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### CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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#### [Evaluation of cerebrovascular reactivity in chronic hepatitis C patients using transcranial color Doppler.](#)

Hepatitis C viral (HCV) infection is associated with systemic inflammation and metabolic complications that might predispose patients to atherosclerosis, including cerebrovascular atherosclerosis. The aim of this study was to assess cerebrovascular reactivity in patients with chronic hepatitis C. Seventeen patients with chronic hepatitis C infection, as well as 11 healthy blood donors in the control group, were assessed for cerebrovascular reactivity according to the well-established breath-holding test that uses the transcranial color Doppler for measurement of blood flow velocity. Results obtained during the breath-holding revealed significantly lower average peak systolic (AvPS start,  $P = 0.018$ ), end-diastolic (AvED start,  $P = 0.031$ ) and mean velocity values at the very beginning of the breath-holding procedure (AvmeanV start,  $P = 0.02$ ), as well as a lower mean peak systolic velocity at the end of the breath-holding test (AvPS max,  $P = 0.02$ ) in the hepatitis C group. Vascular reactivity values, calculated as the breath-holding index, were also significantly lower ( $P = 0.045$ ) in the hepatitis C group. In conclusion, the results of this study suggest an association between chronic HCV infection and altered cerebrovascular reactivity which may ultimately have an unfavorable effect on cerebrovascular hemodynamics and lead to increased risk of cerebrovascular diseases.

#### [The contribution of telemedicine to hepatitis C elimination in a correctional facility.](#)

**BACKGROUND:** micro-elimination has been recently proposed as an efficient strategy to achieve global hepatitis C virus (HCV) elimination. The Spanish Health Ministry Strategic Plan for hepatitis C infection highlighted intervention in prisons as a priority action. However, there are important barriers associated with the specialized care provision to the penitentiary population. **AIMS:** to assess the contribution of telemedicine for HCV elimination in a correctional facility in Spain. **METHODS:** an open label program of HCV elimination via telemedicine was started on February 3rd, 2015 in a large penitentiary of 1,200 inmates, as an alternative to referring patients to specialists. An anonymous satisfaction survey was performed among a random sample of inmates and all participating doctors. **RESULTS:** the prevalence of HCV viremia prior to program initiation was 12.4%. One hundred and thirty-one patients received DAA HCV treatment during the period 2015-2018; 42.74% had a HCV-HIV co-infection. Overall, 97% achieved a sustained virological response (SVR). A second regime of

DAA successfully rescued non-responder patients and the HCV prevalence was zero at the end of the program. Satisfaction was high or very high according to 67% of inmates and all participating doctors. **CONCLUSION:** telemedicine is an effective tool for HCV elimination in penitentiary correctional facilities where referral to specialists is difficult. The extensive use of this technology should be recommended in this setting in order to facilitate equitable access to specialized care.

### [Recurrent hyperkalemia in patients with chronic kidney disease and hepatitis C treated with direct antiviral agents.](#)

**BACKGROUND:** Sofosbuvir is the keystone of direct antiviral agents for the chronic hepatitis C (CHC). The safety of sofosbuvir in patients with stage 4-5 chronic kidney disease (CKD) needs further observation in real world. **CASE PRESENTATION:** Thirty-three patients with stage 5 CKD and hepatitis C virus (HCV) infection from 2 hemodialysis centers accepted sofosbuvir based treatment as we reported previously. Serum potassium concentrations were tested every 4 weeks or on demand. Ten of 33 patients showed recurrence of hyperkalemia. We summarized the characteristics of hyperkalemia occurrence in these 10 patients. Overall, 24 episodes of hyperkalemia were observed in these 10 patients, 21 were under treatment and 3 were after treatment. Patients with or without hyperkalemia before sofosbuvir treatment didn't show significantly differences in the median frequencies of hyperkalemia episodes during the observation period (3.5 vs. 2,  $p = 0.264$ ). **CONCLUSIONS:** Patients with stage 5 CKD and HCV infection treated with sofosbuvir based regimens, even halved sofosbuvir, should be taken caution and closely monitoring serum potassium and renal function is necessary.

### [Patient Sex in the Setting of Liver Transplant in Alcoholic Liver Disease.](#)

**OBJECTIVES:** The aim of this study was to analyze alcoholic cirrhosis in women who were to undergo liver transplant, including their biochemical and clinical characteristics, main complications, survival rates, and main causes of death compared with men with alcoholic cirrhosis. **MATERIALS AND METHODS:** Our study included 400 patients with alcoholic cirrhosis, which we divided according to sex and viral infections. Biochemical parameters and the presence and degree of ascites and encephalopathy, liver function status, and liver rejection and survival rates were analyzed from 1 to 10 years and the main cause of death at 10 years. **RESULTS:** Patients with nonviral alcoholic cirrhosis and liver transplant had significantly better survival rates (84.1%) at 1 year versus those with viral alcoholic cirrhosis (74.5%;  $P = .036$ ). Men with nonviral alcoholic cirrhosis (14%) and women with hepatitis C virus (29%) had the lowest short-term survival rates. In long-term survival analysis, the lowest rate was observed in women with nonviral alcoholic cirrhosis (26.1%), and the highest rate was observed in women with hepatitis C virus (42.9%). Liver graft failure was one of the main causes of death in male patients (19.5%). **CONCLUSIONS:** Women with alcoholic cirrhosis showed a higher rate of ascites and encephalopathy but lower liver graft rejection than men with alcoholic cirrhosis. Survival rates were similar between men and women, although slightly lower in women who had hepatitis C virus.

### [A case report of psychiatric symptoms following direct-acting antiviral and ribavirin combination therapy for chronic hepatitis C in a patient with innate anxiety.](#)

**BACKGROUND:** Direct-acting antivirals (DAAs) result in a highly sustained virological response rate and better patient tolerance. However, this therapeutic approach may, on rare

occasions, give rise to psychiatric symptoms. We describe a case requiring discontinuation of DAA and ribavirin combination therapy due to psychiatric symptoms in a patient with congenital anxious personality traits. The information summarized here will be helpful to physicians treating chronic hepatitis C virus (HCV) infection in patients with underlying psychiatric problems. **CASE PRESENTATION:** A 57-year-old Japanese woman diagnosed with chronic HCV infection was prescribed DAA and ribavirin combination therapy. She had a history of mild innate anxiety and development of psychiatric symptoms due to interferon (IFN) therapy 8 years prior, which subsided with discontinuation of the therapy. Similar psychiatric symptoms such as enervation, palpitations, an episode of hyperventilation, and consciousness disturbances with myotonia were observed after the administration of the antiviral agents. No abnormal findings related to her symptoms were observed on laboratory or imaging results. Psychiatrists diagnosed the patient as having a somatization disorder induced by the antiviral agents on the basis of innate anxiety. After the discontinuation of therapy, her symptoms gradually improved. **CONCLUSIONS:** Although DAAs were not causative factors for psychiatric symptoms in phase 3 studies, a post-marketing study reported psychiatric symptoms such as depression in patients with underlying psychiatric problems. Our case suggests psychiatric symptoms might worsen after DAA and ribavirin administration in patients with underlying psychiatric disorders, and therefore, close monitoring is necessary for these patients, especially if they have a history of psychiatric symptoms after IFN.

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## **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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### **[The Role of Micronutrients in the Infection and Subsequent Response to Hepatitis C Virus](#)**

Micronutrient deficiencies develop for a variety of reasons, whether geographic, socioeconomic, nutritional, or as a result of disease pathologies such as chronic viral infection. As micronutrients are essential for a strong immune response, deficiencies can significantly dampen both the innate and the adaptive arms of antiviral immunity. The innate immune response in particular is crucial to protect against hepatitis C virus (HCV), a hepatotropic virus that maintains chronic infection in up to 80% of individuals if left untreated. While many micronutrients are required for HCV replication, an overlapping group of micronutrients are also necessary to enact a potent immune response. As the

is responsible for the storage and metabolism of many micronutrients, HCV persistence can influence the micronutrients' steady state to benefit viral persistence both directly and by weakening the antiviral response. This review will focus on common micronutrients such as zinc, iron, copper, selenium, vitamin A, vitamin B12, vitamin D and vitamin E. We will explore their role in the pathogenesis of HCV infection and in the response to antiviral therapy. While chronic hepatitis C virus infection drives deficiencies in micronutrients such as zinc, selenium, vitamin A and B12, it also stimulates copper and iron excess; these micronutrients influence antioxidant, inflammatory and immune responses to HCV.

### **[Changes in the Serum Hepcidin-to-ferritin Ratio with Erythroferrone after Hepatitis C Virus Eradication Using Direct-acting Antiviral Agents.](#)**

Objective Hepcidin is a master iron regulator hormone produced by the liver, but precise mechanism underlying its involvement in iron overload in hepatitis C virus (HCV) infection remains unclear. We investigated the serum hepcidin levels against iron overload before and after HCV eradication. Methods We prospectively investigated the iron metabolism

characteristics in 24 patients with HCV genotype 1b infection before and after treatment. We also assessed the serum erythroferrone (ERFE) levels to investigate its association with iron metabolism changes. Patients were treated with Ledipasvir 90 mg and Sofosbuvir 400 mg once daily for 12 weeks and observed for 12 more weeks in order to evaluate their sustained virological response. Results Serum hepcidin levels at baseline were in the normal range, although serum ferritin levels were increased. After HCV eradication, both serum ferritin and hepcidin levels were significantly decreased at 24 weeks from baseline ( $p < 0.001$ ,  $p = 0.006$ , respectively). However, the serum hepcidin-to-ferritin ratios were significantly increased ( $p < 0.001$ ). In addition, the serum ERFE levels were significantly decreased ( $p < 0.001$ ). Increases in the serum hepcidin-to-ferritin ratios were correlated with decreases in the serum ERFE levels ( $r = -0.422$ ,  $p = 0.039$ ). Conclusion Serum hepcidin levels were relatively low against ferritin levels in HCV infection. However, after HCV eradication, the serum hepcidin-to-ferritin ratios were increased. These results indicate the improvement of inadequate hepcidin secretion against iron overload after HCV eradication. Downregulation of ERFE may have affected the improvement of iron metabolism.

### [Identification of Keratin 23 as a Hepatitis C Virus-Induced Host Factor in the Human Liver.](#)

Keratin proteins form intermediate filaments, which provide structural support for many tissues. Multiple keratin family members are reported to be associated with the progression of liver disease of multiple etiologies. For example, keratin 23 (KRT23) was reported as a stress-inducible protein, whose expression levels correlate with the severity of liver disease. Hepatitis C virus (HCV) is a human pathogen that causes chronic liver diseases including fibrosis, cirrhosis, and hepatocellular carcinoma. However, a link between KRT23 and hepatitis C virus (HCV) infection has not been reported previously. In this study, we investigated KRT23 mRNA levels in datasets from liver biopsies of chronic hepatitis C (CHC) patients and in primary human hepatocytes experimentally infected with HCV, in addition to hepatoma cells. Interestingly, in each of these specimens, we observed an HCV-dependent increase of mRNA levels. Importantly, the KRT23 protein levels in patient plasma decreased upon viral clearance. Ectopic expression of KRT23 enhanced HCV infection; however, CRISPR/Cas9-mediated knockout did not show altered replication efficiency. Taken together, our study identifies KRT23 as a novel, virus-induced host-factor for hepatitis C virus.

### [Assessing the Safety of Direct-Acting Antiviral Agents for Hepatitis C](#)

**IMPORTANCE:** Recent reports based on the US Food and Drug Administration's voluntary Adverse Events Reporting System raised questions about the safety of direct-acting antivirals (DAAs) for treatment of the hepatitis C virus (HCV). **OBJECTIVE:** To assess the rates of adverse events in patients with HCV infection exposed to DAAs compared with those not exposed. **DESIGN, SETTING, AND PARTICIPANTS:** A retrospective cohort study calculated unadjusted adverse event rates for exposed vs unexposed time, using claims and clinical data from 3 health systems between January 1, 2012, and December 31, 2017. Of 82 419 eligible adults, a total of 33 808 who met eligibility criteria (age, 18-88 years; HCV quantitative result or genotype from 2012 or later; continuously enrolled; naive to DAA treatment at baseline) were included. Marginal structural modeling methods were used to adjust time-to-event analyses for characteristics that are associated with both outcomes and probability of treatment. **INTERVENTIONS OR EXPOSURES:** Exposure to DAAs compared with no DAA exposure.

**MAIN OUTCOMES AND MEASURES:** Death, multiple organ failure, liver cancer, hepatic decompensation, acute-on-chronic liver event, acute myocardial infarction, ischemic or hemorrhagic stroke, arrhythmia, acute kidney failure, nonliver cancer, hepatitis B reactivation, hospitalizations, and emergency department visits. **RESULTS:** Of the 33 808 patients who met all inclusion criteria, 20 899 (61.8%) were men; mean (SD) age was 57.2 (10.6) years. In unadjusted analyses, DAA exposure was associated with significantly lower rates of death (10.7 vs 33.7 events per 1000 person-years; rate ratio [RR], 0.32, 95% CI, 0.25-0.40). Seven other unadjusted adverse clinical events ratios were below 70% and statistically significant favoring the DAA group: multiple organ failure (RR, 0.56; 95% CI, 0.44-0.72), liver cancer (RR, 0.62; 95% CI, 0.48-0.80), hepatic decompensation (RR, 0.62; 95% CI, 0.52-0.73), acute-on-chronic liver event (RR, 0.68; 95% CI, 0.56-0.84), acute myocardial infarction (RR, 0.64; 95% CI, 0.42-0.97), ischemic stroke (RR, 0.63; 95% CI, 0.42-0.95), and hemorrhagic stroke (RR, 0.47; 95% CI, 0.25-0.89); none favored the non-DAA group. In the marginal structural modeling-adjusted analysis, DAA exposure was associated with statistically significant lower odds of adverse events than non-DAA exposure for death (adjusted odds ratio [aOR], 0.42; 95% CI, 0.30-0.59), multiple organ failure (aOR, 0.67; 95% CI, 0.49-0.90), hepatic decompensation (aOR, 0.61; 95% CI, 0.49-0.76), acute-on-chronic liver event (aOR, 0.71; 95% CI, 0.56-0.91), and arrhythmia (aOR, 0.47; 95% CI, 0.25-0.88). **CONCLUSIONS AND RELEVANCE:** Direct-acting antiviral exposure may not be associated with higher rates of any serious adverse events, including those related to liver, kidney, and cardiovascular systems. Safety concerns based on previous reports did not appear to be supported in this study with more comprehensive data and rigorous statistical methods.

### **In Chronic Hepatitis C Infection, Myeloid-Derived Suppressor Cell Accumulation and T Cell Dysfunctions Revert Partially and Late After Successful Direct-Acting Antiviral Treatment.**

Chronic HCV infection is characterized by several immunological alterations, such as the accumulation of suppressor cells and of hyperactivated T lymphocytes. However, it is unclear whether direct-acting antiviral (DAA)-mediated HCV clearance restores immune dysfunctions. We performed a phenotypic characterization by flow cytometry of different immune cell subsets, including monocytic myeloid-derived suppressor cells (M-MDSCs) and T lymphocytes in 168 patients with persistent HCV infection not treated, under DAA therapies and sustained virological responders. Chronic HCV infection prompted the accumulation of M-MDSCs independently of patient and clinical characteristics, and altered their metabolic properties. HCV RNA was undetectable in the majority of patients just after few weeks of DAA therapy, whereas M-MDSC levels normalized only 6 months after therapy. In addition, HCV infection deeply perturbed the T cell compartment since a re-distribution of memory CD4<sup>+</sup> and CD8<sup>+</sup> T cells was observed at the expenses of naïve cells, and memory T lymphocytes displayed increased activation. Notably, these features were only partially restored by DAA therapies in the CD4, but not in the CD8, compartment as high immune activation levels persisted in the terminally differentiated memory CD8<sup>+</sup> T cells even more than 1 year after sustained virological response. Together, these results suggest that successful DAA therapies do not lead to full immunological reconstitution as fast as viral clearance.



### **Simultaneous assay for protease activities of hepatitis C virus and human immunodeficiency virus based on fluorescence detection.**

Hepatitis C virus protease (HCV-PR) and human immunodeficiency virus protease (HIV-PR) are important for virus maturation, and thus can be used as potential target molecules for the development of antiviral drugs for the treatment of viral infections. In this study, a novel assay was developed to determine HCV-PR activity. This assay is based on a fluorogenic reaction, in which peptide fragments generated from an acetyl peptide substrate by HCV-PR can be selectively converted into a fluorescent derivative, and quantified by high-performance liquid chromatography (HPLC) with fluorescent detection. Herein, several acetyl-peptides can be used as substrates for HPLC. The application of this assay was further validated by simultaneous detection of HCV-PR and HIV-PR in a reaction mixture. The proposed method can differentiate the enzyme activities of HCV-PR and HIV-PR in a sample using their corresponding substrates. The results suggest that this assay can detect various proteases by employing set of substrate peptides under the same reaction conditions.

### **Clusterization of co-morbidities and multi-morbidities among persons living with HIV: a cross-sectional study.**

**BACKGROUND:** Among people living with HIV (PLWH), the prevalence of non-HIV related co-morbidities is increasing. Aim of the present study is to describe co-morbidity and multi-morbidity, their clustering mode and the potential disease-disease interactions in a cohort of Italian HIV patients. **METHODS:** Cross-sectional analysis conducted by the Coordinamento Italiano per lo Studio di Allergia e Infezioni da HIV (CISAI) on adult subjects attending HIV-outpatient facilities. Non-HIV co-morbidities included: cardiovascular disease, diabetes mellitus, hypertension, oncologic diseases, osteoporosis, probable case of chronic obstructive pulmonary disease (COPD), hepatitis C virus (HCV) infection, psychiatric illness, kidney disease. Multi-morbidity was defined as the presence of two or more co-morbidities. **RESULTS:** One thousand and eighty-seven patients were enrolled in the study (mean age  $47.9 \pm 10.8$ ). One hundred-ninety patients (17.5%) had no co-morbidity, whereas 285 (26.2%) had one condition and 612 (56.3%) were multi-morbid. The most recurrent associations were: 1) dyslipidemia + hypertension (237, 21.8%); 2) dyslipidemia + COPD (188, 17.3%); 3) COPD + HCV-Ab+ (141, 12.9%). Multi-morbidity was associated with older age, higher body mass index, current and former smoking, CDC stage C and longer ART duration. **CONCLUSIONS:** More than 50% of PLHW were multi-morbid and about 30% had three or more concurrent comorbidities. The identification of common patterns of comorbidities address the combined risks of multiple drug and disease-disease interactions.

### **Burden of Co-Infection: A Cost Analysis of Human Immunodeficiency Virus in a Commercially Insured Hepatitis C Virus Population.**

**INTRODUCTION:** In patients with hepatitis C virus (HCV), human immunodeficiency virus (HIV) represents a major cause of morbidity and economic burden. Economic evaluations in HIV-HCV typically focus on government-sponsored insurance plans rather than a commercially insured cohort. This study evaluated the clinical and economic burden of HIV-HCV co-infection compared with HCV alone in commercially insured patients throughout the United States.

**METHODS:** Commercial medical and pharmacy claims from 2007 to 2015 from a 10% random sample of enrollees within the IQVIA PharMetrics Plus™ administrative claims database were analyzed. Patients were included based on the presence of a claim with a HCV diagnosis across three separate cross-sectional periods which were created from the full dataset (2007-2009, 2010-2012, and 2013-2015). Costs incurred were categorized as emergency department, inpatient, outpatient medical, outpatient pharmacy, and other, based on the claim place of service. Descriptive statistics and proportion of total costs in each group have been reported for all cost categories. **RESULTS:** The samples included 22,329 from 2007 to 2009, 23,186 from 2010 to 2012, and 27,288 from 2013 to 2015. In all three cross-sections, HIV-HCV individuals were more likely to be male and carriers of hepatitis B virus. Pharmacy costs were \$29,368 in the HCV-only group, compared to \$73,547 in the HIV-HCV group ( $p < 0.0001$ ). Pharmacy costs increased as a proportion of total costs for both groups, increasing after 2012 from 41% to 55% for HIV-HCV and from 19% to 34% for HCV-only. **CONCLUSION:** The present study describes the total direct health care costs in HIV-HCV co-infected individuals and HCV-only patients in commercially insured health plans. Spending on pharmacy increased as a proportion of total health care costs in both groups. Further clinical and economic evaluations in HCV and/or HIV populations in the US should consider system-level factors related to insurance type when applying to the entire population.

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## COMPLEMENTARY AND ALTERNATIVE MEDICINE

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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### [Hepatitis C transmission in young people who inject drugs: Insights using a dynamic model informed by state public health surveillance.](#)

Increasing injection of heroin and prescription opioids have led to increases in the incidence of hepatitis C virus (HCV) infections in US young adults since the early 2000s. How best to interrupt transmission and decrease HCV prevalence in young people who inject drugs (PWID) is uncertain. We developed an age-stratified ordinary differential equation HCV transmission model of PWID aged 15-64, which we fit to Michigan HCV surveillance data among young PWID aged 15-29. We used Latin hypercube sampling to fit to data under 10,000 plausible model parameterizations. We used the best-fitting 10% of simulations to predict the potential impact of primary (reducing injection initiation), secondary (increasing cessation, reducing injection partners, or reducing injection drug use relapse), and tertiary (HCV treatment) interventions (over the period 2017-2030) on acute and chronic HCV cases by the year 2030. Treating 3 per 100 current and former PWID per year could reduce chronic HCV by 27.3% (range: 18.7-30.3%) and acute HCV by 23.6% (range: 6.7-29.5%) by 2030 among PWID aged 15-29 if 90% are cured (i.e. achieved sustained virologic response [SVR] to treatment). Reducing the number of syringe sharing partners per year by 10% was predicted to reduce chronic HCV by 15.7% (range: 9.4-23.8%) and acute cases by 21.4% (range: 14.2-32.3%) among PWID aged 15-29 by 2030. In simulations of combinations of interventions, reducing injection initiation, syringe sharing, and relapse rates each by 10% while increasing cessation rates by 10% predicted a 27.7% (range: 18.0-39.7%) reduction in chronic HCV and a 38.4% (range: 28.3-53.3%) reduction in acute HCV. Our results highlight the need for HCV treatment among both current and former PWID and the scale up of both primary and secondary interventions to concurrently reduce HCV prevalence and incidence in Michigan.

### Assessing the burden of illness of chronic hepatitis C and impact of direct-acting antiviral use on healthcare costs in Medicaid.

**OBJECTIVES:** To quantify the burden of illness of chronic hepatitis C virus (HCV) infection and estimate the impact of interferon-free direct-acting antiviral treatment on healthcare costs in Medicaid. **STUDY DESIGN:** Observational, retrospective analysis. **METHODS:** Medicaid claims data from 2012 for nonelderly adult enrollees with chronic HCV in 16 states were used to estimate the burden of HCV in Medicaid. Annual measures of health services utilization and cost for patients with HCV were compared with a control group of patients without HCV exactly matched on a robust set of individual characteristics and stratified according to liver disease severity, Medicaid eligibility group, and plan type. Subsequently, HCV burden-of-illness estimates were used in a separate analysis of Medicaid State Drug Utilization Data on interferon-free drug utilization and expenditures to estimate the annual and cumulative impact of these curative medications on national Medicaid costs from 2013 through 2022. **RESULTS:** Annual per-person Medicaid healthcare costs attributed to HCV infection were estimated to range from \$10,561 for noncirrhotic disabled adults to \$46,263 for nondisabled adults with end-stage liver disease. The costs were due mainly to inpatient hospitalizations and outpatient hospital visits, prescription drug utilization, outpatient physician's office/clinic visits, and laboratory tests. By 2014, the first full year following the approval of interferon-free treatment, an estimated 12,175 adults with HCV were cured in Medicaid nationwide, each avoiding an estimated \$15,907 per year in healthcare costs associated with the disease. As more patients in Medicaid are treated and net savings continue to grow year after year due to recurring avoidance of health services use and declining drug prices-total cumulative treatment costs since 2013 are expected to be fully offset by total cumulative healthcare expenditure reductions by the end of 2019. By 2022, the recurrent annual avoidance of healthcare costs will have delivered an estimated \$12 billion in total cumulative savings to Medicaid, net of DAA drug expenditures. **CONCLUSIONS:** The introduction of interferon-free HCV treatments enables the avoidance of significant healthcare costs previously associated with treating the disease year after year, producing annual cumulative Medicaid savings beginning in 2019. A main finding from this study is that the cost of a complete DAA treatment course, at 2018 estimated net prices, can be expected to be fully offset by healthcare cost savings after only 16 months, on average, on a per-person basis. Given the tremendous value provided by these curative drugs, Medicaid policies aimed toward restricting access to these treatments based on disease severity or other requirements would be shortsighted.

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## HEPATOCELLULAR (LIVER) CANCER

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### HCV-Induced Epigenetic Changes Associated With Liver Cancer Risk Persist After Sustained Virologic Response.

**BACKGROUND & AIMS:** Chronic hepatitis C virus (HCV) infection is an important risk factor for hepatocellular carcinoma (HCC). Despite effective antiviral therapies, the risk for HCC is decreased but not eliminated after a sustained virologic response (SVR) to direct-acting antiviral (DAA) agents, and the risk is higher in patients with advanced fibrosis. We investigated HCV-induced epigenetic alterations that might affect risk for HCC after DAA treatment in



patients and mice with humanized livers. **METHODS:** We performed genome-wide ChIPmentation-based ChIP-Seq and RNA-seq analyses of liver tissues from 6 patients without HCV infection (controls), 18 patients with chronic HCV infection, 8 patients with chronic HCV infection cured by DAA treatment, 13 patients with chronic HCV infection cured by interferon therapy, 4 patients with chronic hepatitis B virus infection, and 7 patients with nonalcoholic steatohepatitis in Europe and Japan. HCV-induced epigenetic modifications were mapped by comparative analyses with modifications associated with other liver disease etiologies. uPA/SCID mice were engrafted with human hepatocytes to create mice with humanized livers and given injections of HCV-infected serum samples from patients; mice were given DAAs to eradicate the virus. Pathways associated with HCC risk were identified by integrative pathway analyses and validated in analyses of paired HCC tissues from 8 patients with an SVR to DAA treatment of HCV infection. **RESULTS:** We found chronic HCV infection to induce specific genome-wide changes in H3K27ac, which correlated with changes in expression of mRNAs and proteins. These changes persisted after an SVR to DAAs or interferon-based therapies. Integrative pathway analyses of liver tissues from patients and mice with humanized livers demonstrated that HCV-induced epigenetic alterations were associated with liver cancer risk. Computational analyses associated increased expression of SPHK1 with HCC risk. We validated these findings in an independent cohort of patients with HCV-related cirrhosis (n = 216), a subset of which (n = 21) achieved viral clearance. **CONCLUSIONS:** In an analysis of liver tissues from patients with and without an SVR to DAA therapy, we identified epigenetic and gene expression alterations associated with risk for HCC. These alterations might be targeted to prevent liver cancer in patients treated for HCV infection.

### **Ineffective Absorption? Failure of Direct-Acting Therapy for Chronic Hepatitis C in Cirrhotic Patients With Roux-en-Y Gastric Bypass.**

In this era of direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection, treated patients have extremely high rates of sustained virologic response to short courses of therapy regardless of stage of fibrosis. Treatment failure is uncommon and often attributed to medication noncompliance or viral resistance to drug. This report describes 2 Child-Pugh-A cirrhotic patients who failed to clear HCV in response to therapy with DAAs. Each patient had Roux-en-Y gastric bypass (RYGB) surgery preceding DAA therapy. RYGB may create multiple barriers to adequate DAA absorption as a result of changes in gastrointestinal physiology. Treatment monitoring and duration should be carefully considered in this unique patient population.

### **The prognostic factors between different viral etiologies among advanced hepatocellular carcinoma patients receiving sorafenib treatment.**

Sorafenib is currently the first-line therapy for advanced hepatocellular carcinoma (aHCC) patients. However, the outcomes and prognostic factors of sorafenib therapy have not been well investigated. We aimed to investigate the pretreatment factors and outcomes among Taiwanese aHCC patients receiving sorafenib treatment. A total of 347 patients with aHCC and well-compensated liver cirrhosis (Child-Pugh A) status receiving sorafenib were consecutively enrolled from March 2013 through December 2016. Pre-treatment clinical data and viral hepatitis markers were collected and analyzed with their outcomes. The primary endpoint of the

study was overall survival. The factors associated with overall survival were also investigated. The median overall survival of all the patients was 238 days (range, 9-1504 days) with a 1-year overall survival of 43.2%. Positive hepatitis B surface antigen and absence of portal vein thrombosis (PVT) were independent factors associated with better overall survival. The median duration of sorafenib therapy was 93.0 days (range, 4-1504 days). After stopping sorafenib, the median survival was 93.0 days (range, 1-1254 days). The 1-year survival after stopping sorafenib was 21.2%. In chronic hepatitis B patients, total bilirubin level was the only factor associated with overall survival. Hepatitis C antibody RNA negativity, tumor size, PVT, and white blood cell count were the independent factors associated with survival among those chronic hepatitis C patients. There were different prognostic factors stratified by viral etiologies in aHCC patients receiving sorafenib. Viral eradication increased survival in chronic hepatitis C patients.

### **Recurrence rate of hepatocellular carcinoma in patients with treated hepatocellular carcinoma and hepatitis C virus-associated cirrhosis after ombitasvir/paritaprevir/ritonavir+dasabuvir+ribavirin therapy.**

**INTRODUCTION:** Recent studies have suggested a higher recurrence rate of hepatocellular carcinoma (HCC) in patients with a history of HCC and hepatitis C virus (HCV)-associated cirrhosis treated with direct-acting antiviral (DAA) agents. **MATERIAL AND METHODS:** We conducted a prospective analysis of 24 patients with HCV-associated cirrhosis and treated HCC who received ombitasvir/paritaprevir/ritonavir+dasabuvir+ribavirin for 12 weeks. Prior therapies for HCC included resection (9/24 patients), radiofrequency ablation (RFA) (7/24) and trans-arterial chemoembolization (TACE) (8/24). All patients were eligible for treatment if they had no HCC recurrence 6 months after their last procedure. A control group was defined. All patients were followed every 6 months, with dynamic computed tomography and/or magnetic resonance imaging. **RESULTS:** The sustained virological response rate per protocol was 21/24 (87.5%). The study group included 14 (59%) males, median age 64 years (51-77), 50% with associated non-alcoholic steatohepatitis and 24% with Child-Pugh A6 points. HCC recurrence rate/100 patient-years was lower in the DAA-HCC group versus control: 5.5 versus 24.6% patient-years for the resection+RFA group ( $p = 0.044$ ), respectively, and 18.6 versus 72.7% patient-years for TACE group ( $p = 0.002$ ). Survival without recurrence was higher in the resection+RFA group (45 compared to 18 months ( $p < 0.001$ )) and also in the TACE group (44 compared to 11.5 months ( $p = 0.002$ )). **CONCLUSIONS:** DAA therapy significantly reduced the recurrence rate of HCC and improved survival without recurrence in patients with treated HCV-associated HCC.