C treatment uptake among people who inject drugs enrolled in opioid treatment programs in Baltimore.

BACKGROUND: Hepatitis C virus (HCV) infection is a major public health issue among people who inject drugs (PWID) with prevalence of 50-80% in the United States. Effective, simple, oral direct acting agents (DAA) of short duration with minimal side effects have been associated with cure rates > 95%. However, HCV treatment uptake among PWID remains low. We characterized the HCV care continuum, HCV treatment knowledge, as well as barriers and facilitators to HCV treatment uptake among PWID enrolled in two opioid treatment programs (OTPs) in Baltimore, Maryland, USA.

METHODS: Between July and November 2016, 124 HCV infected PWID were recruited from two opioid treatment programs in Baltimore through convenience sampling. Participants completed a 50-item questionnaire to assess HCV treatment knowledge, attitudes, and practices. Progress through the HCV care continuum was assessed
based on a series of questions assessing evaluation for HCV treatment, recommendation for HCV treatment by a provider, and HCV treatment initiation. HCV status was assessed based on participant self-report. RESULTS: The median age was 52 years (IQR 44-58), 56% were male, the majority were African American (69%), and 19% reported HIV co-infection. Participants had been tested for HCV at their primary care provider’s (PCP’s) office (34%), drug treatment center (20%), emergency room (11%), or prison (9%), and most (60%) had been diagnosed with HCV over 5 years prior. The majority reported that HCV was a major health concern for them (91%), were aware there were new treatments for HCV (89%), and that the new treatments cure most people (69%). More than half (60%) had seen a health professional who could treat HCV, 40% had HCV therapy recommended by their HCV specialist, and 20% had started or completed treatment. In univariable analysis, PWID were significantly more likely to have been treated if they were HIV co-infected (OR 3.4 (95% CI 1.3-9.2)) or had a partner or friend concerned about their HCV (OR 3.4 (95% CI 1.2-9.7)), and were significantly less likely to have been treated if they had used any illicit drugs in the preceding 6 months (OR 0.4 (95% CI 0.2-0.99). In multivariable analysis, having a friend or partner concerned about their HCV remained significantly associated with HCV treatment (OR 5.0 (95% CI 1.4-17.7)). When questioned about what would facilitate HCV treatment, the majority (85%) reported that a friend telling them that HCV treatment had helped them and having HCV treatment provided at their opioid treatment program would make them more likely to engage in HCV treatment. CONCLUSION: Despite a high prevalence of HCV among opioid treatment program patients and the availability of effective treatments, uptake remains low. We identified several key barriers and facilitators that can affect HCV treatment uptake.

Strategies for Improving Hepatitis C Treatment Access in the United States: State Officials Address High Drug Prices, Stigma, and Building Treatment Capacity.

CONTEXT: Curative treatments for hepatitis C virus (HCV) can alter the course of a devastating epidemic, but high drug prices have contributed to restrictions on HCV treatment access. OBJECTIVE: We aimed to learn how state health agencies have responded to the challenges of treatment access for HCV. DESIGN: Qualitative study using semistructured key informant interviews focused on aspects of HCV treatment access between June 2016 and March 2017. Content analysis was used to identify dominant themes. SETTING: United States. PARTICIPANTS: Eighteen health officials and treatment advocates across 6 states selected using purposive sampling. RESULTS: Drug pricing is the most important barrier to access, encouraging restrictive authorization criteria from payers that in turn discourage providers from offering treatment. However, payers have not experienced the budget impact that was initially feared. Although authorization criteria are being lifted for fee-for-service Medicaid programs, ensuring that managed care organizations follow suit remains a challenge. The effect of stigma, a shortage of treating providers, and lack of political motivation are additional challenges to expanding treatment. The response to the human immunodeficiency virus epidemic can augment or inform strategies for HCV treatment delivery, but this is limited by the absence of dedicated funding. CONCLUSIONS: While treatment eligibility criteria for HCV treatment are improving, many other barriers remain to achieving the scale-up needed to end the epidemic. Political disinterest, stigma, and a lack of specialty providers are continued barriers in some jurisdictions. States may need to invest in strategies to overcome these barriers, such as engaging in public and provider education and ensuring that treatment by primary care providers is
reimbursed. Despite uncertainty about how federal policy changes to Medicaid may affect states' ability to respond, states can identify opportunities to improve access.

**HEPATOCELLULAR (LIVER) CANCER**

**Drug-eluting bead transarterial chemoembolization (TACE) vs conventional TACE in treating hepatocellular carcinoma patients with multiple conventional TACE treatments history: A comparison of efficacy and safety.**

This study aimed to compare the efficacy and safety of drug-eluting bead transarterial chemoembolization (DEB-TACE) vs conventional TACE (cTACE) in hepatocellular carcinoma (HCC) patients with multiple cTACE treatments history. Eighty-one HCC patients with multiple cTACE treatments history who underwent DEB-TACE (N=42) and cTACE treatment (N=39) were included in this retrospective cohort study and allocated to DEB-TACE and cTACE groups accordingly. Multiple cTACE treatments history was defined as history of three or more cycles cTACE treatments. Then treatment responses were assessed according to the criteria of modified Response Evaluation Criteria in Solid Tumors (mRECIST), and progression free survival (PFS), as well as overall survival (OS), was calculated. In addition, adverse events and liver function related indexes were recorded. Complete response (P=.167) was of no difference while objective response rate (ORR) (P=.003) was increased in DEB-TACE group compared with cTACE group. Patients in DEB-TACE group presented with more favorable PFS (P=.028) and OS (P=.037) compared with cTACE group. Further analysis revealed that DEB-TACE (vs cTACE) was an independent predictive factor for better ORR (P=.001), PFS (P=.006) and OS (P=.001). The albumin (ALB) level at first month after treatment was elevated (P=.015) while the other liver function indexes levels did not vary (all P>.05) in DEB-TACE group compared with cTACE group. The incidences of pain (P=.327), fever (P=.171) and nausea/vomiting (P=.400) during hospitalization were similar between the 2 groups. DEB-TACE is more efficient and equally tolerant compared with cTACE in HCC patients with multiple cTACE treatments history.

**Efficacy of anti-PD-1 antibody SHR-1210 as second-line treatment in hepatocellular carcinoma patient with sorafenib resistance: A case report.**

**RATIONALE:** Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, is an aggressive tumor with very poor prognosis. Regorafenib was the first agent to show a survival benefit over placebo in patients who showed progression while being treated with sorafenib, but it remains an unsatisfactory agent owing to its serious side effects. Therefore, more efficient and milder therapies are needed. **PATIENT CONCERNS:** Herein, we report a patient with advanced HCC with many lung metastases who showed progression during sorafenib treatment. **DIAGNOSES:** HCC with lung metastases (stage IVB). **INTERVENTIONS:** SHR-1210 alone was used as second-line treatment. **OUTCOMES:** Although the lung metastases did not decrease 3 months after the treatment, they decreased significantly at 6 months after the treatment and partially disappeared. The tumor response indicated partial response. Furthermore, all of the lung metastases continued to decrease at about 17 months after treatment. The alpha-fetoprotein levels showed a similar trend. After a follow up of 19 months, the patient remains in good health.
The association of liver function and quality of life of patients with liver cancer.

BACKGROUND: Quality of life (QOL) assessments with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-HCC18, C30 and HCC18 index scores have been shown to be prognostic factors for overall survival (OS) in patients with hepatocellular carcinoma (HCC), independent of disease stage and liver function. Liver function parameters (including bilirubin, albumin, international normalized ratio [INR], Child-Pugh class, ALBI grade, MELD, alkaline phosphatase [ALP]-to-platelet ratio, albumin-to-ALP ratio) have also been found to be independent prognostic factors for OS in HCC patients. There has been scanty data on whether QOL and baseline liver function per se are correlated in HCC patients. This study investigates the correlations between baseline QOL data and liver function variables in HCC patients. METHODS: From 2007 to 2011, 517 patients were enrolled. Baseline QOL was assessed at diagnosis using the EORTC QLQ-C30 and QLQ-HCC18; thereafter C30 and HCC18 index scores were derived. Clinical and laboratory data were collected. For liver function assessment, Child-Pugh class, ALBI grade, MELD, ALP-to-platelet ratio and albumin-to-ALP ratio were derived. Correlation analyses were performed between QOL and liver function data. RESULTS: Complete QOL data were available in 472 HCC patients. After adjusting for clinical variables, significant correlations were found between QOL (QLQ-C30 and QLQ-HCC18) and dichotomized liver function variables (including Child-Pugh class, ALBI grade and the presence of ascites). It was demonstrated that QOL had significant and potentially clinically important correlations with continuous liver function variables (albumin, bilirubin, ALP and albumin-to-ALP ratio), with the highest Spearman's rank correlation coefficient (rho) exceeding 0.4. HCC18 and C30 index scores were also significantly correlated with these liver function variables. HCC18 index score, which had rho up to 0.37, generally performed better than C30 index score, which had rho up to 0.33. CONCLUSIONS: In HCC patients, baseline QOL assessment (using EORTC QLQ-C30, QLQ-HCC18, C30 index-score or HCC18 index-score) is significantly correlated with liver function. Based on the findings of this study, future trials are warranted to assess whether treatment to enhance liver function could improve HCC patients' QOL.

A robust culture method for maintaining tumorigenic cancer stem cells in the hepatocellular carcinoma cell line Li-7.

Cancer tissues contain small populations of highly tumorigenic cells termed cancer stem cells (CSCs). Immortalized cell lines containing CSCs are valuable and powerful experimental tools for research into the characteristics of these stem cells. We previously reported that the hepatocellular carcinoma cell line Li-7 includes abundant CD13+ CD166- CSCs; however, the number of these cells decreases after long-term culture as a result of differentiation to non-CSC populations. To ensure consistent and reproducible results in experiments using Li-7 cells, it is important that the CSC population is maintained stably regardless of culture duration and passage. In the present study, we found that a commercially available culture medium for maintenance of embryonic stem cells and induced pluripotent stem cells, mTeSR1, effectively prevented spontaneous differentiation by CD13+ CD166- cells to CD13- CD166+ cells and therefore maintained the CSC population in Li-7 cell cultures. CD13+ CD166- CSCs maintained using this culture medium retained high tumorigenicity after transplantation into mice; they also showed the ability to differentiate in vitro into non-CSC populations in RPMI-1640 with 10% FBS medium. We analyzed gene expression profiles of CSC and non-CSC populations in Li-7 cultures using an RNA sequencing method. Genes such as FGFR, NOTCH1, and JAG1, that are
associated with tumorigenicity and stemness, were upregulated in the CSC population. Our results suggest that CSCs can be maintained in immortalized cancer cell lines cultured over an extended period using a medium developed for culture of embryonic/induced pluripotent stem cells.

**Role of VDR, GC, and CYP2R1 Polymorphisms in the Development of Hepatocellular Carcinoma in Hepatitis C Virus-Infected Patients.**

**Aims:** This study was designed to determine if vitamin D receptor (VDR), carrier globulin/ binding protein (GC), and cytochrome P-450 family 2, subfamily R, polypeptide 1 (CYP2R1) gene polymorphisms are risk factors in the development of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients from Northeast India. **Materials and Methods:** A total of 351 HCV-infected patients were enrolled of which 167 were diagnosed with chronic hepatitis C (CHC), 124 with liver cirrhosis (LC), and 60 with HCC together with 102 age- and sex-matched healthy controls. VDR (BsmI, ApaI, and TaqI), GC (rs4588, rs7051), and CYP2R1 (rs10741657) gene polymorphisms were genotyped for all subjects. Statistical data were analyzed using SPSS ver. 22.0. **Results:** The frequency of the ApaI CC genotype, ApaI C allele, and bAt haplotype of the VDR gene was significantly higher in HCC and LC patients than controls. After adjusting for other covariates (age, gender, platelet count, AST, ALT, serum albumin, and viral load) logistic regression analysis showed that the ApaI CC genotype and bAt haplotype were independent predictors of HCC development. No significant associations was found for the GC and CYP2R1 polymorphisms examined with the occurrence of HCC. **Conclusions:** The presence of the VDR ApaI CC genotype and bAt haplotype appear to be important indicators in the development of HCC among HCV-infected patients. Larger studies are needed to further clarify and establish this potential causal relationship.

**Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study.**

**BACKGROUND & AIMS:** There is controversy over the effects of direct-acting antiviral (DAA) therapies for hepatitis C virus (HCV) infection on hepatocellular carcinoma (HCC) recurrence and tumor aggressiveness. We compared HCC recurrence patterns between DAA-treated and untreated HCV-infected patients who had achieved a complete response to HCC treatment in a North American cohort. **METHODS:** We conducted a retrospective cohort study of patients with HCV-related HCC with a complete response to resection, local ablation, transarterial chemo- or radioembolization, or radiation therapy from January 2013 through December 2017 at 31 health systems throughout the United States and Canada. Cox regression was used to examine the association between DAA therapy and time to recurrence after a complete response, with DAA therapy analyzed as a time-varying exposure. We also estimated the association between DAA therapy and risk of early HCC recurrence (defined as 365 days after complete response). **RESULTS:** Of 793 patients with HCV-associated HCC, 304 (38.3%) received DAA therapy and 489 (61.7%) were untreated. HCC recurred in 128 DAA-treated patients (42.1%; early recurrence in 52 patients) and 288 untreated patients (58.9%; early recurrence in 227 patients). DAA therapy was not associated with HCC recurrence (hazard ratio 0.90, 95% confidence interval 0.70-1.16) or early HCC recurrence (hazard ratio 0.96, 95% confidence interval 0.70-1.34) after we adjusted for study site, age, sex, Child-Pugh score, α-fetoprotein level, tumor burden, and HCC treatment modality. In DAA-treated and untreated patients, most recurrences were within the Milan criteria (74.2% vs 78.8%; P = .23). A larger
proportion of DAA-treated than untreated patients received potentially curative HCC therapy for recurrent HCC (32.0% vs 24.6%) and achieved a complete or partial response (45.3% vs 41.0%) but this did not achieve statistical significance. **CONCLUSION:** In a large cohort of North American patients with complete response to HCC treatment, DAA therapy was not associated with increased overall or early HCC recurrence. HCC recurrence patterns, including treatment response, were similar in DAA-treated and untreated patients.