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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

A randomized, proof-of-concept clinical trial on repurposing chlorcyclizine for the treatment of chronic hepatitis C. Koh C1, Dubey P2, Han MAT3, et al. Antiviral Res. 2019 Jan 31;163:149-155. doi: 10.1016/j.antiviral.2019.01.017. [Epub ahead of print]
BACKGROUND & AIMS: Chlorcyclizine HCl (CCZ) is a piperazine-class antihistamine with anti-hepatitis C virus (HCV) activity in vitro and in vivo. In a first-in-humans study for HCV, we evaluated the antiviral effects and safety of CCZ±ribavirin (RBV), characterized pharmacokinetic (PK) and viral kinetic (VK) patterns, and provide insights into CCZs mode of action against HCV. **METHODS:** Chronic HCV patients were randomized to CCZ (75 mg twice daily) or CCZ+weight-based RBV (1000/1200 mg daily) for 28 days. Therapy started with a loading dose of CCZ 150 mg ± RBV. Serial assessments of safety, liver tests, PK and VK markers were obtained. **RESULTS:** 24 HCV patients were treated; 54% male, median age 56 years, median HCV RNA 6.30 log IU/ml, without baseline differences between groups. At the end of therapy, subjects treated with CCZ monotherapy did not show any significant or sustained reduction in viremia (p = 0.69), whereas 7/12 (58%) subjects treated with CCZ+RBV had a >3-fold decline in HCV RNA. Subjects who responded demonstrated monophasic (n = 2), biphasic (n = 2) and triphasic (n = 3) VK responses. Contrary to historical RBV monotherapy response, CCZ+RBV demonstrated a continued viral decline suggesting a possible synergistic effect of CCZ+RBV. Mathematical modeling predicts a median effectiveness of CCZ+RBV in blocking viral production (ε) of 59% (Interquartile range, IQR: 50%) and blocking infection (η) of 78% (IQR: 23%). Adverse events (AEs) were mild-moderate without treatment discontinuations for AEs. **CONCLUSIONS:** In this human pilot study, CCZ demonstrated some anti-HCV effects, mostly in combination with RBV. More potent CCZ derivatives with optimal PK features may be more suitable for future therapeutic development.

Direct-Acting Antiviral Therapy not Associated with Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study. Singal AG, Rich NE, Mehta N, et al. Gastroenterology. 2019 Jan 17. pii: S0016-5085(19)30057-5. doi: 10.1053/j.gastro.2019.01.027. [Epub ahead of print]
BACKGROUND & AIMS: There is controversy over the effects of direct-acting antiviral (DAA) therapies for hepatitis C (HCV) infection on hepatocellular carcinoma (HCC) recuZ rrence and tumor aggressiveness. We compared HCC recurrence patterns between DAA-treated

and untreated HCV-infected patients who had achieved a complete response to HCC treatment in a North American cohort. **METHODS:** We conducted a retrospective cohort study of patients with HCV-related HCC with a complete response to resection, local ablation, trans-arterial chemo- or radioembolization, or radiation therapy, from January 2013 through December 2017 at 31 health systems throughout the United States and Canada. Cox regression was used to examine the association between DAA therapy and time to recurrence after a complete response, with DAA therapy analyzed as a time-varying exposure. We also estimated the association between DAA therapy and risk of early HCC recurrence (defined as 365 days after complete response). **RESULTS:** Of 793 patients with HCV-associated HCC, 304 (38.3%) received DAA therapy and 489 (61.7%) were untreated. HCC recurred in 128 DAA-treated patients (42.1%; early recurrence in 52 patients) and 288 untreated patients (58.9%; early recurrence in 227 patients). DAA therapy was not associated with HCC recurrence (hazard ratio, 0.90; 95% CI, 0.70-1.16) or early HCC recurrence (hazard ratio, 0.96; 95% CI, 0.70-1.34), after we adjusted for study site, age, sex, Child Pugh score, alpha-fetoprotein level, tumor burden, and HCC treatment modality. In DAA-treated and untreated patients, most recurrences were within the Milan criteria (74.2% vs 78.8%; P=.23). A larger proportion of DAA-treated than untreated patients received potentially curative HCC therapy for recurrent HCC (32.0% vs 24.6%) and achieved a complete or partial response (45.3% vs 41.0%) but neither achieved statistical significance. **CONCLUSION:** In a large cohort of North American patients with complete response to HCC treatment, DAA therapy was not associated with increased overall or early HCC recurrence. HCC recurrence patterns, including treatment response, were similar in DAA-treated and untreated patients.

[Effectiveness of 8-week sofosbuvir/ledipasvir in the adolescent chronic hepatitis C-infected patients.](#) El-Khayat H1, Kamal EM2, Yakoot M3, et al. Eur J Gastroenterol Hepatol. 2019 Jan 22. doi: 10.1097/MEG.0000000000001360. [Epub ahead of print]
BACKGROUND: The sustained virological response (SVR) rate for the 12-week sofosbuvir (SOF)/ledipasvir (LVD) treatment of adolescent genotype-4 patients is high. The aim of this study is to evaluate 8 versus 12-week treatment efficacy and safety in adolescent genotype-4 patients. **PATIENTS AND METHODS:** In total, 157 chronic hepatitis C-infected adolescent patients (mean age 14±2 years, 62% males) were included in this study. All patients received a morning dose of SOF (400 mg)/LVD (90 mg) as a single tablet for 8 and 12 weeks. Laboratory and biochemical monitoring were performed at weeks 4 and 8, end of treatment (8/12) and 12 weeks after the end of treatment (SVR12). **RESULTS:** In total, SVR12 was 98% [95% confidence interval (CI): 96-100] for all treated patients. For patients treated for 12 weeks, SVR12 was 97.6% (95% CI: 96-101) (82/84 patients), and 98.6% (95% CI: 93-101) (72/73) patients for those treated for 8 weeks. For both regimens, no serious adverse effects, treatment discontinuation or cases of death were detected. The main adverse effects for the 8-week patient group were fatigue (2.8%), headache (1.4%), nausea (1.4%) and epigastric tenderness (1.4%). For the 12-week-treated group, adverse events were epigastric tenderness (1.2%), nausea (1.2%), diarrhoea (2.4%) and rash (2.4%). Three patients were lost to follow-up: two were in the 12-week treatment group and one was in the 8-week group. All of them reached end of treatment but were lost before SVR12. No relapsers were observed in either group. **CONCLUSION:** Eight weeks of treatment of SOF/LVD combination is equally effective and safe as 12 weeks in adolescent genotype-4 patients.

Sofosbuvir-based direct acting antiviral therapies for patients with hepatitis C virus genotype 2 infection. Liu CH1,2,3, Su TH1,2, Liu CJ1,2,4, et al. J Gastroenterol Hepatol. 2019 Jan 29. doi: 10.1111/jgh.14615. [Epub ahead of print]

BACKGROUND AND AIM: Data regarding the comparative effectiveness and safety of sofosbuvir (SOF) in combination with ribavirin (RBV), daclatasvir (DCV) or ledipasvir (LDV) for hepatitis C virus genotype 2 (HCV-2) patients were limited. We aimed to evaluate the performance of these regimens in Taiwan. **METHODS:** 187 HCV-2 patients with compensated liver diseases receiving SOF in combination with RBV (n = 82), DCV (n = 66) or LDV (n = 39) for 12 weeks were retrospectively enrolled. The effectiveness was determined by sustained virologic response 12 weeks off-therapy (SVR12). The patient characteristics potentially related to SVR12 were compared. The safety profiles and laboratory abnormalities were assessed. **RESULTS:** The SVR12 rates were 93.9% (95% confidence interval (CI): 86.5%-97.4%), 98.5% (95% CI: 91.9%-99.7%) and 100% (95% CI: 91.0%-100%) in patients receiving SOF combined with RBV, DCV and LDV, respectively. All patients tolerated treatment well. The stratified SVR12 rates were comparable regardless of baseline characteristics or week 4 viral decline among these regimens. Six (3.2%) patients had serious adverse events (AEs) which were not related to treatment. The rates of fatigue, pruritus and anemia tended to be higher in patients receiving RBV (22.0%, 19.5% and 8.5%) combination than those receiving DCV (10.6%, 6.1% and 1.5%) or LDV (10.3%, 5.1% and 0%) combination. **CONCLUSIONS:** SOF in combination with RBV, DCV or LDV for 12 weeks is effective and well-tolerated for HCV-2 patients. Compared to DCV or LDV combination, the risks of fatigue, pruritus and anemia are higher in patients receiving RBV combination.

Mortality and Kidney Transplantation Outcomes Among Hepatitis C Virus-Seropositive Maintenance Dialysis Patients: A Retrospective Cohort Study. Sawinski D1, Forde KA2, Lo Re V 3rd3, et al. Am J Kidney Dis. 2019 Jan 29. pii: S0272-6386(18)31157-0. doi: 10.1053/j.ajkd.2018.11.009. [Epub ahead of print]

RATIONALE & OBJECTIVE: Hepatitis C virus (HCV) infection is common among maintenance dialysis patients. Few studies have examined both dialysis survival and transplantation outcomes for HCV-seropositive patients because registry data sets lack information for HCV serostatus. **STUDY DESIGN:** Retrospective cohort study. **SETTING & PARTICIPANTS:** Adult long-term dialysis patients treated by a US national dialysis provider between January 1, 2004, and December 31, 2014. **EXPOSURE:** HCV antibody serostatus obtained as part of clinical data from a national dialysis provider. **OUTCOMES:** Mortality on dialysis therapy, entry onto the kidney transplant waiting list, kidney transplantation, and estimated survival benefit from kidney transplantation versus remaining on the waitlist. **ANALYTICAL APPROACH:** After linking clinical data with data from the Organ Procurement and Transplantation Network, Cox and cause-specific hazards regression were implemented to estimate the associations between HCV seropositivity and mortality, as well as entry onto the kidney transplant waitlist. Cox regression was also used to estimate the survival benefit from transplantation versus dialysis among HCV-seropositive individuals. **RESULTS:** Among 442,171 dialysis patients, 31,624 (7.2%) were HCV seropositive. HCV seropositivity was associated with a small elevation in the rate of death (adjusted HR [aHR], 1.09; 95% CI, 1.07-1.11) and a substantially lower rate of entry onto the kidney transplant waitlist (subdistribution HR [sHR], 0.67; 95% CI, 0.61-0.74). Once wait-listed, the kidney transplantation rate was not different for HCV-seropositive (sHR 1.10; 95% CI, 0.96-1.27)

versus HCV-seronegative patients. HCV-seropositive patients lived longer with transplantation (aHR at 3 years, 0.42; 95% CI, 0.27-0.63). Receiving an HCV-seropositive donor kidney provided a survival advantage at the 2-year posttransplantation time point compared to remaining on dialysis therapy waiting for an HCV-negative kidney. **LIMITATIONS:** No data for HCV viral load or liver biopsy. **CONCLUSIONS:** HCV-seropositive patients experience reduced access to the kidney transplantation waitlist despite deriving a substantial survival benefit from transplantation. HCV-seropositive patients should consider foregoing HCV treatment while accepting kidneys from HCV-infected donors to facilitate transplantation and prolong survival.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Expression and immune recognition of polypeptides derived from Hepatitis C virus structural proteins.](#) Halim ASA1, Mohamed MR1, Hamid FFA1, Karim AM1. Indian J Pathol Microbiol. 2019 Jan-Mar;62(1):43-48. doi: 10.4103/IJPM.IJPM_604_18.
BACKGROUND: Hepatitis C virus (HCV) is characterized by a high degree of nucleotide sequence variability between genotypes. This variability extends to functional and immunological determinants. Serological tests using antigenic segments derived from the HCV polyprotein have been used for the diagnosis of HCV infection. However, available diagnostic Kits do not necessarily take type variability into consideration and are not optimized for HCV genotype 4a (HCV4a), the predominant genotype in Egypt. **AIM:** The aim of this study was to express some HCV4a-derived polypeptides in order to identify those with immunodiagnostic utility. **MATERIALS AND METHODS:** Six sequential/overlapping genomic segments encoding 100-266 amino acid peptides from the core (peptide 1), envelope 1 (E1; peptide 2), envelope 2 (E2; peptides 4, 5, and 6), and E1/E2 (peptide 3) regions of the HCV4apolyprotein were selected for in vitro expression as glutathione S-transferase-fusion proteins. The immunoreactivity of the expressed peptides was evaluated against sera from HCV-infected/uninfected individuals using dot blot, western blot, and enzyme-linked immunosorbent assay. **RESULTS:** The expressed polypeptides were recognized by HCV-infected sera from 20 patients, while showing no immunoreactivity toward uninfected serum. Peptide 1 derived from the core protein was found to be the most immunoreactive. **CONCLUSION:** Expressed polypeptides hold good potential for use in the development of improved HCV immune-diagnostics.

[Molecular Identification of Transmitted/Founder Hepatitis C Viruses and Their Progeny by Single Genome Sequencing.](#) Li H1, Zahid MN1, Wang S1, Shaw GM2. Methods Mol Biol. 2019;1911:139-155. doi: 10.1007/978-1-4939-8976-8_9.
Chronic hepatitis C virus (HCV) infection exists as a complex mixture of genetically distinct viruses, commonly referred to as a "quasispecies." Quasispecies complexity can vary substantially during the course of natural infection as a consequence of viral population "bottlenecking." This occurs at the time of transmission from one individual to the next and during the course of chronic infection of an individual when adaptive immune responses eliminate certain viruses but allow others to escape and expand. Antiviral treatment with drugs that fail to eradicate virus can also lead to virus population bottlenecks and emergence of drug-resistant variants. Single genome sequencing (SGS) combined with mathematical modeling and phylogenetic inference is a recently described approach for characterizing the HCV quasispecies in unprecedented detail, allowing for the first time the retention of genetic linkage across genes

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and near full-length genomes and precise identification of transmitted/founder (T/F) genomes. Here, we describe the methodological approach to SGS and show how this strategy allows for the precise and unambiguous molecular identification of transmitted viruses as well as those that repopulate the body after drug or immune-mediated selective sweeps. This is an enabling experimental strategy that allows for a precise genetic, biologic, and antigenic characterization of HCV viruses that are responsible for transmission and persistence. Such an approach can be particularly valuable to future HCV vaccine design efforts, as it has been for human immunodeficiency virus type 1 (HIV-1).

[Combinations of two drugs among NS3/4A inhibitors, NS5B inhibitors and non-selective antiviral agents are effective for hepatitis C virus with NS5A-P32 deletion in humanized-liver mice.](#) Doi A1, Hikita H1, Kai Y1, et al. J Gastroenterol. 2019 Jan 25. doi: 10.1007/s00535-018-01541-x. [Epub ahead of print]
BACKGROUND: The emergence of a deletion mutant at hepatitis C virus (HCV) NS5A-P32 (P32del) has recently been reported in a subset of chronic hepatitis C patients who experience virologic failure after direct-acting antiviral drug (DAA) treatment. This mutation confers extremely high resistance to NS5A inhibitors. No effective treatment has been established for cases with this mutation. **METHODS:** We used a JFH1-based recombinant virus with NS5A from a genotype 1b strain to introduce a P32del mutation. We inoculated human hepatocyte chimeric mice with sera from a patient with ledipasvir/sofosbuvir therapy failure carrying a genotype 1b HCV with NS5A L31M and P32del or from a DAA-naïve patient carrying wild-type virus. **RESULTS:** JFH1-based chimeric viruses with P32del showed sufficient levels of replication for in vitro assay despite the suppression of viral growth and infectious virus production. Variants with P32del exhibited severe resistance to all tested NS5A inhibitors, including daclatasvir, ledipasvir, elbasvir and velpatasvir, but were as susceptible to NS3/4A inhibitors, NS5B inhibitors, interferon alfa-2b, and ribavirin as wild-type viruses in the in vitro assay. The P32del mutant virus caused persistent infection in all inoculated chimeric mice with high viral titer and frequency. The virus was resistant to the ledipasvir/GS-558093 (a nucleotide analog inhibitor of NS5B polymerase) regimen but susceptible to either simeprevir plus GS-558093 or peg-interferon alfa-2b, compared to the wild-type virus. **CONCLUSION:** Therapies combining at least two drugs among NS3/4A inhibitors, NS5B inhibitors and non-selective antiviral agents may be effective for HCV-infected patients with NS5A-P32del.

[Serum lincRNA-p21 expression in primary liver diseases and liver metastatic diseases.](#)
Wang S1, Jiang J2, Zhang C3, Zhang X1, Wang C4. Pathol Res Pract. 2019 Jan 14. pii: S0344-0338(18)31528-0. doi: 10.1016/j.prp.2019.01.014. [Epub ahead of print]
BACKGROUND: LincRNA-p21 is involved in the initiation and progression of many human diseases. We aimed to investigate the expression of LincRNA-p21 in different types of liver diseases. **METHODS:** Serum from patients with primary liver diseases (chronic HBV or HCV infection, hepatitis B virus-related cirrhosis, hepatitis B virus-related HCC, non-HBV/HCV-related HCC, alcoholic liver disease) and HBV negative liver metastatic cancer and control healthy individuals was collected and serum lincRNA-p21 levels were determined by RT-qPCR. Clinicopathological characteristics of the patients were also recorded. **RESULTS:** Serum lincRNA-p21 levels in patients with chronic HBV infection, hepatitis B cirrhosis, hepatitis B virus-related HCC, chronic hepatitis B virus infection, non-HBV/HCV-related HCC, and alcoholic liver disease were higher than those in the control individuals ($P < 0.001$, $P < 0.001$,

P < 0.001, P < 0.001, P < 0.001 and P = 0.002, respectively). The serum lincRNA-p21 level was not significantly different between patients with HBV negative liver metastatic cancer and the normal control (P = 0.80). LincRNA-p21 level was negatively correlated with HBV DNA (P = 0.02), ALT (P = 0.01) and AST (P = 0.01) in patients with liver disease, but not correlated with gender (P = 0.24), age (P = 0.11) and AFP level (P = 0.84). Serum lincRNA-p21 in hepatocellular carcinoma patients was higher than that in liver metastatic cancer patients (P < 0.001). **CONCLUSION:** Serum lincRNA-p21 may serve as a potential biomarker for liver cell damage in patients with hepatitis virus infection, hepatitis B cirrhosis, HBV-related HCC and alcoholic liver disease.

Cost-Effectiveness of Universal Hepatitis C Virus Screening of Pregnant Women in The United States. Chaillon A1, Rand EB2, Reau N3, Martin NK1,4. Clin Infect Dis. 2019 Jan 28. doi: 10.1093/cid/ciz063. [Epub ahead of print]
BACKGROUND: Hepatitis C Virus (HCV) chronic prevalence among pregnant women in the United States (U.S.) U.S. doubled nationally from 2009-2014 (~0.7%), yet many remain undiagnosed. Screening pregnant women is not recommended by the Society of Maternal-Fetal Medicine or the Centers for Disease Control and Prevention, despite new AASLD/IDSA guidelines recommending screening this group. We assessed the cost-effectiveness of HCV screening for pregnant women in the U.S. **METHODS:** An HCV natural history Markov model was used to evaluate the cost-effectiveness of universal HCV screening of pregnant women followed by treatment after pregnancy compared to background risk-based screening from a health care payer perspective. We assumed 0.73% HCV chronic prevalence among pregnant women based on national data. We assume no Medicaid reimbursement restrictions by fibrosis stage at baseline, but explore differing restrictions in sensitivity analyses. We assessed cost (in USD$) and health outcomes (in quality-adjusted life years, QALYs) over a lifetime horizon, using new HCV drug costs of $25,000/treatment. We assess mean incremental cost-effectiveness ratios (ICERs) under a willingness to pay threshold of $50,000/QALY gained. We additionally evaluate potential population impact. **RESULTS:** Universal antenatal screening was cost-effective in all treatment eligibility scenarios (mean ICER <$3,000/QALY gained). Screening remained cost-effective at 0.07% prevalence, the lowest estimated prevalence state in the U.S. (Hawaii). Screening the ~5.04 million pregnant women in 2018 could result in detection and treatment of 33,000 women based on current fibrosis restrictions. **CONCLUSIONS:** Universal screening for HCV among pregnant women in the U.S. is cost effective and should be recommended nationally.

HIV/HCV COINFECTION

JNJ-4178 (AL-335, Odalasvir, and Simeprevir) for 6 or 8 Weeks in Hepatitis C Virus-infected Patients without Cirrhosis: OMEGA-1. Zeuzem S1, Bourgeois S2, Greenbloom S3, et al. Hepatology. 2019 Jan 28. doi: 10.1002/hep.30527. [Epub ahead of print]
The combination of 3 direct-acting antiviral agents (AL-335, odalasvir and simeprevirJNJ-4178 regimen) for 6 or 8 weeks demonstrated good efficacy and safety in a Phase IIa study in chronic hepatitis C virus (HCV) genotype (GT)-1-infected patients without cirrhosis and has now been evaluated in a larger Phase IIb study, OMEGA-1. This multicenter, randomized, open-label study (NCT02765490) enrolled treatment-naïve and interferon (±ribavirin) treatment-experienced patients with HCV GT1, 2, 4, 5, or 6 infection. Patients with HCV GT3 infection and/or liver

cirrhosis were excluded. Patients received AL-335 800 mg, odalasvir 25 mg, and simeprevir 75 mg once daily for 6 or 8 weeks. The primary endpoint was sustained virologic response 12 weeks after the end of treatment (SVR12). In total, 365 patients (GT1a, 29.3%; GT1b, 42.5%; GT2, 12.3%; GT4, 14.2%; GT5, 1.4%; GT6, 0%) were randomized to receive 6 (N = 183) or 8 weeks (N = 182) of treatment. SVR12 rates after 6 (98.9%) or 8 weeks of treatment (97.8%) were non-inferior to a historical control (98%). Viral relapse occurred in 5 (1.4%) patients (4 with HCV GT2c; 1 with GT1a). With the exception of 4 patients in the 8-week group, including 3 patients with missing data at the SVR24 timepoint, all patients who achieved SVR12 also achieved SVR24. One GT1a-infected patient experienced late viral relapse after achieving SVR18. Most adverse events (AEs) were mild with no treatment-related serious AEs. All randomized patients completed treatment. CONCLUSION: In HCV-infected patients, 6 and 8 weeks of treatment with JNJ-4178 resulted in SVR12 rates of 98.9% and 97.8%, respectively, and was well tolerated. This article is protected by copyright.

[Liver stiffness regression after successful Hepatitis C treatment is independent of HIV coinfection.](#) Malin JJ1, Boesecke C2, Schwarze-Zander C2, et al. HIV Med. 2019 Jan 27. doi: 10.1111/hiv.12705. [Epub ahead of print]
OBJECTIVES: The aim of the study was to assess the regression of liver stiffness after successful direct-acting antiviral (DAA) treatment in patients with hepatitis C virus (HCV) monoinfection and HCV/-HIV coinfection. In addition, we aimed to identify factors associated with liver stiffness regression. **METHODS:** We studied patients treated with interferon-free DAA regimens with a sustained virological response at week 12 (SVR12) or 24 (SVR24) post-treatment. Liver stiffness was assessed by transient elastography (TE) before the initiation and after the end of treatment (median 12 weeks). **RESULTS:** Of 214 enrolled patients, 85 (40%) were HCV monoinfected and 129 (60%) HCV/HIV coinfected. Baseline median TE values were 7.8 kPa [interquartile range (IQR) 5.9-12.0 kPa] in mono-infected patients and 10.7 kPa (IQR 7.8-17.0 kPa) in coinfected patients. Overall, the median TE value decreased from 10.1 to 6.8 kPa (n = 214; P < 0.0001). There was no difference between mono- and coinfected patients (-2.2 versus -3.3 kPa, respectively; P = 0.88), which was verified by an analysis of covariance (ANCOVA) adjusting for baseline TE values. Significant ($\geq$ 30%) regression of liver stiffness was achieved by 45% of patients (54% with baseline TE $\geq$ 7.1 kPa). In multivariate analysis, a prior HCV treatment was a negative predictor of liver stiffness regression [odds ratio (OR) 0.31; P = 0.001]. A higher baseline TE value was positively associated with achieving a significant regression (OR 1.06; P = 0.02). HIV coinfection status, HCV genotype, age, sex, treatment duration, controlled attenuation parameter value, bilirubin concentration, platelet count and aspartate aminotransferase concentration were not associated with liver stiffness regression. **CONCLUSIONS:** Regression of liver stiffness after successful DAA treatment did not differ in patients with HCV monoinfection and those with HCV/HIV coinfection. Half of all patients achieved a significant ($\geq$ 30%) regression. Prior treatment for HCV was a negative predictor for this endpoint, while a higher baseline TE value was positively associated with regression.

[Public Health Considerations among People who Inject Drugs with HIV/HCV Co-Infection: A Review.](#) Murdock RM1, Brizzi MB1, Perez O1, Badowski ME2. Infect Dis Ther. 2019 Jan 3. doi: 10.1007/s40121-018-0228-8. [Epub ahead of print]
Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection among persons who inject drugs (PWID) is a major public health concern. There are limited data in clinical trials

on the use of direct-acting antiviral (DAA) therapy for treatment of HCV in co-infected PWID. It is critical for these patients to gain access to treatment in order to decrease progression of liver disease and decrease transmission of both HIV and HCV. Additional harm reduction interventions, including needle and syringe programs and opioid substitution treatment, should be made available to this vulnerable population. Despite the importance of DAA treatment, the cost of DAA therapy and access to medical care is still a barrier to appropriate therapy. The purpose of this review is to present available data on the use of DAAs in co-infected PWID, review guideline recommendations for treatment and retreatment of HCV in co-infected PWID, provide cost considerations for DAA therapy, and provide recommendations about caring for patients who continue to inject drugs.

[Predictive factors of hepatitis C virus eradication after interferon-free therapy in HIV coinfection.](#) Domínguez-Domínguez L1, Bisbal O2, Matarranz M2, Lagarde M2, Pinar Ó3, Hernando A2,4, Lumbreras C2, Rubio R2, Pulido F2.

Real-life cohorts have shown that the effectiveness of all-oral, direct-acting antivirals (DAA) for HCV treatment is > 90%. We aimed to explore the predictive factors of DAA success in HIV coinfection. This is an observational prospective study within the cohort "VIH-DOC", Madrid, Spain. HIV/HCV-coinfected patients were included if they had been treated with DAAs between 9 January 2015 and 31 August 2016. The sustained virological response (SVR) was analysed in the intention-to-treat population. Binary logistic regression was used to study the impact of cirrhosis, anti-HCV therapy experience and the IL28B polymorphism on SVR, besides factors with a p value < 0.15 from the univariate analysis. DAA were prescribed to 423 patients. SVR was confirmed in 92.9%. The univariate analysis showed higher proportion of patients with SVR among those with DAA adherence ≥ 95% (difference + 10.3%, 95% CI 3.5-19.6) and a baseline CD4+ cell count ≥ 200/μL (difference + 14.7%, 95% CI 4.1-31.0). Logistic regression evinced that both DAA adherence and baseline CD4+ cell counts predicted the SVR (OR 3.9, 95% CI 1.8-8.8, and OR 5.2, 95% CI 1.9-13.9, respectively). Moreover, men who reported having sex with other men (MSM) were less likely to achieve SVR (OR 4.2, 95% CI 1.1-16.1). Among MSM, three of three patients without SVR were suspected to have experienced HCV reinfection. DAA for HCV in HIV-coinfected patients is highly effective. DAA adherence ≥ 95% and a baseline CD4+ count ≥ 200/μL predicted a higher probability of SVR. A lower rate of SVR was found in MSM, presumably due to a higher frequency of HCV reinfection.

[Effectiveness of ombitasvir/paritaprevir/ritonavir, dasabuvir for HCV in HIV/HCV coinfected subjects: a comprehensive analysis.](#) Wu J1, Huang P1,2,3, Fan H1, Tian T1, Xia X4, Fu Z1, Wang Y1, Ye X1, Yue M5, Zhang Y6,7,8. Virol J. 2019 Jan 17;16(1):11. doi: 10.1186/s12985-018-1114-4.

BACKGROUND: Data on the treatment of patients with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) coinfection remains limited. A comprehensive analysis was performed to evaluate the efficacy and safety of ombitasvir (OBV)/paritaprevir (PTV)/ritonavir(r) ± dasabuvir (DSV) ± ribavirin (RBV) for treatment in HCV/HIV coinfected patients. **METHODS:** We systematically searched and included studies that enrolled patients with HIV/HCV coinfection using the OBV/PTV/r ± DSV ± RBV regimens and reported sustained virological response after 12 weeks (SVR12) end-of-treatment. Heterogeneity of results was assessed and pooled SVR rates were computed with 95% confidence intervals

(95%CI). Subgroup analysis and assessment of publication bias through Egger's test were further performed. **RESULTS:** Ten studies containing 1358 coinfected patients were included in this study. The pooled estimate of SVR12 was 96.3% (95%CI: 95.1-97.4). Subgroup analysis showed that pooled SVR12 rate was 96.2% (95% CI: 94.8-97.4) for patients with genotype (GT) 1 and 98.8% (95% CI: 95.1-100.0) for those with GT4. The SVR12 rates for the treatment-naïve (TN) and treatment-experienced (TE) patients were 96.8% (95% CI, 94.8-98.5) and 98.9% (95% CI, 96.4-100.0), respectively. Pooled SVR12 rate was 97.8(95%CI: 94.6-99.8) for patients with cirrhosis and 96.7% (95%CI: 95.3-97.8) without cirrhosis. The pooled incidence of any adverse events (AEs) and serious adverse events (SAEs) was 73.9% (95%CI: 38.1-97.6) and 2.7% (95%CI: 0.0-9.5). Publication bias did not exist in this study. **CONCLUSIONS:** The comprehensive analysis showed high efficacy for the OBV/PTV/r ± DSV ± RBV regimen in patients coinfected with HIV and HCV, regardless of genotypes, history of treatment and the presence or absence of cirrhosis.

[HCV Screening and Treatment Uptake among Patients in HIV care During 2014-2015.](#)
Radwan D1, Cachay E2, Falade-Nwulia O1, Moore RD1, Westergaard R3, Mathews WC2, Aberg J4, Cheever L5, Gebo KA1; HIV Research Network. J Acquir Immune Defic Syndr. 2019 Jan 8. doi: 10.1097/QAI.0000000000001949. [Epub ahead of print]
BACKGROUND: Despite the high prevalence of Hepatitis C Virus (HCV) among persons living with HIV (PWH), the prevalence of HCV screening, treatment, and sustained virologic response (SVR) is unknown. This study aims to characterize the continuum of HCV screening and treatment among PWH in HIV care. **SETTING:** Adult patients enrolled at 12 sites of the HIV Research Network located in three regions of the United States were included. **METHODS:** We examined the prevalence of HCV screening, HCV coinfection, direct-acting antiretroviral (DAA) treatment, and SVR-12 between 2014-15. Multivariate logistic regression was performed to identify characteristics associated with outcomes, adjusted for site. **RESULTS:** Among 29,071 PWH (age 18-87, 74.8% male, 44.4% black), 77.9% were screened for HCV antibodies; 95% of those screened had a confirmatory HCV-RNA viral load test. Among those tested, 61% were determined to have chronic HCV. We estimate that only 23.4% of those eligible for DAA were prescribed DAA, but only 17.8% of those eligible evidenced initiating DAA treatment. Those who initiated treatment achieved SVR-12 at a rate of 95.2%. Blacks and people who inject drugs (PWID) were more likely to be screened for HCV than whites or those with heterosexual risk. Persons over age 40, whites, Hispanics, and PWID (AOR 8.70 [7.74-9.78]) were more likely to be coinfected than their counterparts. When examining treatment with DAA, persons over age 50, on ART (AOR, 2.27 [1.11-4.64]), with HIV-1 RNA <400 (AOR, 2.67 [1.71-4.18]), and those with higher Fib-4 scores were more likely to be treated with DAA. **CONCLUSIONS:** While rates of screening for HCV among PWH are high, screening remains far from comprehensive. Rates of SVR were high, consistent with previously published literature. Additional programs to improve screening and make treatment more widely available will help reduce the impact of HCV morbidity among PWH.

[The effects of hepatitis C treatment eligibility criteria on all-cause mortality among people with HIV.](#) Breskin A1, Westreich D1, Hurt CB2, Cole SR1, Hudgens MG3, Seaberg EC4, Thio CL5, Tien PC6, Adimora AA1,2. Clin Infect Dis. 2019 Jan 7. doi: 10.1093/cid/ciz008. [Epub ahead of print]

BACKGROUND: The cost of direct-acting antivirals (DAA) for hepatitis C virus (HCV) prompted many payers to restrict treatment to patients who met non-evidence-based criteria. These restrictions have implications for survival of people with HCV, especially for people with HIV/HCVco-infection who are at high risk for liver disease progression. The goal of this work was to estimate the effects of DAA access policies on 10-year all-cause mortality among people with HIV. **METHODS:** The study population included 3,056 adults with HIV in the Women's Interagency HIV Study and Multicenter AIDS Cohort Study from October 1, 1994 through September 30, 2015. We used the parametric g-formula to estimate 10-year all-cause mortality under DAA access policies that included treating: 1) all people with HCV; 2) only people with suppressed HIV; 3) only people with severe fibrosis; and 4) only people with HIV suppression and severe fibrosis. **RESULTS:** The 10-year risk difference (RD) of treating all co-infected persons with DAAs compared with no treatment was -3.7% (95% CI: -9.1%, 0.6%). Treating only those with suppressed HIV and severe fibrosis yielded a RD of -1.1% (95% CI: -2.8%, 0.6%), with 51% (95% CI: 38%, 59%) of co-infected persons receiving DAAs. Treating a random selection of 51% of co-infected persons at baseline decreased the risk by 1.9% (95% CI: -4.7%, 0.3%). **CONCLUSIONS:** Restrictive DAA access policies may decrease survival compared to treating similar proportions of people with HIV/HCV coinfection with DAAs at random. These findings suggest that lives could be saved by thoughtfully revising access policies.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Nonalcoholic Fatty Liver is Contributing to the Increase in Cases of Liver Disease in US Emergency Departments. Bush H1, Golabi P1, Otgonsuren M1, Rafiq N1,2, Venkatesan C2, Younossi ZM1,2. Clin Gastroenterol. 2019 Jan;53(1):58-64. doi: 10.1097/MCG.0000000000001026.
GOALS/BACKGROUND: We aimed to assess temporal changes in the different types of liver disease (LD) cases and outcomes from emergency departments (EDs) across the United States. **STUDY:** We used data from the National Inpatient Survey database from 2005 to 2011. The International Classification of Diseases, Ninth Revision (ICD-9) clinical modification codes identified hepatitis C virus (HCV), hepatitis B virus (HBV), alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and other LDs including autoimmune hepatitis. We excluded cases without LD, nonhepatocellular carcinoma-related cancers, human immunodeficiency virus infection, or those with missing information. Logistic regression was used to estimate odds ratios with 95% confidence intervals. Controls were matched to cases without LD. **RESULTS:** During the study period, 20,641,839 cases were seen in EDs. Of these, 1,080,008 cases were related to LD and were matched to controls without LD (N=19,557,585). The number of cases with LD increased from 123,873 (2005) to 188,501 (2011) (P<0.0001). Among cases with LD, diagnosis of HCV, HBV, and ALD remained stable during the study years (41.60% vs. 38.20%, 3.70% vs. 2.80%, and 41.4% vs. 38.5%, respectively), whereas NAFLD doubled [6.00% of all LD (2005) to 11.90% of all LD (2011) (P<0.0001)]. Diagnosis of LD in the ED independently predicted increased patient mortality [odds ratio, 1.20 (1.17 to 1.22)]. **CONCLUSIONS:** The number of LD cases presenting to EDs is increasing, and a

diagnosis of LD is associated with a higher patient mortality for those admitted through the ED. There is a dramatic increase of NAFLD diagnoses in the ED.

The HCV care continuum: linkage to HCV care and treatment among patients at an urban health network, Philadelphia, PA. Coyle C1,2, Moorman AC3, Bartholomew T2, Klein G4, Kwakwa H5, Mehta SH1, Holtzman D3. Hepatology. 2019 Jan 11. doi: 10.1002/hep.30501. [Epub ahead of print]

BACKGROUND/AIMS: Improving care and treatment for persons infected with hepatitis C virus (HCV) can reduce HCV-related morbidity and mortality. Our primary objective was to examine the HCV care continuum among patients receiving care at five Federally Qualified Health Centers (FQHCs) in Philadelphia, PA where a testing and linkage to care program had been established. **METHODS:** Among the five FQHCs, one served a homeless population, two served public housing residents, one served a majority Hispanic population, and the last, a "test and treat" site, also provided HCV treatment to patients. We analyzed data from electronic health records of patients tested for HCV antibody from 2012-2016 and calculated the percentage of patients across nine steps of the HCV care continuum ranging from diagnosis to cure. We further explored factors associated with successful patient navigation through two steps of the continuum using multivariable logistic regression. **RESULTS:** Of 885 chronically infected patients, 92.2% received their RNA positive result, 82.7% were referred to an HCV provider, 69.4% were medically evaluated by the provider, 55.3% underwent liver disease staging, 15.0% initiated treatment, 12.0% completed treatment, 8.7% were assessed for sustained virologic response (SVR), and 8.0% achieved SVR. Regression results revealed that test and treat site patients were significantly more likely to be medically evaluated (aOR=2.76; 95% CI=1.82, 4.17) and undergo liver disease staging (aOR=1.92, 95% CI=1.02, 2.86) than patients at the other FQHCs combined. **CONCLUSIONS:** In this U.S. urban setting, over two-thirds of HCV-infected patients were linked to care. Although treatment uptake was low overall, it was highest at the test and treat site. Scaling up treatment services in HCV testing settings will be vital to improve the HCV care continuum. This article is protected by copyright. All rights reserved.

Prevalence of Hepatitis B Virus, Hepatitis C Virus, and HIV Infection Among Patients With Newly Diagnosed Cancer From Academic and Community Oncology Practices. Ramsey SD1, Unger JM2,3, Baker LH4, et al. AMA Oncol. 2019 Jan 17. doi: 10.1001/jamaoncol.2018.6437. [Epub ahead of print]

IMPORTANCE: Universal screening of patients with newly diagnosed cancer for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV is not routine in oncology practice, and experts disagree about whether universal screening should be performed. **OBJECTIVE:** To estimate the prevalence of HBV, HCV, and HIV infection among persons with newly diagnosed cancer. **DESIGN, SETTING, AND PARTICIPANTS:** Multicenter prospective cohort study of patients with newly diagnosed cancer (ie, identified within 120 days of cancer diagnosis) at 9 academic and 9 community oncology institutions affiliated with SWOG (formerly the Southwest Oncology Group) Cancer Research Network, a member of the National Clinical Trials Network, with enrollment from August 29, 2013, through February 15, 2017. The data analysis was conducted using data available through August 17, 2017. **MAIN OUTCOMES AND MEASURES:** The accrual goal was 3000 patients and the primary end point was the presence of HBV infection (previous or chronic), HCV infection, or HIV infection at enrollment. Patients with previous knowledge of infection as well as patients with unknown viral viral status were evaluated.

RESULTS: Of 3092 registered patients, 3051 were eligible and evaluable. Median (range) age was 60.6 (18.2-93.7) years, 1842 (60.4%) were female, 553 (18.1%) were black, and 558 (18.3%) were Hispanic ethnicity. Screened patients had similar clinical and demographic characteristics compared with those registered. The observed infection rate for previous HBV infection was 6.5% (95% CI, 5.6%-7.4%; n = 197 of 3050 patients); chronic HBV, 0.6% (95% CI, 0.4%-1.0%; n = 19 of 3050 patients); HCV, 2.4% (95% CI, 1.9%-3.0%; n = 71 of 2990 patients); and HIV, 1.1% (95% CI, 0.8%-1.6%; n = 34 of 3045). Among those with viral infections, 8 patients with chronic HBV (42.1%; 95% CI, 20.3%-66.5%), 22 patients with HCV (31.0%; 95% CI, 20.5%-43.1%), and 2 patients with HIV (5.9%; 95% CI, 0.7%-19.7%) were newly diagnosed through the study. Among patients with infections, 4 patients with chronic HBV (21.1%; 95% CI, 6.1%-45.6%), 23 patients with HCV (32.4%; 95% CI, 21.8%-44.5%), and 7 patients with HIV (20.6%; 95% CI, 8.7%-37.9%) had no identifiable risk factors. **CONCLUSIONS AND RELEVANCE:** Results of this study found that a substantial proportion of patients with newly diagnosed cancer and concurrent HBV or HCV are unaware of their viral infection at the time of cancer diagnosis, and many had no identifiable risk factors for infection. Screening patients with cancer to identify HBV and HCV infection before starting treatment may be warranted to prevent viral reactivation and adverse clinical outcomes. The low rate of undiagnosed HIV infection may not support universal screening of newly diagnosed cancer patients.

[Impact of Substance Use Disorder on the Rate of Sustained Virological Response in Veterans With Chronic Hepatitis C Treated With Direct-Acting Antivirals.](#) Ottman AA1, Townsend ML1, Hashem MG1, Britt RB1. Ann Pharmacother. 2019 Jan 17:1060028018824988. doi: 10.1177/1060028018824988. [Epub ahead of print]
BACKGROUND: Substance use disorders (SUDs) are commonly encountered in patients with chronic hepatitis C virus (HCV) infection. It is important to consider the impact of SUDs on HCV treatment. **OBJECTIVE:** To compare the rate of clinical cure (sustained virological response at least 12 weeks after end of therapy [SVR12]) in veterans with chronic HCV infection treated with direct-acting antivirals (DAAs) with and without ongoing or recent substance use. **METHODS:** This single-center, retrospective cohort study evaluated 220 HCV patients treated with DAAs based on 2 groups: SUD (ongoing or recent substance use) or non-SUD (without ongoing or recent substance use). The primary end point was SVR12 achievement. Secondary end points included safety, adherence, early discontinuation, SVR12 achievement among SUD subgroups, and enrollment in a SUD treatment program. **RESULTS:** Most patients were African American men with an average age of 60 years and infected with HCV genotype 1. Almost half of the patients had advanced fibrosis or cirrhosis. There was no difference in SVR12 between groups (SUD: 96.2%; non-SUD: 94.3%; P = 0.54). Overall, 35.5% of patients missed at least 1 dose of DAA therapy, with a significant difference noted between groups (SUD: 44.5%; non-SUD: 26.4%; P = 0.005). Early discontinuation of DAA therapy was similar between groups. SVR12 among SUD subgroups ranged from 92.9% to 100%. In the SUD group, 27.3% of patients were enrolled in a SUD treatment program. **CONCLUSION AND RELEVANCE:** This study suggests that recent/ongoing substance use does not affect achievement of clinical cure of chronic HCV and reinforces treatment in this patient population.

[Estimating the Number of People Who Inject Drugs in A Rural County in Appalachia.](#)

OBJECTIVES: To demonstrate how we applied the capture-recapture method for population estimation directly in a rural Appalachian county (Cabell County, WV) to estimate the number of people who inject drugs (PWID). **METHODS:** We conducted 2 separate 2-week periods of data collection in June ("capture") and July ("recapture") 2018. We recruited PWID from a syringe services program and in community locations where PWID were known to congregate. Participants completed a survey that included measures related to sociodemographics, substance use, and HIV and hepatitis C virus prevention. **RESULTS:** In total, 797 surveys were completed; of these surveys, 49.6% (n = 395) reflected PWID who reported injection drug use in the past 6 months and Cabell County residence. We estimated that there were 1857 (95% confidence interval = 1147, 2567) PWID in Cabell County. Among these individuals, most reported being White (83.4%), younger than 40 years (70.9%), and male (59.5%). The majority reported injecting heroin (82.0%), methamphetamine (71.0%), and fentanyl (56.3%) in the past 6 months. **CONCLUSIONS:** Capture-recapture methods can be applied in rural settings to estimate the size of PWID populations.

[**Implementation of Value-based Medicine (VBM) to Patients With Chronic Hepatitis C (HCV) Infection.**](#)
INTRODUCTION: With the significant clinical and economic burden of chronic HCV, effective treatment must be provided efficiently and appropriately. VBM is predicated upon improving health outcomes (clinical and quality) while optimizing the cost of delivering these outcomes. This review explores the concepts of VBM and how it can be used as a strategy for HCV eradication, using the United States as a case example. Once treated with interferon-based regimens, patients with HCV experienced low cure rates, very poor health-related quality of life (HRQoL), decreased work productivity and significant costs. In this context, the old treatment of HCV produced little value to the patient and the society. However, the development of new antiviral regimens for HCV which are free of interferon, has greatly improved treatment success rates as documented with very high cure rates and by improving patient-reported outcomes (PROs), including HRQoL. However, the short-term economic investment to deliver this curative treatment to all HCV-infected patients can be sizeable. In contrast, if one takes the long-term view from the societal perspective, these new treatment regimens can lead to savings by reducing the costs of long-term complications of HCV infection. **CONCLUSIONS:** All of the necessary tools are now available to implement strategies to eradicate HCV. The new all oral direct acting antivirals brings value to the patients and the society because it leads to improvements of clinically important outcomes. Furthermore, the costs associated with these treatment regimens can be recovered by preventing the future economic burden of HCV-complications.

[**A Novel Measure to Assess Variation in Hepatitis C Prevalence Among Homeless and Unstably Housed Veterans, 2011-2016.**](#)
We constructed a novel measure of homelessness to examine differences in hepatitis C virus (HCV) prevalence across 3 categories of unstably housed and homeless veterans and across US

Department of Veterans Affairs Medical Center facilities. We used Veterans Affairs administrative data to classify a cohort of 434 240 veterans as at risk of homelessness, currently homeless, or formerly homeless, and we examined variation in HCV prevalence by using descriptive measures and mixed-effect logistic regression models. HCV prevalence was highest among veterans who were formerly homeless (16.7%; 32 490 of 195 000), followed by currently homeless (12.4%; 22 050 of 178 056) and at risk of homelessness (8.2%; 5015 of 61 184). Veterans Affairs Medical Center-level prevalence ranged from 5.4% to 21.5%. Differences in HCV prevalence were significant by sex, race/ethnicity, and age. Targeting specific populations of homeless veterans for tailored HCV interventions and allocating additional resources to certain Veterans Affairs Medical Centers may be warranted.

[Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model.](#) Heffernan A1, Cooke GS2, Nayagam S3, Thursz M4, Hallett TB5. Lancet. 2019 Jan 28. pii: S0140-6736(18)32277-3. doi: 10.1016/S0140-6736(18)32277-3. [Epub ahead of print]

BACKGROUND: The revolution in hepatitis C virus (HCV) treatment through the development of direct-acting antivirals (DAAs) has generated international interest in the global elimination of the disease as a public health threat. In 2017, this led WHO to establish elimination targets for 2030. We evaluated the impact of public health interventions on the global HCV epidemic and investigated whether WHO's elimination targets could be met. **METHODS:** We developed a dynamic transmission model of the global HCV epidemic, calibrated to 190 countries, which incorporates data on demography, people who inject drugs (PWID), current coverage of treatment and prevention programmes, natural history of the disease, HCV prevalence, and HCV-attributable mortality. We estimated the worldwide impact of scaling up interventions that reduce risk of transmission, improve access to treatment, and increase screening for HCV infection by considering six scenarios: no change made to existing levels of diagnosis or treatment; sequentially adding the following interventions: blood safety and infection control, PWID harm reduction, offering of DAAs at diagnosis, and outreach screening to increase the number diagnosed; and a scenario in which DAAs are not introduced (ie, treatment is only with pegylated interferon and oral ribavirin) to investigate the effect of DAA use. We explored the effect of varying the coverage or impact of these interventions in sensitivity analyses and also assessed the impact on the global epidemic of removing certain key countries from the package of interventions. **FINDINGS:** By 2030, interventions that reduce risk of transmission in the non-PWID population by 80% and increase coverage of harm reduction services to 40% of PWID could avert 14·1 million (95% credible interval 13·0-15·2) new infections. Offering DAAs at time of diagnosis in all countries could prevent 640 000 deaths (620 000-670 000) from cirrhosis and liver cancer. A comprehensive package of prevention, screening, and treatment interventions could avert 15·1 million (13·8-16·1) new infections and 1·5 million (1·4-1·6) cirrhosis and liver cancer deaths, corresponding to an 81% (78-82) reduction in incidence and a 61% (60-62) reduction in mortality compared with 2015 baseline. This reaches the WHO HCV incidence reduction target of 80% but is just short of the mortality reduction target of 65%, which could be reached by 2032. Reducing global burden depends upon success of prevention interventions, implementation of outreach screening, and progress made in key high-burden countries including China, India, and Pakistan. **INTERPRETATION:** Further improvements in blood safety and infection control, expansion or creation of PWID harm reduction services, and extensive

screening for HCV with concomitant treatment for all are necessary to reduce the burden of HCV. These findings should inform the ongoing global action to eliminate the HCV epidemic. **FUNDING:** Wellcome Trust.

[Race, Age, and Geography Impact Hepatitis C Genotype Distribution in the United States.](#)
Gordon SC1, Trudeau S2, Li J2, et al. J Clin Gastroenterol. 2019 Jan;53(1):40-50. doi: 10.1097/MCG.0000000000000872.
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.

[Alcohol-related Liver Disease is Rarely Detected at Early Stages Compared With Liver Diseases of Other Etiologies Worldwide.](#) Shah ND1, Ventura-Cots M2, Abraldes JG3, et al. Clin Gastroenterol Hepatol. 2019 Jan 29. pii: S1542-3565(19)30073-4. doi: 10.1016/j.cgh.2019.01.026. [Epub ahead of print]
BACKGROUND & AIMS: Despite recent advances in treatment of viral hepatitis, liver-related mortality is high, possibly due to the large burden of advanced alcohol-related liver disease (ALD). We investigated whether patients with ALD are initially seen at later stages of disease development than patients with hepatitis C virus (HCV) infection or other etiologies.
METHODS: We performed a cross-sectional study of 3453 consecutive patients with either early or advanced liver disease (1699 patients with early and 1754 with advanced liver disease) seen at 17 tertiary care liver or gastrointestinal units worldwide, from August 2015 through March 2017. We collected anthropometric, etiology, and clinical information as well as and model for end-stage liver disease (MELD) scores. We used unconditional logistic regression to estimate the odds ratios for evaluation at late stages of the disease progression. **RESULTS:** Of the patients analyzed, 81% had 1 etiology of liver disease and 17% had 2 etiologies of liver disease. Of patients seen at early stages for a single etiology, 31% had HCV infection, 21% had HBV infection, and 17% had non-alcoholic fatty liver disease, whereas only 3.8% had ALD. In contrast, 29% of patients seen for advanced disease had ALD. Patients with ALD were more likely to be seen at specialized centers, with advanced-stage disease, compared to patients with

HCV-associated liver disease (odds ratio, 14.1; 95% CI, 10.5-18.9; P <.001). Of patients with 2 etiologies of liver disease, excess alcohol use was associated with 50% of cases. These patients had significantly more visits to healthcare providers, with more advanced disease, compared to patients without excess alcohol use. The mean MELD score for patients with advanced ALD (16) was higher than for patients with advanced liver disease not associated with excess alcohol use (13) (P<.01). **CONCLUSION:** In a cross-sectional analysis of patients with liver disease worldwide, we found that patients with ALD are seen with more advanced-staged disease than patients; with HCV-associated liver disease. Of patients with 2 etiologies of liver disease, excess alcohol use was associated with 50% of cases. Early detection and referral programs are needed for patients with ALD, worldwide.

HEPATOCELLULAR (LIVER) CANCER

Impact of immigration in presentation and outcomes of hepatocellular carcinoma in the USA. Ashhab AA1, Rodin H2, Powell J1, Debes JD1,3. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):24-28. doi: 10.1097/MEG.0000000000001212.
BACKGROUND AND AIMS: Hepatocellular carcinoma's (HCC) epidemiology and prognosis differs among regions across the globe, largely because of environmental factors and underlying liver disease. Little is known about the changes led by immigration and the effect on HCC outcome. We aimed to understand the effect of immigration on HCC. **PATIENTS AND METHODS:** A retrospective cohort study of patients diagnosed with HCC was carried out in a ertiary center in the USA between 2005 and 2016. We characterized individuals as US born or having immigrated there after being born elsewhere. Variables related to clinical presentation, surveillance, therapy, and survival were evaluated. **RESULTS:** A total of 232 HCC cases were included, 169 US born (73%) and 63 immigrants (27%). Both groups were diagnosed with HCC at similar ages (60 vs. 62 years, P=0.13). Hepatitis C was the most common underlying liver disease in the US-born population compared with the immigrant population (83 vs. 52%, P<0.001), whereas hepatitis B was more common in the latter (4 vs. 29%, P<0.001). Interestingly, hepatitis B virus-related HCC was diagnosed at similar ages in US-born and immigrant individuals (59 and 57 years). At the time of diagnosis, both populations had similar tumor sizes, rates of metastasis, and diagnosis during surveillance. One-year survival was similar in both groups (65 vs. 63%). **CONCLUSION:** Immigrants that develop HCC have different underlying liver disease than those born in the USA, but similar HCC characteristics and outcomes, even when including hepatitis B virus-related HCCs. Our study, albeit small, suggests that changes in the environment by immigration leads to clinical adaptation of HCC.

Low Rates of Retention Into Hepatocellular Carcinoma (HCC) Surveillance Program After Initial HCC Screening. Robinson A1, Tavakoli H1, Cheung R2, Liu B1, Bhuket T1, Wong RJ1. J Clin Gastroenterol. 2019 Jan;53(1):65-70. doi: 10.1097/MCG.0000000000001024.
GOALS: To evaluate rates and predictors of retention into hepatocellular carcinoma (HCC) surveillance beyond initial screening among underserved cirrhosis patients. **BACKGROUND:** Although initial HCC screening among cirrhosis patients remains low, few studies have evaluated retention to HCC surveillance beyond initial screening. **METHODS:** We retrospectively evaluated all consecutive adults with cirrhosis from 2014 to 2017 at a single underserved safety net hospital system to determine rates of HCC surveillance at 6 months and at 1 year beyond initial screening. Rates of HCC surveillance was stratified by sex, race/ethnicity,

and etiology of liver disease. Multivariate Cox proportional hazards models evaluated predictors of retention into HCC surveillance. **RESULTS:** Among 235 cirrhosis patients [hepatitis C virus: 35.7%, hepatitis B virus (HBV): 15.7%, alcoholic cirrhosis: 36.2%, nonalcoholic steatohepatitis (NASH): 8.1%], mean age of cirrhosis diagnosis was 54.2±8.9 years. Overall, 74.8% received initial screening within 1 year of cirrhosis diagnosis. Among those who completed initial screening, 47.6% [95% confidence interval (CI), 41.4-54.2) received second surveillance within 1 year. On multivariate analyses, patients with NASH and HBV were significantly more likely to receive second HCC surveillance compared with hepatitis C virus, HBV (hazard ratio, 2.32; 95% CI, 1.18-4.56; P=0.014) and NASH (hazard ratio, 2.49; 95% CI, 1.22-5.11; P=0.012). No sex or race-specific/ethnicity-specific differences in HCC surveillance retention were observed. **CONCLUSIONS:** Although overall rates of initial HCC screening among cirrhosis patients is nearly 75%, retention into continued HCC surveillance is poor, with less than half of patients undergoing subsequent HCC surveillance. Cirrhosis patients with HBV and NASH were more likely to be retained into HCC surveillance.

[**Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: relevance of non-characterized nodules.**](#) Mariño Z1, Darnell A2, Lens S1, et al. J Hepatol. 2019 Jan 23. pii: S0168-8278(19)30015-7. doi: 10.1016/j.jhep.2019.01.005. [Epub ahead of print]

BACKGROUND & AIMS: Despite the very high efficacy of direct acting antivirals (DAA) to eradicate hepatitis C virus infection, the impact on hepatocellular carcinoma development remains controversial. We analyzed the clinical and radiological outcome of cirrhotic patients treated with interferon-free regimens to estimate the risk of developing hepatocellular carcinoma. **METHODS:** Retrospective, multicenter study focusing on cirrhotic patients treated with direct acting antivirals until December 2016. Clinical and radiologic characteristics before starting antiviral therapy, at follow-up and at hepatocellular carcinoma development were collected. Diagnosis of hepatocellular carcinoma was centrally validated and its incidence was expressed as HCC/100 patients-year. **RESULTS:** 1,123 patients were included (60.6% males, 83.8% Child-Pugh A) and 95.2% achieved sustained virological response. Median time of follow-up was 19.6 months. Seventy-two patients developed hepatocellular carcinoma within a median of 10.3 months after starting antiviral treatment. HCC incidence was 3.73 HCC/100 patients-year (95% CI 2.96;4.70). Baseline liver function, alcohol intake and hepatic decompensation were associated to higher risk. The relative risk was significantly increased in patients with non-characterized nodules at baseline 2.83 (95%CI 1.55;5.16) vs absence of non-characterized nodules. When excluding these patients, the risk remained increased. **CONCLUSION:** These data expose a clear-cut time association between interferon-free treatment and HCC. There is need to further investigate the mechanisms involved in the increased risk of hepatocellular carcinoma emergence at short term. **LAY SUMMARY:** In this cohort of cirrhotic patients, interferon-free therapies achieved a high rate of sustained virological response (>95%); however, a 3.73% risk of developing de novo hepatocellular carcinoma per 100 persons/year with a clear-cut time association with antiviral therapy was registered. The presence of non-characterized nodules in radiologic assessments before starting DAA was associated to a 9.6% risk of developing hepatocellular carcinoma per 100 persons/year among cirrhotic patients treated with DAA. Thus, patients who started DAA and had indeterminate nodules have up to almost 3 times higher risk of developing HCC than those patients without or with well-defined benign nodules. The time association between starting DAA and developing HCC, together with the association

with the presence of non-characterized nodules at the baseline ultrasound, suggests that antiviral therapy elicits a mechanism (probably immune-related) that primes the growth and clinical recognition of hepatocellular carcinoma early during follow-up. As a result, liver cancer risk at short term is significantly increased.

[Among Medicare Patients With Hepatocellular Carcinoma, Non-alcoholic Fatty Liver Disease is the Most Common Etiology and Cause of Mortality.](#) Hester D1, Golabi P2, Paik J2, Younossi I3, Mishra A1, Younossi ZM1,2.

GOALS: The main purpose of this study was to assess the recent trends in mortality and health care utilization of hepatocellular carcinoma (HCC) among Medicare population in the United States. **BACKGROUND:** The incidence of HCC is increasing in the United States. **MATERIALS AND METHODS:** Data were obtained for a sample of Medicare beneficiary from 2005 to 2014. Diagnosis of HCC and etiology of liver disease were based on ICD-9 codes. Temporal trends in HCC rates, clinical, demographical and utilization parameters were analyzed by joinpoint regression model. **RESULTS:** Study cohort included 13,648 Medicare recipients with HCC (mean age: 70.0 y, 62.8% male and 76.0% white). Non-alcoholic fatty liver disease (NAFLD) was the most common cause of HCC in the inpatient (32.07%) and outpatient (20.22%) followed by hepatitis C virus (HCV) (19.2% and 9.75%, respectively). Between 2005 and 2014, HCC rate per 100,000 Medicare recipients increased from 46.3 to 62.8 [average annual percentage change (AAPC) =3.4%, P<0.001]. Rate of HCV-HCC increased from 6.18 to 16.54 (AAPC=11.8%, P<0.001) while the NAFLD-HCC increased from 9.32 to 13.61, P<0.001). Overall 1-year mortality decreased from 46.2% to 42.1% (AAPC=-1.7%, P=0.004). Total charges increased from $67,679 to $99,420 (AAPC=5.1%, P<0.001) for inpatients and from $11,933 to $32,084 (P<0.001) for outpatients. On comparison of patients with hepatitis B virus-HCC, those with NAFLD-HCC (odds ratio: 1.87, P<0.001) had higher risk of mortality. On comparison of patients with hepatitis B virus-HCC, those with HCV-HCC had higher charges (percent change: 24.33%, 95% confidence interval: 1.02%-53.02%, P=0.040). **CONCLUSIONS:** Although HCC rates are increasing, the overall mortality is decreasing. NAFLD is the most important cause of HCC and an independent predictor of HCC in the outpatient setting for Medicare patients with HCC.

[Association Between Noninvasive Fibrosis Markers and Postoperative Mortality After Hepatectomy for Hepatocellular Carcinoma.](#) Maegawa FB1,2, Shehorn L3, Aziz H4, Kettelle J1,2, Jie T2, Riall TS2. JAMA Netw Open. 2019 Jan 4;2(1):e187142. doi: 10.1001/jamanetworkopen.2018.7142.

IMPORTANCE: The selection criteria for hepatectomy for hepatocellular carcinoma (HCC) is not well established. The role of noninvasive fibrosis markers in this setting is unknown in the US population. **OBJECTIVE:** To evaluate whether aspartate aminotransferase-platelet ratio index (APRI) and fibrosis 4 (Fib4) values are associated with perioperative mortality and overall survival after hepatectomy for HCC. **DESIGN, SETTING, AND PARTICIPANTS:** In a multicenter cohort study, Veterans Administration Corporate Data Warehouse was used to evaluate a retrospective cohort of 475 veterans who underwent hepatectomy for HCC between January 1, 2000, and December 31, 2012, in Veterans Administration hospitals. Data analysis occurred between September 30, 2016, and December 30, 2017. Logistic regression, survival analysis, and change in concordance index analysis were performed to evaluate the association between APRI and Fib4 values and mortality. **EXPOSURES:** The cohort was stratified based on

preoperative APRI and Fib4 values. Analysis was performed accounting for the validated and established predictors of outcome. **MAIN OUTCOMES AND MEASURES:** Thirty-day mortality, 90-day mortality, and overall survival were the primary outcomes. An APRI value greater than 1.5 was considered high risk (cirrhosis), and an Fib4 value greater than 4.0 was considered high risk (advanced fibrosis). Portal hypertension (diagnosis of ascites or encephalopathy indicates presence of portal hypertension) and Child-Turcotte-Pugh (CTP) class (A indicates preserved liver function; B, mild to moderate liver dysfunction) served as 2 other measures of liver function. **RESULTS:** A total of 475 patients with HCC underwent hepatectomy. The mean (SD) age was 65.6 (9.4) years; Model for End-Stage Liver Disease score, 8.9 (3.1); and body mass index, 28.1 (4.9) (calculated as weight in kilograms divided by height in meters squared). A total of 361 patients (76.0%) were men, 294 (61.9%) were white; 308 (64.8%) were hepatitis C positive, and 346 (72.8%) were categorized as CTP class A. The most common surgical procedure was partial lobectomy, with 321 (67.6%) procedures. The APRI value greater than 1.5 vs 1.5 or lower was associated with increased 30-day mortality (odds ratio [OR], 6.45; 95% CI, 2.80-14.80) and 90-day mortality (OR, 2.65; 95% CI, 1.35-5.22), as was Fib4 greater than 4.0 vs Fib4 4.0 or lower for 30-day mortality (OR, 5.41; 95% CI, 2.35-12.50) and 90-day mortality (OR, 2.74; 95% CI, 1.41-5.35). Survival analysis showed that overall survival was significantly different for APRI greater than 1.5 vs 1.5 or lower (mean survival time, 3.6 vs 5.4 years; log-rank P < .001) and Fib4 greater than 4.0 vs 4.0 or lower (mean survival time, 4.1 vs 5.3 years; log rank P = .01). Adjusted Cox proportional hazards regression analysis revealed that elevated APRI was significantly associated with worse survival (hazard ratio [HR], 1.13; 95% CI, 1.03-1.23) but Fib4 values were not (HR, 1.04; 95% CI, 0.99-1.09). Change in concordance index showed that APRI and Fib4 improved the ability of CTP class and portal hypertension to predict postoperative mortality. **CONCLUSIONS AND RELEVANCE:** Elevated APRI and Fib4 values, which are noninvasive markers of fibrosis, were associated with higher perioperative mortality. The APRI was also associated with worse overall survival. Use of APRI and Fib4 measures improved the ability of established markers to predict postoperative mortality. These findings suggest incorporating APRI and Fib4 to the selection process for hepatectomy for HCC as predictors associated with mortality may be warranted.

[**Dipeptidyl Peptidase 4 Inhibitors Reduce Hepatocellular Carcinoma by Activating Lymphocyte Chemotaxis in Mice.**](#) Nishina S1, Yamauchi A2, Kawaguchi T3, et al. Cell Mol Gastroenterol Hepatol. 2018 Sep 11;7(1):115-134. doi: 10.1016/j.jcmgh.2018.08.008. eCollection 2019.
BACKGROUND & AIMS: CD26, a multifunctional transmembrane glycoprotein, is expressed in various cancers and functions as dipeptidyl peptidase 4 (DPP4). We investigated whether CD26 expression is associated with hepatocellular carcinoma (HCC) progression and whether DPP4 inhibitors exert antitumor effects against HCC. **METHODS:** CD26 expression was examined in 41 surgically resected HCC specimens. The effects of DPP4 inhibitors on HCC were examined by using HCC cell lines (Huh-7 and Li-7), xenograft tumors in nude mice, and a nonalcoholic steatohepatitis-related HCC mouse model. **RESULTS:** CD26 expression in HCC specimens was associated with increased serum DPP4 activity, as well as a more advanced stage, less tumor immunity, and poorer prognosis in HCC patients. The HCC cell lines and xenograft tumors exhibited CD26 expression and DPP4 activity. The DPP4 inhibitors did not exhibit antitumor effects in vitro, but natural killer (NK) and/or T-cell tumor accumulation suppressed growth of xenograft tumor and HCC in vivo. The antitumor effects of DPP4 inhibitors were

abolished by the depletion of NK cells or the neutralization of CXCR3, a chemokine receptor on NK cells. EZ-TAXIScan, an optical horizontal chemotaxis apparatus, identified enhanced NK and T-cell chemotaxis by DPP4 inhibitors ex vivo in the presence of Huh-7 cells and the chemokine CXCL10, which binds to CXCR3. The DPP4 inhibitors prevented the biologically active form of CXCL10 from being truncated by Huh-7 cell DPP4 activity. DPP4 inhibitors also suppressed tumor angiogenesis. **CONCLUSIONS:** These results provide a rationale for verifying whether DPP4 inhibitors clinically inhibit the progression of HCC or augment the antitumor effects of molecular-targeting drugs or immunotherapies against HCC.

[Complex Association of Virus- and Host-Related Factors with Hepatocellular Carcinoma Rate following Hepatitis C Virus Clearance.](#) Akuta N1,2, Suzuki F3,2, Sezaki H3,2, et al. J Clin Microbiol. 2019 Jan 2;57(1). pii: e01463-18. doi: 10.1128/JCM.01463-18. Print 2019 Jan. Little is known about the effects of virus- and host-related factors on hepatocarcinogenesis in patients who show viral clearance after HCV RNA eradication by direct-acting antivirals (DAAs). The subjects of this retrospective study were 1,922 patients with HCV genotype 1 (HCV-1)- or HCV-2-related chronic liver disease who showed a sustained virological response (SVR; defined as negative results for HCV RNA at 12 weeks after the cessation of all-oral DAAs). All patients were confirmed to be hepatocellular carcinoma (HCC) free before and during DAAs. HCC was diagnosed in 43 patients during the follow-up, with an incidence rate per 1,000 person years of 9.44. The cumulative HCC rates were 1.2, 2.0, and 3.1% at the end of 1, 2, and 3 years, respectively. The annual rate of HCC during the first 3 years was 1.0%. The incidence rate was significantly higher in patients infected with the HCV-1b core amino acid (aa) 70 mutant than in those infected with HCV-2a/2b, and the rate in patients infected with the HCV-1b core aa 70 wild type tended to be higher than that in patients infected with HCV-2a/2b. The rate in patients infected with the HCV-1b NS5A aa 93 mutant was significantly higher than that in patients infected with HCV-2a/2b. However, the rate was not different between patients infected with the IL28B rs8099917 TT genotype and patients infected with the non-TT genotype. Multivariate analysis identified a Wisteria floribunda agglutinin-positive Mac-2 binding protein (WFA+M2BP) cutoff index (COI) of ≥2.5 and infection with the HCV-1b core aa 70 mutant subgroup to be pretreatment predictors of posttreatment HCC. The same analysis identified an alpha-fetoprotein concentration of ≥5 μg/liter and an WFA+M2BP COI of ≥1.0 to be predictors of HCC at 24 weeks after the end of antiviral therapy. We conclude that both virus- and host-related factors seem to influence the development of HCC after HCV RNA eradication.

[No difference between direct-acting antivirals for hepatitis C in hepatocellular carcinoma risk.](#) Mun EJ1, Green P2, Berry K2, Ioannou GN3,2. Eur J Gastroenterol Hepatol. 2019 Jan;31(1):47-52. doi: 10.1097/MEG.0000000000001242.
BACKGROUND AND AIMS: It is unclear whether there are differences between direct-acting antivirals (DAAs) for hepatitis C virus in risk of hepatocellular carcinoma (HCC) after antiviral therapy. We aimed to compare different DAA regimens with respect to risk of de novo HCC following antiviral therapy. **PATIENTS AND METHODS:** We identified 33 137 patients who initiated hepatitis C virus antiviral treatment in the Veterans Affair healthcare system between 6 December 2013 and 31 December 2015 with one of four DAA-only regimens (± ribavirin): paritaprevir/ritonavir/ombitasvir/dasabuvir (n=6289), sofosbuvir (n=4356), sofosbuvir+simeprevir (n=3210), and ledipasvir/sofosbuvir (n=19 282). We retrospectively followed patients until 15 June 2017 to identify incident (de novo) cases of HCC. We used

propensity score-adjusted Cox proportional hazards regression to compare different DAA regimens with respect to HCC risk. **RESULTs:** During a mean follow-up of 1.52 years, 741 new cases of HCC were diagnosed after antiviral treatment (annual incidence=1.47%). Patients treated with sofosbuvir+simeprevir had the highest annual HCC incidence (2.47%), followed by sofosbuvir (1.91%), ledipasvir/sofosbuvir (1.26%), and paritaprevir/ritonavir/ ombitasvir/ dasabuvir (0.95%). However, there were great differences between DAA-treated patients in the prevalence of cirrhosis, markers of advanced fibrosis, thrombocytopenia, and other HCC risk factors. After adjustment for baseline characteristics associated with HCC, there were no significant differences in HCC risk between the four DAA regimens. **CONCLUSION:** There are no significant differences between DAA regimens in HCC risk after antiviral treatment. This suggests that DAAs do not have direct carcinogenic effects as it would be unlikely that different DAAs would have identical carcinogenic effects.