AUGUST 2017

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Treatment Discontinuation, Adherence, and Real-World Effectiveness Among Patients Treated with Ledipasvir/Sofosbuvir in the United States. Puenpatom A1, Hull M2, McPheeters J3, Schwebke K3. Infect Dis Ther. 2017 Jul 4. doi: 10.1007/s40121-017-0163-0. [Epub ahead of print]

INTRODUCTION: Ledipasvir/sofosbuvir (LDV/SOF) for hepatitis C virus (HCV) treatment provides an oral interferon-free treatment regimen with high rates of sustained virologic response (SVR). This study assessed treatment discontinuation, factors associated with treatment completion, and real-world effectiveness. **METHODS:** Patients with HCV treated with LDV/SOF between October 2014 and June 2015 and enrolled in a large US health plan were identified. Expected treatment duration was calculated based on IDSA/AASLD treatment guidelines and US labels using data for genotype, initial treatment regimen, baseline cirrhosis, and prior treatments. Logistic regression was used to identify factors associated with treatment completion, controlling for patient characteristics. **RESULTS:** The study included 1483 LDV/SOF patients. Mean age was 59.7 years, most were male (63.9%), had commercial insurance (51.9%), and were treatment-naïve (85.6%). Cirrhosis or end stage liver disease was present in 46.1%. Among patients with an expected 8-week treatment regimen, 49.4% were treated for longer. Most patients (99.8%) with expected 12-week treatment durations were adherent to the expected treatment duration. Treatment-experienced patients [odds ratio (OR) 0.124, p < 0.001] and those on Medicare (OR 0.382, p = 0.039) had lower odds of completing the expected treatment regimen, while males were more likely to complete treatment than females (OR 3.235, p = 0.003). SVR12 in patients treated with LDV/SOF was 89.4% (n = 76/85). **CONCLUSION:** Half of patients eligible for an 8-week treatment regimen with LDV/SOF were treated longer, while most patients with a 12-week regimen were adherent to the expected treatment duration. Prior HCV treatment, female gender, and Medicare Advantage insurance were associated with lower odds of treatment completion. Overall SVR12 was 89.4%. **FUNDING:** Merck & Co. Inc.

Relationship between pharmacotherapy complexity and patient satisfaction with treatment for hepatitis C. Robustillo-Cortés MLA1, Almeida-González CV2, Morillo-Verdugo R3. Farm Hosp. 2017 Jul 1;41(4):470-478. doi: 10.7399/fh.2017.41.4.10701.

OBJECTIVE: To establish the relationship between the complexity of treatment for hepatitis C and patient satisfaction. Method: An observational, prospective, single-center study, which

included HCV patients treated between October 2014 and February 2016. The primary endpoint was the assessment of satisfaction with treatment, measured by the HCV-ESTAR questionnaire, structured into two dimensions: clinical and lifestyle satisfaction, on a 0-60 score. A reliability analysis was performed. The data collected were: treatment prescribed for HCV, concomitant medication, and Sustained Viral Response. The complexity index of the complete pharmacotherapy was calculated by the computer application MRCI. T-Student was used to identify the complexity of treatment as a marker of dissatisfaction. **RESULTS:** The study included 171 patients (83.0% male). The mean satisfaction score was 47.9±7.5. The reliability of the complete questionnaire was high (Cronbach alpha, 0.864; intraclass coefficient, 0.843). There was correlation between the Complexity Index and satisfaction (P<0.05). A reduction of 5 points in the Complexity Index increased fourfold the value of satisfaction with treatment (p<0.0001). Similarly, a reduction in 12 points in the Concomitant Medication Index doubled the satisfaction (p=0.028). Regarding the overall complexity, 10 points less doubled the satisfaction (p<0.05). Finally, patients with higher values of satisfaction presented a higher response rate (p=0.029). **CONCLUSIONS:** An increase in pharmacotherapeutical complexity has an impact on satisfaction, and at the same time, on achieving Sustained Viral Response.

Long-term follow-up of patients with chronic hepatitis C treated with α-interferon and ribavirin antiviral therapy: clinical and fibrosis impact of treatment response. Cordero-Ruiz P1, Carmona-Soria I, Rodríguez-Téllez M, Caunedo-Alvarez A, Quezada-Pacheco RH, Flores-Cucho A, Romero-Gómez M, Vilches-Arenas Á. Eur J Gastroenterol Hepatol. 2017 Jul;29(7):792-799. doi: 10.1097/MEG.0000000000000886.
The slow progression of chronic hepatitis C (CHC) infection requires long observation periods to detect clinical changes. We compare the incidence of clinical events, hepatocellular carcinoma (HCC), overall mortality, liver-related mortality, and fibrosis progression between patients with a sustained virological response (SVR) and nonresponders (NR) after a 13-year follow-up period. **STUDY:** One hundred and eighty-two CHC patients, who received interferon and ribavirin treatment between 1996 and 2000, were included. Clinical events were evaluated during follow-up. At the end of follow-up, transient elastography was used to assess fibrosis progression. **RESULTS:** Of the 182 patients, 46.7% (n=85) achieved an SVR. Twenty-seven patients developed hepatic decompensation (one SVR) and 15 developed HCC (three SVR). Twenty-nine patients died (eight SVR). Twelve of the 29 deaths were liver related (two SVR). Independent factors associated with hepatic decompensation were NR to treatment [hazard ratio (HR)=23.35; 95% confidence interval (CI): 2.90-189.25; P=0.003], advanced fibrosis at baseline (HR=9.11; 95% CI: 4.13-20.09), and treatment delay after diagnosis (HR=1.02; 95% CI: 1.00-1.03; P=0.012). Only the latter two were associated with HCC development and liver-related mortality. An assessment of liver fibrosis was performed on 125 patients (66 SVR). Fibrosis values were significantly lower in SVR patients, showing less progression to advanced stages of fibrosis [SVR: 6.6 (2.8); 95% CI: 5.8-7.3] than NR [NR: 14.0 (11.1); 95% CI: 11.1-16.9; P<0.001]. **CONCLUSION:** In patients with CHC, SVR is durable and reduces clinical events. The risk of HCC development is lower, but not eliminated. Sustained responders showed fibrosis stabilization or improved fibrosis values.

Silence Surrounding Hepatitis C Status in Risk Relationships Among Rural People Who Use Drugs. Hofmeister MG1, Havens JR2, Young AM3,4. J Prim Prev. 2017 Jul 21. doi: 10.1007/s10935-017-0483-6. [Epub ahead of print]

Hepatitis C virus (HCV) has reached epidemic proportions in rural Central Appalachia in recent years. We sought to identify demographic, behavioral, and interpersonal characteristics associated with HCV serostatus disclosure among high risk people who use drugs (PWUD) in Appalachian Kentucky. HCV antibody-positive participants (n = 243), drawn from the fifth follow-up assessment of a longitudinal study of rural PWUD, completed interviewer-administered questionnaires eliciting demographic and interpersonal characteristics, risk behaviors, and information about HCV disclosure. We assessed correlates of HCV disclosure using gender-stratified multivariate logistic regression. Participants reported having disclosed their HCV-positive status to a current sex partner (44.0%), family member (35.8%), close friend (9.5%), or past sex partner (6.6%). Of those reporting current (n = 72) or past (n = 215) injection drug use (IDU), only 2.8% disclosed to current and 0.9% disclosed to past IDU partners, respectively. Female participants were more likely than male participants to disclose to current sex partners and family member(s). In multivariate analyses, adjusting for time since testing HCV positive, older age and lifetime history of drug treatment were associated with decreased odds of HCV disclosure among females, while only lifetime history of drug treatment was associated with decreased odds of HCV disclosure among males. In summary, the almost complete absence of disclosure to current or former injection drug use partners was concerning. However, most participants (69.1%) reported disclosing their HCV status to at least one of their social referents, suggesting that family members, partners, and friends of people living with HCV could play a critical role in encouraging uptake of treatment. Although further research is warranted, it is clear that interventions are needed to encourage HCV disclosure among those most at risk of transmitting HCV.

[Disease Burden, Early Discontinuation, and Healthcare Costs in Hepatitis C Patients with and without Chronic Kidney Disease Treated with Interferon-Free Direct-Acting Antiviral Regimens.](#) Puenpatom A1, Hull M2, McPheeters J3, Schwebke K3. Clin Drug Investig. 2017 Jul;37(7):687-697. doi: 10.1007/s40261-017-0526-z.
BACKGROUND: Hepatitis C virus (HCV) is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD). Direct-acting antiviral agents (DAAs) have improved HCV management in CKD patients, however real-world clinical practice data are limited.
OBJECTIVE: This study examined the prevalence of CKD among HCV patients receiving oral DAAs in a real-world setting. Comorbidities, early discontinuation rates, and healthcare costs were compared between patients with and without CKD. **METHODS:** Patients with HCV who were treated with oral DAAs between November 2013 and June 2015, and who were enrolled in a US health plan, were identified. Early discontinuation was calculated based on observed versus expected treatment duration, and expected treatment duration was based on genotype, initial treatment regimen, baseline cirrhosis, and prior treatments. Healthcare costs were calculated during the baseline, treatment, and post-treatment periods. **RESULTS:** This study included 3438 patients receiving oral DAAs, of whom 6.9% had a CKD diagnosis. CKD patients were more often male (70.8 vs. 62.9%, p = 0.02) and older (mean age 62.0 vs. 58.8 years, p < 0.001) than non-CKD patients, and had a higher prevalence of most comorbidities. Among early discontinuers, CKD patients were more likely to experience anemia (19.4 vs. 7.7%, p = 0.028). **CONCLUSIONS:** Few patients with CKD receive DAA treatment for HCV infections. HCV patients with CKD had significantly more comorbidities and higher baseline healthcare costs than patients without CKD. Compared with non-CKD patients, CKD patients were equally likely

to discontinue DAA treatment early but had higher rates of anemia. This study highlights the need for more renal-friendly HCV therapies.

Exposure-Safety Response Relationship for Ombitasvir, Paritaprevir/Ritonavir, Dasabuvir, and Ribavirin in Patients with Chronic Hepatitis C Virus Genotype 1 Infection: Analysis of Data from Five Phase II and Six Phase III Studies.
Lin CW1, Menon R2, Liu W1, Podsadecki T1, Shulman N1, DaSilva-Tillmann B1, Awni W1, Dutta S1. Clin Drug Investig. 2017 Jul;37(7):647-657. doi: 10.1007/s40261-017-0520-5.
BACKGROUND AND OBJECTIVES: All-oral direct-acting antiviral regimens that include combinations of ombitasvir, paritaprevir, ritonavir, and dasabuvir with or without ribavirin were evaluated in hepatitis C virus-infected patients in phase II/III clinical studies. The objective of these analyses was to quantify the relationship between exposures of the components of the regimen and laboratory values and to determine covariates that could influence the relationship. **METHODS:** Exposure-safety response relationships between individual components of the direct-acting antiviral regimens and clinically important laboratory values were explored using data from 2998 patients from 11 phase II/III clinical studies. Multivariate logistic regression analyses were used to identify significant relationships between predictor variables and response variables. **RESULTS:** No statistically significant associations were observed between ombitasvir, dasabuvir, or ritonavir exposures and maximum post-baseline alanine aminotransferase (ALT) or total bilirubin grade or minimum hemoglobin grade. A two-fold increase in paritaprevir exposure from therapeutic exposure was predicted to increase the probability of experiencing a grade 3 or higher increase in ALT by 0.5% and bilirubin by 1.1%. In the phase II/III clinical studies, ALT and bilirubin increases were reversible with continued dosing or after treatment cessation. Other correlates with adverse events of clinical importance included concomitant ribavirin treatment, sex, race, and presence of cirrhosis, consistent with previous observations. **CONCLUSIONS:** Exposure-response analyses from phase II/III studies with the combination direct-acting antiviral regimen indicated no statistically significant relationships with ombitasvir, dasabuvir, or ritonavir exposure, but a statistically significant association was observed between paritaprevir exposure and the probability of experiencing a grade 3 or higher increase in ALT or bilirubin.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Template-dependent multiple displacement amplification for profiling human circulating RNA. Wang W1,2, Ren Y1, Lu Y1, Xu Y1, Crosby SD3, Di Bisceglie AM1,4, Fan X1,4. Biotechniques. 2017 Jul 1;63(1):21-27. doi: 10.2144/000114566.
Multiple displacement amplification (MDA) is widely used in whole-genome/transcriptome amplification. However, template-independent amplification (TIA) in MDA is a commonly observed phenomenon, particularly when using high concentrations of random hexamer primers and extended incubation times. Here, we demonstrate that the use of random pentamer primers with 5′ ends blocked by a C18 spacer results in MDA solely in a template-dependent manner, a technique we have named tdMDA. Together with an optimized procedure for the removal of residual genomic DNA during RNA extraction, tdMDA was used to profile circulating RNA from 0.2 mL of patient sera. In comparison to regular MDA, tdMDA demonstrated a lack of quantifiable DNA amplification in the negative control, a remarkable reduction of unmapped reads from Illumina sequencing ($7 \pm 10.9\%$ versus $58.6 \pm 39\%$, P = 0.006), and increased

mapping rates of the serum transcriptome ($26.9 \pm 7.9\%$ versus $5.8 \pm 8.2\%$, $P = 3.8 \times 10\text{-}4$). Transcriptome profiles could be used to separate patients with chronic hepatitis C virus (HCV) infection from those with HCV-associated hepatocellular carcinoma (HCC). We conclude that tdMDA should facilitate RNA-based liquid biopsy, as well as other genome studies with biological specimens having ultralow amounts of genetic material.

Current progress in host innate and adaptive immunity against hepatitis C virus infection.

Hepatitis C virus (HCV) infects more than 170 million people worldwide and is the main cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Although the newly developed direct-acting antivirals (DAAs) have transformed the treatment of HCV infection, controlling HCV infection on a global scale remains a challenge because of the high cost, low resistance barrier of DAAs and lack of HCV vaccine. The host immune responses associated with HCV infection, especially HCV-specific T cellular immunity, determine the outcome of HCV infection: either acute or chronic infection. It is important to fully interpret the immunopathogenesis of HCV infection and consequently to exploit effective strategies to eliminate HCV. Here, we review the current progress in HCV immunology, which will deepen our understanding of the spectrum of HCV infection and immunity in humans.

Noninvasive serum models to predict significant liver related events in chronic hepatitis C.

AIM: We aim to compare 20 noninvasive fibrosis scores (NIFS), derived from routine blood tests, for predicting significant liver-related adverse events (SLRE) in patients with chronic hepatitis C (CHC) after anti-viral treatment (AVT) with the goal to identify independent predictors for these outcomes. **METHODS:** From 1605 patients who received AVT (pegylated interferon and ribavirin) from January 2002 to June 2014, 20 NIFS were calculated from routine blood tests prior to AVT. Areas under the receiver-operating characteristic curve (AUROC) were calculated for each of these NIFS for predicting non-response to AVT and development of SLRE on follow-up. **RESULTS:** Mean age was 41.9 ± 9.7 years, and patients were predominantly genotype 4 (65%). After AVT, there were 1089 (67.8%) responders, 482 (30%) non-responders and 34 (2.1%) relapsers. After median follow-up of 6580.5 patient-years, 60 (3.8%) had SLRE, 52 (3.2%) had decompensation, and 11 (0.7%) had hepatocellular carcinoma (HCC). The predictive accuracy of NIFS and liver biopsy (LB) for non-response to AVT was low. FIB-4, FibroQ and King score showed high accuracy for predicting adverse events. For predicting decompensation, HCC and SLRE, FibroQ (0.881), King score (0.905) and FibroQ (0.877) had the highest AUROC, respectively. On multivariate analysis, independent predictors for treatment non-response (age, ALT, GGT, platelet count), HCC (albumin, GGT) and SLRE (albumin, GGT, platelet count) were identified. **CONCLUSIONS:** Some simple pretreatment blood parameters and NIFS showed high accuracy for predicting development of SLRE post treatment. Application of these simple scores can improve assessment of long-term liver prognosis for CHC.

Immune phenotype and function of natural killer and T cells in chronic hepatitis C patients who received a single dose of anti-MicroRNA-122, RG-101. Stelma F1,2, van der Ree MH1,2, Sinnige MJ2, et al. Hepatology. 2017 Jul;66(1):57-68. doi: 10.1002/hep.29148. Epub 2017 Jun 7.

MicroRNA-122 is an important host factor for the hepatitis C virus (HCV). Treatment with RG-101, an N-acetylgalactosamine-conjugated anti-microRNA-122 oligonucleotide, resulted in a significant viral load reduction in patients with chronic HCV infection. Here, we analyzed the effects of RG-101 therapy on antiviral immunity. Thirty-two chronic HCV patients infected with HCV genotypes 1, 3, and 4 received a single subcutaneous administration of RG-101 at 2 mg/kg (n = 14) or 4 mg/kg (n = 14) or received a placebo (n = 2/dosing group). Plasma and peripheral blood mononuclear cells were collected at multiple time points, and comprehensive immunological analyses were performed. Following RG-101 administration, HCV RNA declined in all patients (mean decline at week 2, 3.27 log10 IU/mL). At week 8 HCV RNA was undetectable in 15/28 patients. Plasma interferon-γ-induced protein 10 (IP-10) levels declined significantly upon dosing with RG-101. Furthermore, the frequency of natural killer (NK) cells increased, the proportion of NK cells expressing activating receptors normalized, and NK cell interferon-γ production decreased after RG-101 dosing. Functional HCV-specific interferon-γ T-cell responses did not significantly change in patients who had undetectable HCV RNA levels by week 8 post-RG-101 injection. No increase in the magnitude of HCV-specific T-cell responses was observed at later time points, including 3 patients who were HCV RNA-negative 76 weeks postdosing. **CONCLUSION:** Dosing with RG-101 is associated with a restoration of NK-cell proportions and a decrease of NK cells expressing activation receptors; however, the magnitude and functionality of ex vivo HCV-specific T-cell responses did not increase following RG-101 injection, suggesting that NK cells, but not HCV adaptive immunity, may contribute to HCV viral control following RG-101 therapy. (Hepatology 2017;66:57-68).
© 2017 The Authors. Hepatology published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases.

The Influence of Hepatitis C Virus Therapy on the DNA Base Excision Repair System of Peripheral Blood Mononuclear Cells. Czarny P1, Merecz-Sadowska A2, Majchrzak K2, Jabłkowski M3, Szemraj J1,4, Śliwiński T5, Karwowski B2. DNA Cell Biol. 2017 Jul;36(7):535-540. doi: 10.1089/dna.2017.3653. Epub 2017 Jun 1.

Hepatitis C virus (HCV) can infect extrahepatic tissues, including lymphocytes, creating reservoir of the virus. Moreover, HCV proteins can interact with DNA damage response proteins of infected cells. In this article we investigated the influence of the virus infection and a new ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin (OBV/PTV/r ± DSV ± RBV) anti-HCV therapy on the PBMCs (peripheral blood mononuclear cells, mainly lymphocytes) DNA base excision repair (BER) system. BER protein activity was analyzed in the nuclear and mitochondrial extracts (NE and ME) of PBMC isolated from patients before and after therapy, and from subjects without HCV, using modeled double-strand DNA, with 2'-deoxyuridine substitution as the DNA damage. The NE and ME obtained from patients before therapy demonstrated lower efficacy of 2'-deoxyuridine removal and DNA repair polymerization than those of the control group or patients after therapy. Moreover, the extracts from the patients after therapy had similar activity to those from the control group. However, the efficacy of apurinic/apyrimidinic site excision in NE did not differ between the studied groups. We postulate that infection of lymphocytes by the HCV can lead to a decrease in the activity of BER enzymes.

However, the use of novel therapy results in the improvement of glycosylase activity as well as the regeneration of endonuclease and other crucial repair enzymes.

HIV/HCV COINFECTION

Short article: Anger and quality of life in patients co-infected with HIV and hepatitis C virus: a cross-sectional study (ANRS CO13-HEPAVIH). Marcellin F1, Protopopescu C, Esterle L, et al. Eur J Gastroenterol Hepatol. 2017 Jul;29(7):786-791. doi: 10.1097/MEG.0000000000000883.
OBJECTIVE: The aim of this study is to document the relationship between anger dimensions (state, trait, expression, and control) and quality of life (QoL) in patients co-infected with HIV and hepatitis C virus (HCV). **PATIENTS AND METHODS:** This is a cross-sectional study nested in the ANRS CO13-HEPAVIH French national cohort. Anger and QoL were assessed using self-administered questionnaires in 536 HIV-HCV-co-infected patients. Correlations between anger scores (STAXI-2 scale) and QoL scores (WHOQOL-HIV BREF scale) were assessed using Spearman's coefficients. Multiple linear regression models were then used to test the relationship between the different dimensions of anger and QoL after adjustment for statistically significant psychosocial, sociobehavioral, and clinical characteristics. **RESULTS:** Patients with excessive alcohol use or history of injecting drug use had higher levels of anger. All dimensions of anger were significantly correlated with impaired QoL for all six dimensions of the WHOQOL-HIV BREF scale. Greater internal experience of anger and impaired anger control were confirmed as independent correlates of impaired QoL related to psychological health, social relationships, and patients' beliefs after adjustment for depressive symptoms, functional impact of fatigue, socioeconomic status, and HIV-related characteristics. **CONCLUSION:** Anger issues need close monitoring in HIV-HCV-co-infected patients, especially in patients with addictive behaviors. Screening for problems in anger management and implementing individualized psychotherapeutic strategies may help improve QoL in this population.

Risk of liver decompensation with cumulative use of mitochondrial toxic nucleoside analogues in HIV/hepatitis C virus coinfection. Lo Re Rd V1,2,3, Zeldow B2, Kallan MJ2, et al. Pharmacoepidemiol Drug Saf. 2017 Jul 19. doi: 10.1002/pds.4258. [Epub ahead of print]
PURPOSE: Among patients dually infected with human immunodeficiency virus (HIV) and chronic hepatitis C virus (HCV), use of antiretroviral therapy (ART) containing mitochondrial toxic nucleoside reverse transcriptase inhibitors (mtNRTIs) might induce chronic hepatic injury, which could accelerate HCV-associated liver fibrosis and increase the risk of hepatic decompensation and death. **METHODS:** We conducted a cohort study among 1747 HIV/HCV patients initiating NRTI-containing ART within the Veterans Aging Cohort Study (2002-2009) to determine if cumulative mtNRTI use increased the risk of hepatic decompensation and death among HIV-/HCV-coinfected patients. Separate marginal structural models were used to estimate hazard ratios (HRs) of each outcome associated with cumulative exposure to ART regimens that contain mtNRTIs versus regimens that contain other NRTIs. **RESULTS:** Over 7033 person-years, we observed 97 (5.6%) decompensation events (incidence rate, 13.8/1000 person-years) and 125 (7.2%) deaths (incidence rate, 17.8 events/1000 person-years). The risk of hepatic decompensation increased with cumulative mtNRTI use (1-11 mo: HR, 1.79 [95% confidence interval (CI), 0.74-4.31]; 12-35 mo: HR, 1.39 [95% CI, 0.68-2.87]; 36-71 mo: HR,

2.27 [95% CI, 0.92-5.60]; >71 mo: HR, 4.66 [95% CI, 1.04-20.83]; P = .045) versus nonuse. Cumulative mtNRTI use also increased risk of death (1-11 mo: HR, 2.24 [95% CI, 1.04-4.81]; 12-35 mo: HR, 2.05 [95% CI, 0.68-6.20]; 36-71 mo: HR, 3.04 [95% CI, 1.12-8.26]; >71 mo: HR, 3.93 [95% CI, 0.75-20.50]; P = .030). **CONCLUSIONS:** These findings suggest that cumulative mtNRTI use may increase the risk of hepatic decompensation and death in HIV/HCV coinfection. These drugs should be avoided when alternatives exist for HIV/HCV patients.

[Injection Drug Use, Unemployment, and Severe Food Insecurity Among HIV-HCV Co-Infected Individuals: A Mediation Analysis.](#) McLinden T1, Moodie EEM1, Hamelin AM1, et al. AIDS Behav. 2017 Jul 19. doi: 10.1007/s10461-017-1850-2. [Epub ahead of print]

Severe food insecurity (FI), which indicates reduced food intake, is common among HIV-hepatitis C virus (HCV) co-infected individuals. Given the importance of unemployment as a proximal risk factor for FI, this mediation analysis examines a potential mechanism through which injection drug use (IDU) is associated with severe FI. We used biannual data from the Canadian Co-infection Cohort (N = 429 with 3 study visits, 2012-2015). IDU in the past 6 months (exposure) and current unemployment (mediator) were self-reported. Severe FI in the following 6 months (outcome) was measured using the Household Food Security Survey Module. An overall association and a controlled direct effect were estimated using marginal structural models. Among participants, 32% engaged in IDU, 78% were unemployed, and 29% experienced severe FI. After adjustment for confounding and addressing censoring through weighting, the overall association (through all potential pathways) between IDU and severe FI was: risk ratio (RR) = 1.69 (95% confidence interval [CI] = 1.15-2.48). The controlled direct effect (the association through all potential pathways except that of unemployment) was: RR = 1.65 (95% CI = 1.08-2.53). We found evidence of an overall association between IDU and severe FI and estimated a controlled direct effect that is suggestive of pathways from IDU to severe FI that are not mediated by unemployment. Specifically, an overall association and a controlled direct effect that are similar in magnitude suggests that the potential impact of IDU on unemployment is not the primary mechanism through which IDU is associated with severe FI. Therefore, while further research is required to understand the mechanisms linking IDU and severe FI, the strong overall association suggests that reductions in IDU may mitigate severe FI in this vulnerable subset of the HIV-positive population.

[Non-invasive liver fibrosis assessment and HCV treatment initiation within a systematic screening program in HIV/HCV coinfected patients.](#) Chromy D1,2, Schwabl P1,2, Bucsics T1,2, et al. Wien Klin Wochenschr. 2017 Jul 25. doi: 10.1007/s00508-017-1231-x. [Epub ahead of print]

BACKGROUND AND AIM: Hepatitis C virus (HCV) therapy should be considered without delay in all patients with significant (SIGFIB) or advanced liver fibrosis (ADVFIB). We aimed to investigate the rates of treatment initiation with interferon-free regimens within a screening program for SIGFIB/ADVFIB in human immunodeficiency virus/HCV coinfected patients (HIV/HCV). **METHODS:** The FIB-4 was calculated in all HIV/HCV from 2014-2016. HIV/HCV were counselled by the HIV clinic and referred to the Division of Gastroenterology and Hepatology for transient elastography (TE) and evaluation for HCV therapy. Patients were stratified by FIB-4 of </≥1.45 (established cut-off for ruling out ADVFIB) and SIGFIB/ADVFIB were defined by liver stiffness >7.1 kPa/>9.5 kPa, respectively. **RESULTS:** Among 1348 HIV+ patients, 16% (210/1348) had detectable HCV-RNA. One hundred HIV/HCV had a FIB-4 ≥1.45.

Among these, 57% (57/100) underwent TE. The majority of these patients had SIGFIB (75%; 43/57) or ADVFIB (37%; 21/57), however, interferon-free treatment was initiated in only 56% (24/43). In addition, fifty-two percent (57/110) of HIV/HCV with FIB-4 <1.45 underwent TE. Interestingly, 40% (23/57) and 18% (10/57) of these patients showed SIGFIB or even ADVFIB, respectively, and 78% (18/23) finally received interferon-free treatment. Overall, only 20% (42/210) of HIV/HCV received interferon-free treatment. **CONCLUSION:** FIB-4 was not useful for ruling out SIGFIB/ADVFIB in our cohort of HIV/HCV. Treatment was initiated only in a small proportion (20%) of HIV/HCV during the first 2 years of interferon-free treatment availability, although the observed proportion of patients with SIGFIB (assessed by TE) was considerably higher (58%). Thus, it requires the ongoing combined efforts of both HIV and HCV specialists to increase treatment uptake rates in this special population.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Prevalence and risk factors for HIV, hepatitis B, and hepatitis C in people with severe mental illness: a total population study of Sweden. Bauer-Staeb C1, Jörgensen L2, Lewis G1, Dalman C2, Osborn DPJ1, Hayes JF3. Lancet Psychiatry. 2017 Jul 4. pii: S2215-0366(17)30253-5. doi: 10.1016/S2215-0366(17)30253-5. [Epub ahead of print]

BACKGROUND: Severe mental illness is associated with increased morbidity and mortality. The elevated risk of blood-borne viruses (BBVs) in people with severe mental illness is of concern, but the full extent of this problem is unclear. We aimed to determine the prevalence of and risk factors for BBVs in people with severe mental illness. **METHODS:** In this nationwide, population-based, cross-sectional study, we estimated the point prevalence of HIV, hepatitis B (HBV), and hepatitis C (HCV) in people with severe mental illness, including the total adult (≥18 years) Swedish population. We defined severe mental illness as a clinical diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or other psychotic illness according to the Swedish version of the International Statistical Classification of Diseases version 8, 9, or 10. We used multivariable logistic regression to determine the odds of BBVs in individuals with severe mental illness, relative to the general population, and to identify independent risk factors (age, sex, immigration status, socioeconomic status, education, and substance misuse) for BBV infection. We also did a sensitivity analysis excluding BBV diagnoses made before the introduction of the Register for Infection Disease Control (1997). **FINDINGS:** Of 6 815 931 adults in Sweden, 97 797 (1·43%) individuals had a diagnosis of severe mental illness. Prevalence of BBVs was elevated in people with severe mental illness, of which 230 (0·24%) had HIV, 518 (0·53%) had HBV, and 4476 (4·58%) had HCV. After accounting for sociodemographic characteristics, the odds of HIV were 2·57 (95% CI 2·25-2·94, p<0·0001) times higher in people with severe mental illness than in the general population, whereas the odds of HBV were 2·29 (2·09-2·51, p<0·0001) times higher and the odds of HCV were 6·18 (5·98-6·39, p<0·0001) times higher. Substance misuse contributed most to the increased risk of BBV: after adjustment, odds ratios were 1·61 (1·40-1·85, p<0·0001) for HIV, 1·28 (1·16-1·41, p<0·0001) for HBV, and 1·72 (1·67-1·78, p<0·0001) for HCV. **INTERPRETATION:** Our results highlight the need to address the issue of higher prevalence of BBVs in people with severe mental illness and identify interventions preventing infection. Targeting of comorbid substance misuse would have particular effect on reduction of BBV prevalence in this population. **FUNDING:** Medical Research Council and Swedish Research Council.

[In an Era of Highly Effective Treatment, Hepatitis C Screening of the General Population of the United States for Hepatitis C Should be Considered.](#)
Younossi Z1,2, Blissett D3, Blissett R3, Henry L4, Younossi Y4, Beckerman R3, Hunt S4. Liver Int. 2017 Jul 18. doi: 10.1111/liv.13519. [Epub ahead of print]
BACKGROUND AND AIMS: Hepatitis C virus (HCV) treatment with all oral direct acting antiviral agents (DAA's) achieve sustained virologic response (SVR) rates of 98%. Re-assessment of general US population screening for HCV is imperative. This study compared the cost-effectiveness (CE) of three HCV screening strategies: screen all (SA), screen Birth Cohort (BCS), and screen high risks (HRS). **METHODS:** Using a previous designed decision-analytic Markov model, estimations of the natural history of HCV and CE evaluation of the three HCV screening strategies over a lifetime horizon in the US population was undertaken. Based on age and risk status, 16 cohorts were modelled. Health states included: Fibrosis stages 0 to 4, decompensated cirrhosis, HCC, LT, post-LT, and death. The probability of liver disease progression was based on the presence or absence of virus. Treatment was with approved all-oral DAAs; 86% were assumed to be seen annually by a primary care provider; SVR rates, transition probabilities, utilities, and costs were from the literature. One-way sensitivity analyses tested the impact of key model drivers. **RESULTS:** SA cost $272.0 billion [$135,279 per patient] and led to 12.19 QALYs per patient. BCS and HRS cost $274.5 billion ($136,568 per patient) and $284.5 billion ($141,502 per patient) with 11.65 and 11.25 QALYs per patient, respectively. Compared to BCS, SA led to an additional 0.54 QALYs per patient and saved $2.59 billion; compared to HRS, SA led to 0.95 additional QALYs per patient and saved $12.5 billion. **CONCLUSIONS:** Screening the entire US population and treating active viremia was projected as cost-saving.

[Impact of an Electronic Health Record Alert in Primary Care on Increasing Hepatitis C Screening and Curative Treatment for Baby Boomers.](#) Konerman MA1, Thomson M1, Gray K2, Moore M2, Choxi H3, Seif E2, Lok AS1. Hepatology. 2017 Jul 17. doi: 10.1002/hep.29362. [Epub ahead of print]
Despite effective treatment for chronic hepatitis C (CHC), deficiencies in diagnosis and access preclude disease elimination. Screening of baby boomers remains low. The aims of this study were to assess the impact of an electronic health record (EHR) based prompt on HCV screening rates in baby boomers in primary care, and access to specialty care and treatment among those newly diagnosed. We implemented an EHR based "Best Practice Advisory" (BPA) that prompted primary care providers (PCPs) to perform HCV screening for patients seen in primary care clinic: 1) born between 1945-1965; 2) lacked a prior diagnosis of HCV infection; and 3) lacked prior documented anti-HCV testing. The BPA had associated educational materials, order set, and streamlined access to specialty care for newly diagnosed patients. Pre and post BPA screening rates were compared and care of newly diagnosed patients analyzed. In the 3 years prior to BPA implementation, 52,660 baby boomers were seen in primary care clinics, and 28% were screened. HCV screening increased from 7.6% for patients with a PCP visit in the 6 months prior to BPA to 72% over the 1-year post BPA. Of 53 newly diagnosed patients, all were referred for specialty care, 11 had advanced fibrosis or cirrhosis, 20 started treatment and 9 achieved SVR thus far. **CONCLUSIONS:** Implementation of an EHR based prompt increased HCV screening rates among baby boomers in primary care by 5 fold due to efficiency in determining needs for HCV screening and work-flow design. Streamlined access to specialty care enabled

patients with previously undiagnosed advanced disease to be cured. This intervention can be easily integrated into EHR systems to increase HCV diagnosis and linkage to care.

Trends in HIV and HCV Risk Behaviors and Prevalent Infection Among People Who Inject Drugs in New York City, 2005-2012.

BACKGROUND: We assess trends in HIV and hepatitis C virus (HCV) risk behaviors and prevalent infection among people who inject drugs (PWID) in New York City (NYC). **METHODS:** PWID in NYC were sampled using respondent-driven sampling in 2005, 2009, and 2012 (serial cross sections) for the Centers for Disease Control and Prevention-sponsored National HIV Behavioral Surveillance study. Participants were interviewed about their current (≤12 months) risk behaviors and tested for HIV and HCV. The crude and adjusted risk ratio (RR) and 95% confidence interval (95% CI) for linear time trends were estimated using generalized estimating equations regression with a modified Poisson model. **RESULTS:** The sample comprised 500, 514, and 525 participants in 2005, 2009, and 2012, respectively. Significant (P < 0.05) linear trends in risk behaviors included a decline in unsafe syringe sources (60.8%, 31.3%, 46.7%; RR = 0.86, 95% CI: 0.81 to 0.92), an increase in all syringes from syringe exchanges or pharmacies (35.4%, 67.5%, 50.3%; RR = 1.15, 95% CI: 1.09 to 1.22), and an increase in condomless vaginal or anal sex (53.6%, 71.2%, 70.3%; RR = 1.14, 95% CI: 1.09 to 1.19). Receptive syringe sharing (21.4%, 27.0%, 25.1%), sharing drug preparation equipment (45.4%, 43.4%, 46.7%), and having ≥2 sex partners (51.2%, 44.0%, 50.7%) were stable. Although HIV seroprevalence declined (18.1%, 12.5%, 12.2%), HCV seroprevalence was high (68.2%, 75.8%, 67.1%). In multivariate analysis, adjusting for sample characteristics significantly associated with time, linear time trends remained significant, and the decline in HIV seroprevalence gained significance (adjusted RR = 0.76, 95% CI: 0.64 to 0.91, P = 0.003). **CONCLUSIONS:** This trend analysis suggests declining HIV prevalence among NYC PWID. However, HCV seroprevalence was high and risk behaviors were considerable. Longitudinal surveillance of HIV and HCV risk behaviors and infections is needed to monitor trends and for ongoing data-informed prevention among PWID.

Cross-border injection drug use and HIV and hepatitis C virus seropositivity among people who inject drugs in San Diego, California.

BACKGROUND: The prevalence of HIV and Hepatitis C Virus (HCV) are significantly lower among people who inject drugs (PWID) in San Diego, CA, USA compared with PWID in Tijuana, Mexico, located directly across the border. We investigated associations between cross-border injection drug use (IDU), HIV and HCV seroprevalence and engagement in injecting risk behaviours while on each side of the border. **METHODS:** Using baseline interviews and serologic testing data from STAHR II, a longitudinal cohort study of PWID in San Diego, bivariate and multivariable logistic regression analyses examined associations between recent (past six months) cross-border IDU and HIV and HCV antibody seropositivity, socio-demographics, drug use characteristics, and participants' connections to, and perceptions about Mexico. Chi-squared tests and McNemar tests examined associations between cross-border IDU

and injecting risk behaviours. **RESULTS:** Of the 567 participants (93% U.S.-born, 73% male, median age 45 years), 86 (15%) reported recent cross-border IDU. Cross-border IDU was not associated with HIV (OR: 0.85, 95% CI: 0.37-1.95) or HCV seropositivity (OR: 1.01, 95% CI: 0.62-1.65). Age, identifying as Hispanic or Latino/a, and being concerned about risk of violence when travelling to Mexico were independently associated with decreased odds of recent cross-border IDU. Injecting cocaine at least weekly, having ever lived in Mexico and knowing PWID who reside in Mexico were associated with increased odds of recent cross-border IDU. PWID who reported cross-border IDU were significantly less likely to engage in receptive needle sharing, equipment sharing, and public injection while in Mexico compared with in San Diego (all p<0.001). **CONCLUSION:** Prevalence of HIV and HCV infection was similar among PWID who had and had not injected in Mexico, possibly due to practising safer injecting while in Mexico. Research is needed to elucidate contextual factors enabling U.S. PWID to inject safely while in Mexico.

[Hepatitis C Treatment Regimens Are Cost-Effective: But Compared With What?](#) Mattingly TJ 2nd1, Slejko JF1, Mullins CD1. Ann Pharmacother. 2017 Jul 1:1060028017722007. doi: 10.1177/1060028017722007. [Epub ahead of print]
BACKGROUND: Numerous economic models have been published evaluating treatment of chronic hepatitis C virus (HCV) infection, but none provide a comprehensive comparison among new antiviral agents. **OBJECTIVE:** Evaluate the cost-effectiveness of all recommended therapies for treatment of genotypes 1 and 4 chronic HCV. **METHODS:** Using data from clinical trials, observational analyses, and drug pricing databases, Markov decision models were developed for HCV genotypes 1 and 4 to compare all recommended drugs from the perspective of the third-party payer over a 5-, 10-, and 50-year time horizon. A probabilistic sensitivity analysis (PSA) was conducted by assigning distributions for clinical cure, age entering the model, costs for each health state, and quality-adjusted life years (QALYs) for each health state in a Monte Carlo simulation of 10 000 repetitions of the model. **RESULTS:** In the lifetime model for genotype 1, effects ranged from 18.08 to 18.40 QALYs and total costs ranged from $88 107 to $184 636. The lifetime model of genotype 4 treatments had a range of effects from 18.23 to 18.43 QALYs and total costs ranging from $87 063 to $127 637. Grazoprevir/elbasvir was the optimal strategy followed by velpatasvir/sofosbuvir as the second-best strategy in most simulations for both genotypes 1 and 4, with drug costs and efficacy of grazoprevir/elbasvir as the primary model drivers. **CONCLUSIONS:** Grazoprevir/elbasvir was cost-effective compared with all strategies for genotypes 1 and 4. Effects for all strategies were similar with cost of drug in the initial year driving the results.

[Still "at risk": An examination of how street-involved young people understand, experience, and engage with "harm reduction" in Vancouver's inner city.](#) Bozinoff N1, Small W2, Long C3, DeBeck K4, Fast D5. Int J Drug Policy. 2017 Jul;45:33-39. doi: 10.1016/j.drugpo.2017.05.006. Epub 2017 Jun 1.
BACKGROUND: Vancouver is an international leader in implementing interventions to reduce harms related to drug use. However, street-involved young people who use drugs continue to be vulnerable to overdose death, hepatitis C (HCV) infection, and high rates of syringe sharing. To better understand this in the context of the intensive public health response, we examined how young people, who are involved in the 'street drug scene', understood, experienced and engaged with harm reduction. **METHODS:** Twelve semi-structured interviews were conducted in 2013

with 13 young people (ages 17-28) recruited from the At-Risk Youth Study, a prospective cohort of street-involved and drug-using young people. These interviews were embedded within a larger, eight-year program of ethnographic research and explored participants' understandings of harm reduction, their use of specific services, and their ideas about improving their day-to-day lives. Interviews were transcribed verbatim and a thematic analysis was performed. **RESULTS:** Young peoples' ideas about harm reduction were diverse and expansive. They articulated the limitations of existing programs, indicating that while they are positioned to reduce the risk of HIV and HCV transmission, they offer little meaningful support to improve young peoples' broader life chances. Young people described strategies to mitigate risk and harm in their own lives, including transitioning to drugs deemed less harmful and attempting to gain access to drug treatment. Finally, young people indicated that spatial considerations (e.g., distance from Vancouver's Downtown Eastside) strongly determined access to services. **CONCLUSIONS:** In Vancouver, a large, well established harm reduction infrastructure seeks to reduce HIV and HCV transmission among street-involved young people. However, young peoples' multiple understandings, experiences and engagements with harm reduction in this setting illustrate the limitations of the existing infrastructure in improving their broader life chances.

"Where's My Choice?" An Examination of Veteran and Provider Experiences With Hepatitis C Treatment Through the Veteran Affairs Choice Program. Tsai J1, Yakovchenko V, Jones N, Skolnik A, Noska A, Gifford AL, McInnes DK. Med Care. 2017 Jul;55 Suppl 7 Suppl 1:S13-S19. doi: 10.1097/MLR.0000000000000706.
BACKGROUND: The Department of Veterans Affairs (VA) is the country's largest provider for chronic hepatitis C virus (HCV) infection. The VA created the Choice Program, which allows eligible veterans to seek care from community providers, who are reimbursed by the VA.
OBJECTIVES: This study aimed to examine perspectives and experiences with the VA Choice Program among veteran patients and their HCV providers. **RESEARCH DESIGN:** Qualitative study based on semistructured interviews with veteran patients and VA providers. Interview transcripts were analyzed using rapid assessment procedures based in grounded theory.
SUBJECTS: A total of 38 veterans and 10 VA providers involved in HCV treatment across 3 VA medical centers were interviewed. **MEASURES:** Veterans and providers were asked open-ended questions about their experiences with HCV treatment in the VA and through the Choice Program, including barriers and facilitators to treatment access and completion. **RESULTS:** Four themes were identified: (1) there were difficulties in enrollment, ongoing support, and billing with third-party administrators; (2) veterans experienced a lack of choice in location of treatment; (3) fragmented care led to coordination challenges between VA and community providers; and (4) VA providers expressed reservations about sending veterans to community providers. **CONCLUSIONS:** The Choice Program has the potential to increase veteran access to HCV treatment, but veterans and VA providers have described substantial problems in the initial years of the program. Enhancing care coordination, incorporating shared decision-making, and establishing a wide network of community providers may be important areas for further development in designing community-based specialist services for needy veterans.

Pharmacy Use in the First Year of the Veterans Choice Program: A Mixed-methods Evaluation. Gellad WF1, Cunningham FE, Good CB, Thorpe JM, Thorpe CT, Bair B, Roman K, Zickmund SL. Med Care. 2017 Jul;55 Suppl 7 Suppl 1:S26-S32. doi: 10.1097/MLR.0000000000000661.

BACKGROUND: The Veterans Choice Program (VCP) was created to ensure timely access to health care in the Department of Veterans Affairs (VA). Under this program, medications may be ordered by select non-VA clinicians to be dispensed by VA pharmacies, creating new challenges in ensuring medication safety. **OBJECTIVES:** To examine pharmaceutical use during the first year of the VCP and to understand barriers and facilitators for VA pharmacists to dispensing medications under the VCP. **STUDY DESIGN:** Mixed-methods evaluation. **METHODS:** We captured all prescriptions dispensed through the VCP and described the demographics of VCP users and their medications. We also conducted semistructured interviews of VA pharmacists, focusing on VA formulary management and experiences dispensing opioid and hepatitis C (HCV) medications. Codebook development and coding followed iterative qualitative methods. **RESULTS:** Overall, 17,346 Veterans received 56,426 VCP prescriptions from November 7, 2014 through November 7, 2015. The total medication cost was $27 million, 90% of which was for only 2772 HCV prescriptions. Topical eye drops and opioids represented the most commonly dispensed prescriptions (15.6% and 9.2% of all prescriptions, respectively). Pharmacists reported numerous challenges to dispensing VCP medications, including time required to contact non-VA clinicians about formulary issues, requiring controlled substance prescriptions to be hand delivered to VA pharmacies, and lack of access to laboratory data required to safely dispense medications. **CONCLUSIONS:** HCV-related medication costs predominated the first year of VCP, but this is likely to change going forward. The safe use of opioids, efficient management of nonformulary medications, and unintended new barriers to access created by the VCP must be addressed.

BACKGROUND AND RATIONALE: Tobacco use is common among persons living with hepatitis C (PLHC), yet little is known about their smoking behaviors and beliefs. Modern hepatitis C treatment offers a unique opportunity to intensively engage this population about other health risks, including smoking. **MAIN RESULTS:** Seventy-seven tobacco users (40 hepatitis C virus [HCV] seropositive and 37 HCV seronegative) enrolled in an interview study in a New York City clinic. The mean age was 51.6, 57.1% were male, 40.3% Latino, and 49.4% black. 67.5% were single and 18.2% were employed. HCV+ smokers differed from HCV- smokers in having a higher prevalence of illicit substance use, depression, and hypertension. PLHC smokers were highly motivated to quit, with 52.5% stating an intention to quit within 30 days. Most of the PLHC smokers had used cessation-directed pharmacotherapy, but almost none had tried a quitline or a quit smoking website. PLHC smokers scored higher on the intrapersonal locus of control subscale. Almost a quarter (22.5%) believed that smoking "helped fight the HCV." **CONCLUSIONS:** PLHC smokers have a high burden of psychiatric and substance use comorbidity. They exhibit characteristics that distinguish them from uninfected smokers, and many harbor false beliefs about imagined benefits of smoking. They are highly motivated to quit but underutilize cessation aids. Without aggressive intervention, smoking-related morbidity will likely mute the health benefits and longevity gains associated with hepatitis C treatment. Research such as this may prove useful in guiding the development of future tobacco treatment strategies. **IMPLICATIONS:** This is the first paper to examine, in detail, sociobehavioral correlates of tobacco use in PLHC. PLHC are recognized by the Department of Health and Human Services as a high-priority health disparities population. We are not aware of any tobacco

treatment services designed specifically for PLHC. The first step in designing an intervention is defining the characteristics of the target group. Our findings will begin to address this need, and may prove useful in optimizing tobacco treatment strategies for smokers living with hepatitis C.

[Implementation of a Large System-Wide Hepatitis C Virus Screening and Linkage to Care Program for Baby Boomers.](#) Castrejón M1, Chew KW1, Javanbakht M2, Humphries R3, Saab S4, Klausner JD1,2. Open Forum Infect Dis. 2017 May 27;4(3):ofx109. doi: 10.1093/ofid/ofx109. eCollection 2017 Summer.

BACKGROUND: We implemented and evaluated a large health system-wide hepatitis C virus (HCV) screening and linkage to care program for persons born between 1945 and 1965 ("baby boomers"). **METHODS:** An electronic health record (EHR) clinical decision support (CDS) tool for HCV screening for baby boomers was introduced in August 2015 for patients seen in the outpatient University of California, Los Angeles healthcare system setting. An HCV care coordinator was introduced in January 2016 to facilitate linkage to HCV care. We compared HCV testing in the year prior (August 2014-July 2015) to the year after (August 2015-July 2016) implementation of the CDS tool. Among patients with reactive HCV antibody testing, we compared outcomes related to the care cascade including HCV ribonucleic acid (RNA) testing, HCV RNA positivity, and linkage to HCV specialty care. **RESULTS:** During the study period, 19606 participants were screened for HCV antibody. Hepatitis C virus antibody screening increased 145% (from 5676 patients tested to 13930 tested) after introduction of the CDS intervention. Screening increased across all demographic groups including age, sex, and race/ethnicity, with the greatest increases among those in the older age groups. The addition of an HCV care coordinator increased follow-up HCV RNA testing for HCV antibody positive patients from 83% to 95%. Ninety-four percent of HCV RNA positive patients were linked to care postimplementation. **CONCLUSIONS:** Introduction of an EHR CDS tool and care coordination markedly increased the number of baby boomers screened for HCV, rates of follow-up HCV RNA testing, and linkage to specialty HCV care for patients with chronic HCV infection.

[Introducing treat-to-target strategies of autoimmune extrahepatic manifestations of chronic hepatitis C virus infection.](#) Retamozo S1,2,3, Brito-Zerón P2,4,5, Quartuccio L6, De Vita S6, Ramos-Casals M2,5,7. Expert Rev Clin Pharmacol. 2017 Jul 27:1-17. doi: 10.1080/17512433.2017.1357466. [Epub ahead of print]

INTRODUCTION: The hepatitis C virus (HCV) is recognized as one of the hepatic viruses most often associated with extrahepatic manifestations (EHMs). It is currently accepted that cryoglobulinemic vasculitis (CV) is the key autoimmune extrahepatic disease associated with HCV infection. Therapeutic approaches have mainly been based on the use of old antiviral interferon (IFN)-based regimens and immunosuppressive therapies, often with an inadequate balance between therapeutic benefits and excess side effects. Areas covered: Therapeutic management of HCV patients with EHMs, including both non-autoimmune (cardiovascular, hematological, general features) and autoimmune complications (organ-specific and systemic autoimmune diseases). Therapies included antiviral (IFN, ribavirin, direct-acting antivirals - DAAs-) and non-antiviral (immunosuppressive agents, rituximab, plasma exchanges) options. The review analyses the current evidence for proposing a treat-to-target (T2T) approach for HCV-related autoimmune EHMs based on an organ-by-organ strategy. Expert commentary: Eradication of HCV must be considered the key T2T in the therapeutic approach to HCV-related

EHMs, as there has been a disruptive change due to the appearance of direct-acting antivirals (DAAs) as game-changers in HCV therapy, with an efficacy reaching nearly 100%. In this scenario, the central role played until now by IFN and ribavirin is not currently supported and they will not be used in the future.

[Scaling up HCV prevention and treatment interventions in rural USA - model projections for tackling an increasing epidemic.](#) Fraser H1, Zibbell J2, Hoerger T2, et al. Addiction. 2017 Jul 22. doi: 10.1111/add.13948. [Epub ahead of print]
BACKGROUND AND AIMS: Effective strategies are needed to address dramatic increases in hepatitis C virus (HCV) infection among people who inject drugs (PWID) in rural settings of the United States (US). We determined the required scale-up of HCV treatment with or without scale-up of HCV prevention interventions to achieve a 90% reduction in HCV chronic prevalence or incidence by 2025 and 2030 in a rural US setting. **DESIGN:** An ordinary differential equation model of HCV transmission calibrated to HCV epidemiological data obtained primarily from a HIV-outbreak investigation in Indiana. **SETTING:** Scott County, Indiana (population 24,181), USA, a rural setting with negligible baseline interventions, increasing HCV epidemic since 2010, and 55.3% chronic HCV prevalence amongst PWID in 2015 PARTICIPANTS: PWID MEASUREMENTS: Required annual HCV treatments per 1000 PWID (and initial annual percentage of infections treated) to achieve a 90% reduction in HCV chronic prevalence or incidence by 2025/30, either with or without scaling-up syringe service programs (SSPs) and medication-assisted treatment (MAT) to 50% coverage. Sensitivity analyses considered whether this impact could be achieved without retreatment of reinfections, and whether greater intervention scale-up was required due to the increasing epidemic in this setting. **FINDINGS:** To achieve a 90% reduction in incidence and prevalence by 2030, without MAT and SSP scale-up, 159 per 1000 PWID (initially 25% of infected PWID) need to be HCV-treated annually. However, with MAT and SSP scaled-up, treatment rates are halved (89 per 1000 annually or 15%). To reach the same target by 2025 with MAT and SSP scaled-up, 121 per 1000 PWID (20%) need treatment annually. These treatment requirements are 3-fold higher than if the epidemic was stable, and the impact targets are unattainable without retreatment. **CONCLUSIONS:** Combined scale-up of hepatitis C virus (HCV) treatment and prevention interventions is needed to decrease the increasing burden of HCV incidence and prevalence in rural Indiana, USA, by 90% by 2025/30.

[Race, Age, and Geography Impact Hepatitis C Genotype Distribution in the United States.](#)
Gordon SC1, Trudeau S, Li J, Zhou Y, et al. J Clin Gastroenterol. 2017 Jul 21. doi: 10.1097/MCG.0000000000000872. [Epub ahead of print]
GOALS: To determine the impact of geography and patient characteristics on hepatitis C virus (HCV) genotype and subtype distribution in a large sample of patients under routine clinical care **BACKGROUND**: HCV genotype impacts disease course and response to treatment. Although several studies have reported genotype distribution within specific US populations, there are no comprehensive descriptions in large, geographically diverse cohorts. **STUDY:** Using data from the Chronic Hepatitis Cohort Study, we present the distribution of HCV genotypes (GT) and subtypes (ST) among a racially diverse cohort of over 8000 HCV-infected patients from four large US health systems. **RESULTS**: Genotype distribution varied significantly by geographic and demographic factors. In age-adjusted analyses, African American patients had significantly higher prevalence of GT1 (85%) than other racial categories, largely driven by a markedly higher

proportion of GT1 subtype b (~34%) than in Asian/other (24%) and white (21%) patients. GT3 represented an increasing proportion of infections as birth decade progressed, from 4% in patients born before 1946 to 18% of those born after 1976. Within the cohort of "living/uncured" patients, highly elevated alanine aminotransferase (>2 times the upper limit of normal) was significantly more common in GT3 patients, whereas Fibrosis-4 Index scores indicative of cirrhosis were most common in the combined group of GT4&6 patients. **CONCLUSION:** Distribution of HCV genotypes and subtypes in the United States is more variable than suggested by previous national-level estimates and single-center studies. "Real-world" prevalence data may improve targeting of prevention, screening, and treatment efforts for hepatitis C.

Impact of alcohol consumption among patients in hepatitis C virus treatment.
Vieira-Castro ACM1, Oliveira LCM1,2. Arq Gastroenterol. 2017 Jul 13:0. doi: 10.1590/S0004-2803.201700000-33. [Epub ahead of print]
BACKGROUND: Recent studies have questioned the recommendation of abstinence from alcohol for at least 6 months for alcoholic patients to be treated for hepatitis C.
OBJECTIVE: The present study aimed to assess the impact of alcohol consumption among patients undergoing hepatitis C treatment. **METHODS:** In this cross-sectional study, 121 patients [78 (64.5%) men; 28-70 years] were evaluated. They were divided as follows: patients who consumed <12 g of ethanol/day throughout life (Group 1), 12-59 g/day (Group 2) and ≥60 g/day (Group 3). Patients were treated with pegyla-ted-interferon plus ribavirin.
RESULTS: These three groups could not be distinguished in terms of the severity of liver fibrosis and frequency of HCV genotype-1 infection. In Group 3, treatment discontinuation (32.4%) was higher than in the Group 1 (9.4%) or Group 2 (0%), it was higher among patients who drank during treatment (66.7% vs 21.4%) and among those who had not been abstinent for at least 6 months (72.7% vs 15.4%). Moderate alcohol drinkers showed good adherence and did not discontinue the treatment. The frequencies of sustained viral response among patients in Group 3 (44.4%) were similar to those in Group 1 (61%) and Group 2 (68.4%).
CONCLUSION: Heavy drinkers more often discontinued treatment for hepatitis C, but those that received this treatment had acceptable sustained viral response rates. These results suggest that heavy drinkers should not be systematically excluded from the treatment, but they should be monitored to avoid drinking and abandoning treatment, mainly those who have not been abstinent for at least 6 months.

HEPATOCELLULAR (LIVER) CANCER

Prognostic Factors and Predictors of Sorafenib Benefit in Patients With Hepatocellular Carcinoma: Analysis of Two Phase 3 Studies. Bruix J1, Cheng AL2, Meinhardt G3, Nakajima K3, De Sanctis Y3, Llovet J4. J Hepatol. 2017 Jul 4. pii: S0168-8278(17)32134-7. doi: 10.1016/j.jhep.2017.06.026. [Epub ahead of print]
BACKGROUND AND AIMS: Sorafenib, an oral multikinase inhibitor, significantly prolonged overall survival (OS) versus placebo in patients with unresectable hepatocellular carcinoma (HCC) in two phase 3 studies, SHARP (Sorafenib HCC Assessment Randomized Protocol) and Asia-Pacific (AP). To assess prognostic factors for HCC and predictive factors of sorafenib benefit, we conducted a pooled exploratory analysis from these placebo-controlled phase 3 studies. **METHODS:** To identify potential prognostic factors for OS, univariate and multivariate (MV) analyses were performed for baseline variables by Cox proportional hazards model.

Hazard ratios (HRs) and median OS were evaluated across pooled subgroups. To assess factors predictive of sorafenib benefit, the interaction term between treatment for each subgroup was evaluated by Cox proportional hazard model. **RESULTS:** In 827 patients (448 sorafenib; 379 placebo) analyzed, strong prognostic factors for poorer OS identified from MV analysis in both treatment arms were presence of macroscopic vascular invasion (MVI), high alpha fetoprotein (AFP), and high neutrophil-to-lymphocyte ratio (NLR; ≤ vs >median [3.1]). Sorafenib OS benefit was consistently observed across all subgroups. Significantly greater OS sorafenib benefit versus placebo was observed in patients without extrahepatic spread (EHS; HR, 0.55 vs 0.84), with hepatitis C virus (HCV) (HR, 0.47 vs 0.81), and a low NLR (HR, 0.59 vs 0.84). **CONCLUSIONS:** In this exploratory analysis, presence of MVI, high AFP, and high NLR were prognostic of poorer OS. Sorafenib benefit was consistently observed irrespective of prognostic factors. Lack of EHS, HCV, and lower NLR were predictive of a greater OS benefit with sorafenib. **LAY SUMMARY:** This exploratory pooled analysis showed that treatment with sorafenib provides a survival benefit in all subgroups of patients with HCC; however, the magnitude of benefit is greater in patients with disease confined to the liver (without extrahepatic spread), or in those with hepatitis C virus, or a lower neutrophil-to-lymphocyte ratio, an indicator of inflammation status. These results help inform the prognosis of patients receiving sorafenib therapy and provide further refinements for the design of trials testing new agents versus sorafenib.

[Risk of hepatitis C virus related hepatocellular carcinoma between subjects with spontaneous and treatment-induced viral clearance.](#) Huang CF1,2, Yeh ML1,2, et al. Oncotarget. 2017 Jul 4;8(27):43925-43933. doi: 10.18632/oncotarget.14937.
BACKGROUND/AIMS: Both spontaneous hepatitis C virus (HCV) clearance and the achievement of sustained virological response (SVR) by anti-viral therapy greatly reduce the incidence of hepatocellular carcinoma (HCC). The current study aimed to compare the risk of HCC between the two patient groupsMethods: A total of 313 subjects with spontaneous HCV clearance (SC) and 564 age- and sex-matched patients in the treatment-induced SVR group were enrolled for analysis. **RESULTS:** Nineteen (2.2%) of the 877 patients developed HCC during 6,963 person-years of follow-up. Fourteen (2.5%) SVR patients and 5 (1.6%) SC patients developed HCC (P=0.004). Cox regression analysis of factors predictive of HCC included SVR (versus SC: hazard ratio [HR]/ 95% confidence interval [CI]: 5.83/1.27-26.88), diabetes (HR/CI:3.41/1.21-9.58), and age (HR/CI: 1.07/1.01-1.14). Of the 564 SVR patients, eleven (5.9%) of the 187 patients with fibrosis stage 2-4 (F2-4) and 2 (0.9%) of the 226 patients with F01 developed HCC (P=0.01). Compared to SC subjects, only SVR patients with F2-4 (P<0.001) but not F0-1(P=0.60) had a higher risk of HCC development. Cox-regression analysis using liver fibrosis as a variable demonstrated that factors associated with HCC included SVR with F2-4 (versus SC: HR/CI: 10.06/2.20-45.98), diabetes (HR/CI:3.23/1.14-9.19), and age (HR/CI: 1.08 1.02-1.15). **CONCLUSIONS:** Compared to subjects with spontaneous viral clearance, subjects with antiviral treatment-induced HCV viral clearance remain at high risk for HCC development, especially if they have significant hepatic fibrosis. These results may provide important information for decision-making regarding the prioritization of current direct antiviral agents in resource-limited countries.

[**MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals.**](#)
Donati B1, Dongiovanni P2, Romeo S3,4, et al. Sci Rep. 2017 Jul 3;7(1):4492. doi: 10.1038/s41598-017-04991-0.
Nonalcoholic fatty liver disease (NAFLD) represents an emerging cause of hepatocellular carcinoma (HCC), especially in non-cirrhotic individuals. The rs641738 C > T MBOAT7/TMC4 variant predisposes to progressive NAFLD, but the impact on hepatic carcinogenesis is unknown. In Italian NAFLD patients, the rs641738 T allele was associated with NAFLD-HCC (OR 1.65, 1.08-2.55; n = 765), particularly in those without advanced fibrosis (p < 0.001). The risk T allele was linked to 3'-UTR variation in MBOAT7 and to reduced MBOAT7 expression in patients without severe fibrosis. The number of PNPLA3, TM6SF2, and MBOAT7 risk variants was associated with NAFLD-HCC independently of clinical factors (p < 0.001), but did not significantly improve their predictive accuracy. When combining data from an independent UK NAFLD cohort, in the overall cohort of non-cirrhotic patients (n = 913, 41 with HCC) the T allele remained associated with HCC (OR 2.10, 1.33-3.31). Finally, in a combined cohort of non-cirrhotic patients with chronic hepatitis C or alcoholic liver disease (n = 1121), the T allele was independently associated with HCC risk (OR 1.93, 1.07-3.58). **In conclusion,** the MBOAT7 rs641738 T allele is associated with reduced MBOAT7 expression and may predispose to HCC in patients without cirrhosis, suggesting it should be evaluated in future prospective studies aimed at stratifying NAFLD-HCC risk.

[**The role of thiazolidinediones in hepatocellular carcinoma risk reduction: a population-based cohort study in Taiwan.**](#) Huang MY1,2, Chung CH3, Chang WK2, Lin CS4, Chen KW5, Hsieh TY2, Chien WC3,6, Lin HH2. Am J Cancer Res. 2017 Jul 1;7(7):1606-1616. eCollection 2017.
OBJECTIVES: The aim of this study was to investigate the effect of thiazolidinediones (TZDs) on the risk of hepatocellular carcinoma (HCC) development among diabetes mellitus (DM) patients. **METHODS:** We conducted a population-based case-control study in Taiwan based on data from the Taiwan National Health Insurance Research Database. A total of 76,349 newly diagnosed DM patients were identified from claims between 2000 and 2010. Among diabetics, 3,026 and 12,104 patients respectively, received or did not receive TZDs. Comparison frequency was matched with age, sex, and index date, excluding those with cancer at baseline. The incidence of HCC at the end of 2010 and the risks associated with the presence of hepatitis B and C infections were analyzed. The effect of TZDs use on the reduction of HCC risk was also assessed. **RESULTS:** The incidence of HCC was lower in the TZD cohort compared with the non-TZD cohort (418.3 vs. 484.6 per 100,000 person-years), with an adjusted hazard ratio (HR) of 0.53 (95% confidence interval = 0.38-0.77) using multivariable Cox proportional hazard regression. In the stratified analysis, HCC risk reduction was greater for diabetics without the comorbidities of cirrhosis, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, end-stage renal disease, and hyperlipidemia, in the TZD cohort than in the non-TZD cohort. Male sex, cirrhosis, hepatitis B, and hepatitis C were significant independent factors predicting HCC (HRs of 1.43, 13.96, 2.31, and 2.15, respectively). **CONCLUSIONS:** This study suggests that the use of TZDs may reduce the risk of developing HCC among DM patients. Comorbidity with cirrhosis and/or hepatitis B/C infection appears to be associated with an extremely increased risk of developing HCC in this patient subset. These high-risk patients should be closely monitored.

Diabetes, hepatocellular carcinoma, and mortality in hepatitis C-infected patients: A population-based cohort study. Huang TS1,2,3, Lin CL3,4,5, Lu MJ3, Yeh CT5,6,7, Liang KH6, Sun CC2,8, Shyu YC3,9, Chien RN3,4,5. J Gastroenterol Hepatol. 2017 Jul;32(7):1355-1362. doi: 10.1111/jgh.13670.
BACKGROUND AND AIM: The effect of diabetes mellitus (DM) on the development of hepatocellular carcinoma (HCC) and all-cause mortality after HCC development in chronic hepatitis C virus (HCV)-infected patients remains inconclusive. This cohort study aimed to investigate these issues using the Taiwanese National Health Insurance Research Database. **METHODS:** We retrieved and enrolled newly diagnosed DM patients with HCV from the Longitudinal Cohort of Diabetes Patients database. Propensity score matching-including age, sex, alcohol-related liver disease, and baseline liver cirrhosis-was used to identify and enroll HCV patients without DM from the Longitudinal Health Insurance Database (n = 1686). A multi-state model was used to investigate transitions from "start-to-HCC," "start-to-death," and "HCC-to-death." **RESULTS:** The multi-state model showed higher cumulative hazards for "start-to-HCC," "start-to-death," and "HCC-to-death" transitions in the DM (vs non-DM) cohort. The cumulative probability of death with or without HCC after 10 years of follow-up was higher in the DM cohort than in the non-DM cohort. Multivariable transition-specific Cox models demonstrated that DM significantly increased the risk for transition from "start-to-HCC" (adjusted hazard ratio [aHR] 1.36; 95% confidence interval [CI] 1.16-1.59; P < 0.001), "start-to-death" (aHR 2.61; 95% CI: 2.05-3.33; P < 0.001), and "HCC-to-death" (aHR 1.36; 95% CI 1.10-1.68; P = 0.005). The effect of liver cirrhosis on "start-to-HCC" and "start-to-death" transitions decreased over time, particularly within 2 years. **CONCLUSIONS:** Diabetes mellitus increased the risk of HCC development in HCV-infected patients and the risk of all-cause mortality in patients with or without HCC.

Hepatocellular carcinoma in patients with chronic hepatitis C and cirrhosis in Denmark: a nationwide cohort study. Hallager S1, Ladelund S2, Kjaer MS3,4, J Viral Hepat. 2017 Jul 27. doi: 10.1111/jvh.12764. [Epub ahead of print]
Cirrhosis in patients with chronic hepatitis C increases the risk of hepatocellular carcinoma (HCC) and surveillance with ultrasound (US) and alpha-fetoprotein (AFP) is recommended. This study aimed to estimate changes in the HCC incidence rate (IR) over time, HCC stage and prognosis, and AFP and US performed in patients with hepatitis C and cirrhosis. Eligible patients were identified in the Danish Database for Hepatitis B and C and data from national health registries and patient charts were obtained. Tumor stage was based on Barcelona-Clinic Liver Cancer stage, TNM classification and size and number of lesions combined into stage 0 - 3. We included 1,075 patients with hepatitis C and cirrhosis, free of HCC and liver transplant at baseline. During 4,988 person years (PY) 115 HCC cases were diagnosed. The HCC incidence rate increased from 0.8/100 PY [CI95% 0.4 - 1.5] in 2002-2003 to 2.9/100 PY [2.4 - 3.4] in 2012-2013. One-year cumulative incidence of at least one AFP or US was 53% among all patients. The positive predictive value of an AFP ≥ 20 ng mL-1 was 17%. Twenty-three (21%) patients were diagnosed with early stage HCC (stage 0/1) and 84 (79%) with late stage. Median survival after HCC for early stage HCC disease was 30.1 months and 7.4 months for advanced HCC (stage 2/3). The incidence rate of HCC increased over time among patients with hepatitis C and cirrhosis in Denmark. Application of AFP and US was suboptimal and most patients were diagnosed with advanced HCC with a poor prognosis. This article is protected by copyright. All rights reserved.

[**Circulating microRNAs panel as a diagnostic tool for discrimination of HCV-associated hepatocellular carcinoma.**](#)
Ali HEA1, Abdel Hameed R2, Effat H3, et al. Clin Res Hepatol Gastroenterol. 2017 Jul 24. pii: S2210-7401(17)30148-1. doi: 10.1016/j.clinre.2017.06.004. [Epub ahead of print]
Early diagnosis of hepatocellular carcinoma (HCC) can significantly improve the overall survival of HCC patients. However, current diagnostic markers are compromised and limited by their low sensitivity and specificity. In this work, circulating microRNAs (miRs) were utilized as a diagnostic tool to test their efficiency to segregate HCC and hepatitis C virus (HCV)-infected patients from healthy subjects. Nine HCC-related miRs (miR-21, miR-30c, miR-93, miR-122, miR-125b, miR-126, miR-130a, miR-193b and miR-222) were analyzed by Real-Time PCR in 86 serum samples; 34 HCC and 52 HCV patients in addition to 25 healthy subjects. The sensitivity and specificity of these miRs were assessed. Our results demonstrated that the median serum level of seven miRs was significantly reduced (P ranges from <0.01 to<0.001) in HCC patients whereas nine miRs were reduced (P<0.001) in HCV compared to healthy controls. Receiver operating characteristic (ROC) curve analyses had shown high diagnostic accuracy (AUC=1.0) when seven and nine combined miRs were considered in HCC and HCV groups, respectively compared to their counterparts. However, a combination of differentially expressed miRs did not improve the discriminatory power (AUC=0.742) when HCC compared to non-HCC groups. miR-122 showed the highest sensitivity and specificity to stratify HCC and HCV versus normal individuals and HCC versus HCV patients. **We conclude** that differentially expressed miRs in the serum of HCV and HCC patients can be utilized as surrogate and non-invasive biomarker for segregation of HCV and HCC patients from healthy subjects.

[**Impact of Sustained Virological Response to Interferon Therapy on Recurrence of Hepatitis C Virus-Related Hepatocellular Carcinoma.**](#) Shinkawa H1, Hasegawa K2, Arita J1, Akamatsu N1, Kaneko J1, Sakamoto Y1, Kokudo N1. Ann Surg Oncol. 2017 Jul 13. doi: 10.1245/s10434-017-6008-y. [Epub ahead of print]
BACKGROUND: Although achieving a sustained virological response (SVR) in hepatitis C virus (HCV) infection is recognized as improving liver function and reducing hepatocellular carcinoma (HCC) development, its impact on HCC recurrence is unclear. This study investigated how preoperative SVR achievement by interferon treatment affects HCC recurrence in patients undergoing hepatic resection. **METHODS:** The study subjects were 521 patients with HCV infection who underwent initial and curative hepatic resection for HCC. To adjust for confounding factors between the SVR and non-SVR groups, propensity score-matching analysis was performed. **RESULTS:** After propensity score matching, 45 of the 49 patients in the SVR group, and an equal number of the 472 patients in the non-SVR group, were matched. The two groups had similar distributions of clinicopathological characteristics. In the matched cohort, the 3-, 5-, and 7-year recurrence-free survival rates after surgery were 56, 45, and 37%, respectively, in the SVR group, and 34, 23, and 7.2%, respectively, in the non-SVR group (p = 0.033). Additionally, the 3-, 5-, and 7-year overall survival rates after surgery were 82, 80, and 75%, respectively, in the SVR group, and 78, 64, and 44%, respectively, in the non-SVR group (p = 0.065). The 1- and 2-year cumulative recurrence rates in the early phase showed no significant difference between the SVR and non-SVR groups (p = 0.27). however, the 3-, 5-, and 7-year cumulative recurrence rates in the late phase were 14, 32, and 43%, respectively, in the SVR

group, and 33, 55, and 86%, respectively, in the non-SVR group (p = 0.037). **CONCLUSION:** Achievement of SVR may reduce postoperative recurrence after hepatic resection.

Disparities in liver cancer occurrence in the United States by race/ethnicity and state.
Islami F1, Miller KD2, Siegel RL3, Fedewa SA4, Ward EM5, Jemal A6. CA Cancer J Clin. 2017 Jul 8;67(4):273-289. doi: 10.3322/caac.21402. Epub 2017 Jun 6.
Liver cancer is highly fatal, and death rates in the United States are increasing faster than for any other cancer, having doubled since the mid-1980s. In 2017, it is estimated that the disease will account for about 41,000 new cancer cases and 29,000 cancer deaths in the United States. In this article, data from the Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics are used to provide an overview of liver cancer incidence, mortality, and survival rates and trends, including data by race/ethnicity and state. The prevalence of major risk factors for liver cancer is also reported based on national survey data from the Centers for Disease Control and Prevention. Despite the improvement in liver cancer survival in recent decades, only 1 in 5 patients survives 5 years after diagnosis. There is substantial disparity in liver cancer death rates by race/ethnicity (from 5.5 per 100,000 in non-Hispanic whites to 11.9 per 100,000 in American Indians/Alaska Natives) and state (from 3.8 per 100,000 in North Dakota to 9.6 per 100,000 in the District of Columbia) and by race/ethnicity within states. Differences in risk factor prevalence account for much of the observed variation in liver cancer rates. Thus, in contrast to the growing burden, a substantial proportion of liver cancer deaths could be averted, and existing disparities could be dramatically reduced, through the targeted application of existing knowledge in prevention, early detection, and treatment, including improvements in vaccination against hepatitis B virus, screening and treatment for chronic hepatitis C virus infections, maintaining a healthy body weight, access to high-quality diabetes care, preventing excessive alcohol drinking, and tobacco control, at both the state and national levels. CA Cancer J Clin 2017;67:273-289. © 2017 American Cancer Society.