



February 2019

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[Pharmacokinetics of Daclatasvir, Sofosbuvir, and GS-331007 in a Prospective Cohort of Hepatitis C Virus-Positive Kidney Transplant Recipients.](#) Schrezenmeier E1, Hoffmann F2, Jaeger C2, et al. Ther Drug Monit. 2019 Feb;41(1):53-58. doi: 10.1097/FTD.0000000000000567.

BACKGROUND: Limited data exist on the pharmacokinetic profile of novel direct-acting antivirals in kidney transplant recipients. Daclatasvir is primarily eliminated through the biliary route and sofosbuvir through the renal route; here, we report the pharmacokinetic profile of combined treatment with these compounds in a prospective study of hepatitis C virus (HCV)-positive kidney transplant recipients (EudraCT: 2014-004551-32). **METHODS:** In this study, plasma samples of 16 HCV-positive kidney transplant recipients receiving daclatasvir and sofosbuvir were collected at 4 time points at days 1, 7, 14, 21, 56, and 84 after start of treatment. Inclusion criteria were stable graft function and an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m. Daclatasvir, sofosbuvir, and GS-331007 (inactive metabolite of sofosbuvir) plasma concentrations were determined using ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry. **RESULTS:** All patients showed a rapid virological response with HCV RNA below the detection limit 21 days after the start of therapy (medium time to viral clearance). No difference of the areas under the concentration-time curve (AUC) of daclatasvir, sofosbuvir, and GS-331007 was observed between patients with an eGFR below or ≥ 60 mL/min. For GS-331007, no relevant changes of trough levels were observed over time. Mean GS-331007 trough levels were 339.5 ± 174.9 ng/mL in patients with an eGFR ≥ 60 mL/min and 404.3 ± 226 ng/mL in patients with an eGFR <60 mL/min at day 7 (P = 0.52). At day 84, GS-331007 trough levels were 357.8 ± 200.8 and 404.2 ± 70.2 ng/mL in patients with an eGFR ≥ 60 mL/min and in patients with an eGFR <60 mL/min, respectively (P = 0.51). The accumulation ratios of renally eliminated GS-331007 for AUC and C_{max} did not significantly differ between the 2 eGFR groups at day 7. **CONCLUSIONS:** An impaired eGFR (30-60 mL/min) does not lead to a dose accumulation of daclatasvir, sofosbuvir, and GS-331007. This study provides the rationale for future studies investigating the pharmacokinetic profile of sofosbuvir-based HCV treatment in kidney transplant recipients with an eGFR <30 mL/min.

Real-World Study on Sofosbuvir-based Therapies in Asian Americans With Chronic Hepatitis C.

Pan CQ^{1,2}, Tiongson BC^{3,4}, Hu KQ⁵, et al. J Clin Gastroenterol. 2019 Feb;53(2):147-154. doi: 10.1097/MCG.0000000000001078.

BACKGROUND: Limited data exist with regard to treatment outcomes in Asian Americans with chronic hepatitis C (CHC). We evaluated sofosbuvir (SOF)-based regimens in a national cohort of Asian Americans. **METHODS:** Eligible Asian Americans patients with CHC who had posttreatment follow-up of 24 weeks for SOF -based therapies from December 2013 to June 2017 were enrolled from 11 sites across the United States. The primary endpoint was sustained virologic response (SVR) rates at posttreatment weeks 12 and 24. Secondary endpoints were to evaluate safety by tolerability and adverse events (AEs). **RESULTS:** Among 231 patients screened, 186 were enrolled. At baseline, 31% (57/186) patients were cirrhotic, 34% (63/186) were treatment experienced. Most of the subjects (42%, 79/186) received ledispavir/SOF therapy. The overall SVR₁₂ was 95%, ranging from 86% in genotype (GT) 1b on SOF+ribavirin to 100% in GT 1b patients on ledipasvir/SOF at subgroup analyses. SVR₁₂ was significantly lower in cirrhotic than in noncirrhotic patients [88% (50/57) vs. 98% (126/129), P<0.01]. Stratified by GT, SVR₁₂ were: 96% (43/45) in GT 1a; 93% (67/72) in GT 1b; 100% (23/23) in GT 2; 90% (19/21) in GT 3; 100% (1/1) in GT 4; 83% (5/6) in GT 5; and 100% (16/16) in GT 6. Cirrhotic patients with treatment failure were primarily GT 1, (GT 1a, n=2; GT 1b, n=4) with 1 GT 5 (n=1). Patients tolerated the treatment without serious AEs. Late relapse occurred in 1 patient after achieving SVR₁₂. **CONCLUSIONS:** In Asian Americans with CHC, SOF-based regimens were well tolerated without serious AEs and could achieve high SVR₁₂ regardless of hepatitis C viral infection GT.

Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir in Patients With Hepatitis C Virus Genotype 1 or 4 Infection and Advanced Kidney Disease.

Lawitz E¹, Gane E², Cohen E³, et al. Kidney Int Rep. 2018 Oct 9;4(2):257-266. doi: 10.1016/j.ekir.2018.10.003. eCollection 2019 Feb.

INTRODUCTION: Hepatitis C virus (HCV) infection is common in patients with end-stage renal disease. We investigated the safety and efficacy of ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) ± dasabuvir (DSV) ± ribavirin (RBV) in 2 phase 3, open-label, multicenter studies in patients with stage 4 or 5 chronic kidney disease (CKD). **METHODS:** RUBY-I, Cohort 2 enrolled treatment-naïve or -experienced patients with HCV genotype (GT) 1a or 1b infection, with or without cirrhosis. Patients received 12 weeks (24 weeks for GT1a patients with cirrhosis) of OBV/PTV/r + DSV; all GT1a patients received RBV. RUBY-II enrolled treatment-naïve patients with GT1a or GT4 infection without cirrhosis. All patients received 12 weeks of RBV-free treatment: OBV/PTV/r + DSV for GT1a-infected patients; OBV/PTV/r for GT4-infected patients. The primary endpoint was sustained virologic response at posttreatment week 12 (SVR₁₂). **RESULTS:** RUBY-I, Cohort 2 and RUBY-II enrolled 66 patients, including 50 (76%) on dialysis; 15 (23%) had compensated cirrhosis. Overall, the SVR₁₂ rate was 95% (63/66); 1 patient had virologic failure. There were 3 discontinuations due to adverse events. Seventy-three percent (27/37) of patients receiving RBV had adverse events leading to RBV dose modification. The RBV-free RUBY-II study had no hemoglobin-associated adverse events. **CONCLUSION:** Treatment with OBV/PTV/r ± DSV ± RBV was well tolerated and patients with HCV GT1 or 4 infection and stage 4 or 5 CKD had high SVR₁₂ rates, including patients with compensated cirrhosis and/or prior treatment experience.

[Impact of hepatitis C treatment on pain intensity, prescription opioid use and arthritis.](#)

Kumthekar A1, Shull S2, Lovejoy TI2,3, Morasco BJ2,3, Chang M2,3, Barton J2,3. Int J Rheum Dis. 2019 Feb 6. doi: 10.1111/1756-185X.13479. [Epub ahead of print]

OBJECTIVE: To assess the impact of direct acting anti-viral (DAA) therapy for hepatitis C virus (HCV) infection on changes in pain intensity and prescription opioid use among Veterans.

METHODS: We conducted a retrospective cohort study of Veterans with HCV who were seen in a rheumatology clinic at least once while receiving DAA therapy between January 1, 2010 and December 31st 2016. Demographic characteristics, HCV status, HCV treatment characteristics, numeric rating scale (NRS) pain scores and opioid prescription data were extracted from the electronic medical record. Pain scores were averaged over 6 months prior to HCV treatment and 6 months after completion of treatment. Prescription opioid dose was converted to a morphine equivalent daily dose (MEDD) and averaged across the two 6-month intervals. Generalized estimating equations were used to model the change in average pain and MEDD from pre- to post-HCV treatment. Effect size was assessed using Cohen's d. **RESULTS:** A total of 121 Veterans, 91% male with average age of 59 were included. Average pre-treatment pain was 4.4 (SD 2.4). The average reduction in pain scores was 0.6 points (P = 0.02, Cohen's d = 0.22) after treatment. Among 67 patients prescribed chronic opioid therapy at baseline, average pre-treatment MEDD was 52.4 mg (SD = 62.5 mg) and post-DAA treatment average MEDD was 49.5 mg (SD = 69.3 mg), representing a decrease by 2.9 mg (P < 0.01, Cohen's d = 0.14). Opioid dose reduction was seen in 43/67 patients and 12 patients discontinued opioids entirely.

CONCLUSION: Among US Veterans, subjective pain scores had modest improvement and opioid prescriptions were mildly reduced following treatment with DAA.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Hepatitis C Virus Escape Studies of Human Antibody AR3A Reveal a High Barrier to Resistance and Novel Insights on Viral Antibody Evasion Mechanisms.](#)

Velázquez-Moctezuma R1, Galli A1, Law M2, Bukh J3, Prentoe J3. J Virol. 2019 Feb 5;93(4). pii: e01909-18. doi: 10.1128/JVI.01909-18. Print 2019 Feb 15.

Yearly, ~2 million people become hepatitis C virus (HCV) infected, resulting in an elevated lifetime risk for severe liver-related chronic illnesses. Characterizing epitopes of broadly neutralizing antibodies (NAbs), such as AR3A, is critical to guide vaccine development. Previously identified alanine substitutions that can reduce AR3A binding to expressed H77 envelope were introduced into chimeric cell culture-infectious HCV recombinants (HCVcc) H77(core-NS2)/JFH1. Substitutions G523A, G530A, and D535A greatly reduced fitness, and S424A, P525A, and N540A, although viable, conferred only low-level AR3A resistance. Using highly NAb-sensitive hypervariable region 1 (HVR1)-deleted HCVcc, H77/JFH1 Δ HVR1 and J6(core-NS2)/JFH1 Δ HVR1, we previously reported a low barrier to developing AR5A NAb resistance substitutions. Here, we cultured Huh7.5 cells infected with H77/JFH1, H77/JFH1 Δ HVR1, or J6/JFH1 Δ HVR1 with AR3A. We identified the resistance envelope substitutions M345T in H77/JFH1, L438S and F442Y in H77/JFH1 Δ HVR1, and D431G in J6/JFH1 Δ HVR1. M345T increased infectivity and conferred low-level AR3A resistance to H77/JFH1 but not H77/JFH1 Δ HVR1. L438S and F442Y conferred high-level AR3A resistance to H77/JFH1 Δ HVR1 but abrogated the infectivity of H77/JFH1. D431G conferred AR3A resistance to J6/JFH1 Δ HVR1 but not J6/JFH1. This was possibly because D431G conferred broadly increased neutralization sensitivity to J6/JFH1 Δ 431G but not J6/JFH1 Δ HVR1/D431G.

while decreasing scavenger receptor class B type I coreceptor dependency. Common substitutions at positions 431 and 442 did not confer high-level resistance in other genotype 2a recombinants [JFH1 or T9(core-NS2)/JFH1]. Although the data indicate that AR3A has a high barrier to resistance, our approach permitted identification of low-level resistance substitutions. Also, the HVR1-dependent effects on AR3A resistance substitutions suggest a complex role of HVR1 in virus escape and receptor usage, with important implications for HCV vaccine development. **IMPORTANCE:** Hepatitis C virus (HCV) is a leading cause of liver-related mortality, and limited treatment accessibility makes vaccine development a high priority. The vaccine-relevant cross-genotype-reactive antibody AR3A has shown high potency, but the ability of the virus to rapidly escape by mutating the AR3A epitope (barrier to resistance) remains unexplored. Here, we succeeded in inducing only low-level AR3A resistance, indicating a higher barrier to resistance than what we have previously reported for AR5A. Furthermore, we identify AR3A resistance substitutions that have hypervariable region 1 (HVR1)-dependent effects on HCV viability and on broad neutralization sensitivity. One of these substitutions increased envelope breathing and decreased scavenger receptor class B type I HCV coreceptor dependency, both in an HVR1-dependent fashion. Thus, we identify novel AR3A-specific resistance substitutions and the role of HVR1 in protecting HCV from AR3-targeting antibodies. These viral escape mechanisms should be taken into consideration in future HCV vaccine development.

[Inconsistent temporal patterns of genetic variation of HCV among high-risk subjects may impact inference of transmission networks.](#) Rose R1, Rodriguez C2, Dollar JJ2, Lamers SL2, Massaccesi G3, Osburn W3, Ray SC3, Thomas DL3, Cox AL3, Laeyendecker O4. *Infect Genet Evol.* 2019 Feb 22. pii: S1567-1348(19)30026-7. doi: 10.1016/j.meegid.2019.02.025. [Epub ahead of print]

Hepatitis-C Virus (HCV) sequences are often used to establish networks of people who inject drugs (PWID). However, the degree to which within-host evolutionary dynamics affect those inferences has not been carefully studied. Here, we analyzed 702 longitudinally-sampled HCV E1 sequences from 88 HCV+ people who inject drugs (PWID) in the Baltimore Before and After Acute Study of Hepatitis (BBAASH) cohort. Individuals were tested for HCV RNA over multiple visits to the clinic, and the HCV E1 gene was sequenced for HCV+ samples. Genetic clustering was performed on the full set of sequences using a 3% genetic distance threshold to define epidemiological linkage. Maximum-likelihood (ML) phylogenies were inferred to assess evolutionary relationships. We found 22 clusters containing sequences sampled over five or more years (long-term clusters, LTC), of which 17 had >1 subject. In six of the multi-subject LTC, one subject had a sequence sampled >3 years earlier or later than the next-closest subject in the cluster (time-gap LTC). ML trees showed that, in three of the time-gap LTC, two subjects had identical sequences despite 7-10 years separating the sampling times. In four of the time-gap LTC for whom additional data were available, the subject with the later detected shared variant had both different variants and visits with no detectable HCV RNA (RNA-) prior to the appearance of the shared variant. In the subject with the earlier detection of the shared variant, different variants and RNA- visits were also detected in multiple cases subsequent to appearance of the shared variant. Complex patterns of shared viral variation among PWID reflect on-going re-infection, multiple transmission partners, and/or inconsistent detection of viral variants. Our results suggest that transmission events are currently underestimated by analysis of sequences at a single point in time.

Sofosbuvir-Based Therapy in Hepatitis C Virus-Infected Cancer Patients: A Prospective Observational Study.

Torres HA^{1,2}, Economides MP^{1,3}, Angelidakis G¹, et al. *Am J Gastroenterol.* 2019 Feb;114(2):250-257. doi: 10.1038/s41395-018-0383-2.

BACKGROUND: Data are sparse on treatment of chronic hepatitis C virus (HCV) in cancer patients. We evaluated the efficacy and safety of sofosbuvir-based therapy (SOFBT) in cancer patients. **METHODS:** Patients treated with SOFBT at our center during 2014-2017 were included in a prospective observational study. Efficacy [sustained virologic response at 12 weeks after the end of treatment (SVR12)], cancer-related outcomes and adverse events (AEs) were assessed. **RESULTS:** We included 153 patients. Most were men (109; 71%), white (92; 60%), non-cirrhotic (105; 69%), and with HCV genotype 1 (110; 72%). The most common cancers were hepatocellular carcinoma (HCC) (27; 18%) and multiple myeloma (14; 9%). The overall SVR12 rate was 91% (128/141). SVR12 was 100% in patients treated with ledipasvir/sofosbuvir for 8 weeks. Of the 32 patients initially excluded from cancer clinical trials because of HCV, 27 (84%) were granted cancer therapy access after starting SOFBT. Six patients with indolent non-Hodgkin's lymphoma (NHL) received SOFBT without cancer treatment. Two achieved complete remission, one had partial remission, and two had stable cancer. Within 6 months after SOFBT, 5% (6/121) of patients in remission or with stable cancer, had progression or recurrence (two with HCC and one each with esophageal cancer, cholangiocarcinoma, NHL, and tonsillar cancer). No de novo HCCs occurred. AEs were most commonly grade 1-2 (90%). **CONCLUSIONS:** SOFBT in HCV-infected cancer patients is effective and safe, may permit access to investigational cancer therapy expanding treatment options, may induce remission of NHL, and may be used for 8 weeks.

Safety and Efficacy of Elbasvir/Grazoprevir in Asian Participants with Hepatitis C Virus Genotypes 1 and 4 Infection.

Wei L¹, Kumada H², Perumalswami PV³, Tanwandee T⁴, et al. *J Gastroenterol Hepatol.* 2019 Feb 19. doi: 10.1111/jgh.14636. [Epub ahead of print]

BACKGROUND AND AIM: Estimates suggest that in Asia more than 31 million individuals have hepatitis C virus infection. The present analysis was conducted to assess the efficacy and safety of elbasvir/grazoprevir in Asian participants enrolled in the elbasvir/grazoprevir phase 2/3 clinical trials. **METHODS:** This is an integrated analysis of data from 12 international phase 2/3 clinical trials. Asian participants with chronic hepatitis C virus genotype 1 or 4 infection who received elbasvir 50 mg/grazoprevir 100 mg once daily for 12 weeks or elbasvir/grazoprevir plus ribavirin for 16 weeks were included in this analysis. The primary end point was sustained virologic response at 12 weeks after completion of therapy (SVR12). **RESULTS:** Seven hundred eighty Asian participants from 15 countries were included in this analysis. SVR12 was achieved by 756/780 (96.9%) of all participants, including 748/772 (96.9%) of those who received elbasvir/grazoprevir for 12 weeks and 8/8 (100%) of those who received elbasvir/grazoprevir plus ribavirin for 16 weeks. In the genotype 1b-infected population, the SVR12 rate was 97.5%, and there was no impact of age, high baseline viral load, or presence of cirrhosis. The most frequently reported adverse events were nasopharyngitis (8.0%), upper respiratory tract infection (5.4%), and diarrhea (5.2%). Twenty participants receiving elbasvir/grazoprevir for 12 weeks reported a total of 25 serious adverse events and 7 (0.9%) discontinued treatment because of an adverse event. **CONCLUSION:** Elbasvir/grazoprevir administered for 12 weeks is an effective and generally well-tolerated treatment option for Asian individuals with hepatitis C virus GT1b infection.

[Transplanting hepatitis C virus-infected hearts into uninfected recipients: A single-arm trial.](#) McLean RC1, Reese PP2,3, Acker M4, et al. Am J Transplant. 2019 Feb 15. doi: 10.1111/ajt.15311. [Epub ahead of print]

The advent of direct-acting antiviral therapy for hepatitis C virus (HCV) has generated tremendous interest in transplanting organs from HCV-infected donors. We conducted a single-arm trial of orthotopic heart transplantation (OHT) from HCV-infected donors into uninfected recipients, followed by elbasvir/grazoprevir treatment after recipient HCV was first detected (NCT03146741; sponsor: Merck). We enrolled OHT candidates aged 40-65 years; LVAD support and liver disease were exclusions. We accepted hearts from HCV-genotype 1 donors. From 5/16/2017 to 4/10/2018, 20 patients consented for screening and enrolled, and 10 (median age 52.5 years; 80% male) underwent OHT. The median wait from UNOS opt-in for HCV nucleic-acid-test (NAT)+ donor offers to OHT was 39 days (IQR 17, 57). The median donor age was 34 years (IQR 31, 37). Initial recipient HCV RNA levels ranged from 25 IU/mL - 40 million IU/mL, but all 10 patients had rapid decline in HCV NAT after elbasvir/grazoprevir treatment. Nine recipients achieved SVR-12. The 10th recipient had a positive cross-match, experienced antibody-mediated rejection and multi-organ failure, and died on day 79. No serious adverse events occurred from HCV transmission or treatment. These short-term results suggest that HCV-negative candidates transplanted with HCV-infected hearts have acceptable outcomes. This article is protected by copyright. All rights reserved.

HIV/HCV COINFECTION

[Sexually transmitted hepatitis C infection: the evolving epidemic in HIV-positive and HIV-negative MSM.](#) Lockart I1,2, Matthews GV3, Danta M1,2. Curr Opin Infect Dis. 2019 Feb;32(1):31-37. doi: 10.1097/QCO.0000000000000515.

PURPOSE OF REVIEW: The scale-up of direct-acting antiviral (DAA) therapy and introduction of preexposure prophylaxis (PrEP) has changed the epidemiology of sexually acquired hepatitis C virus (HCV) amongst HIV-positive and HIV-negative MSM. **RECENT FINDINGS:** Sexually acquired HCV continues to occur predominantly amongst HIV-positive MSM. Despite an increased uptake of DAA therapy the incidence of acute HCV has not declined consistently amongst HIV-positive MSM, likely a result of high infection and reinfection rates. Increasing cases of sexually acquired HCV have been reported amongst HIV-negative MSM accessing PrEP. Despite a lower prevalence of HCV at baseline, HIV-negative MSM accessing PrEP have an equally high overall incidence of HCV compared with HIV-positive MSM during follow-up. Behavioural factors (high-risk sexual behaviours and sexualized drug use) appear to be driving this HCV epidemic amongst MSM and effective behavioural interventions and early identification of reinfections are essential to control the HCV epidemic amongst MSM.

SUMMARY: An improved understanding of the epidemiology of sexually acquired HCV will allow implementation of more effective public health interventions to control the transmission of HCV amongst HIV-positive and HIV-negative MSM.

[Solid Organ Transplantation in the HIV-Infected Patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice.](#) Blumberg EA1, Rogers CC2; American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Feb 17:e13499. doi: 10.1111/ctr.13499. [Epub ahead of print]

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the management of transplantation in HIV infected individuals. Transplantation has become the standard of care for patients with HIV and end stage kidney or liver disease. Although less data exist for thoracic organ and pancreas transplantation, it is likely that transplantation is also safe and effective for these recipients as well. Despite what is typically a transient decline in CD4+ T lymphocytes, HIV remains well-controlled and infection risks are similar to those of HIV uninfected transplant recipients. The availability of effective directly active antivirals for the treatment of Hepatitis C is likely to improve outcomes in HIV and HCV co-infected individuals, a population previously noted to have decreased survival. Drug interactions remain an important consideration and integrase inhibitor based regimens are preferred due to the absence of interactions with calcineurin and mTOR inhibitors. Additionally, despite the use of more potent immunosuppression, rejection rates exceed those found in HIV uninfected recipients. Ongoing research evaluating HIV positive organ donors may provide support for utilizing these donors for HIV positive patients in need of transplantation. This article is protected by copyright. All rights reserved.

[Effect of incident hepatitis C infection on CD4+ cell count and HIV RNA trajectories based on a multinational HIV seroconversion cohort.](#) van Santen DK1, van der Helm JJ1,2,

Touloumi G3, et al. AIDS. 2019 Feb 1;33(2):327-337. doi: 10.1097/QAD.0000000000002040.

BACKGROUND: Most studies on hepatitis C virus (HCV)/HIV-coinfection do not account for the order and duration of these two infections. We aimed to assess the effect of incident HCV infection, and its timing relative to HIV seroconversion (HIVsc) in HIV-positive MSM on their subsequent CD4 T-cell count and HIV RNA viral load trajectories. **METHODS:** We included MSM with well estimated dates of HIVsc from 17 cohorts within the CASCADE Collaboration. HCV-coinfected MSM were matched to as many HIV monoinfected MSM as possible by HIV-infection duration and combination antiretroviral therapy (cART) use. We used multilevel random-effects models stratified by cART use to assess differences in CD4 cell count and HIV RNA viral load trajectories by HCV-coinfection status. **FINDINGS:** We matched 214 (ART-naive) and 147 (on cART) HCV-coinfected MSM to 5384 and 3954, respectively, matched controls. The timing of HCV seroconversion (HCVsc) relative to HIVsc had no demonstrable effect on HIV RNA viral load or CD4 cell count trajectories. In the first 2-3 years following HCVsc CD4 cell counts were lower among HCV-coinfected MSM, but became comparable with HIV monoinfected MSM thereafter. In ART-naive MSM, during the first 2 years after HCVsc, HIV RNA viral load levels were lower or comparable with HIV monoinfected, tending to be higher thereafter. In MSM on cART, HCV had no significant effect on having a detectable HIV RNA viral load. **INTERPRETATION:** Irrespective of the duration of HIV infection when HCV is acquired, CD4 cell counts were temporarily lower following HCVsc, even when on cART. The clinical implications of our findings remain to be further elucidated.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

[An interview project with native American people: a community-based study to identify actionable steps to reduce health disparities.](#) Leston J1, Crisp C2, Lee C3, Rink E4. Public

Health. 2019 Feb 12. pii: S0033-3506(18)30376-7. doi: 10.1016/j.puhe.2018.12.002. [Epub ahead of print]

OBJECTIVES: The primary objective of this study was to work with tribal communities to define and develop their own healthcare services and strategies for positive change regarding injection drug use, human immunodeficiency virus (HIV), and hepatitis C virus (HCV) infection. The secondary objective of this study was to incorporate community capacity building strategies to develop and sustain programming and resources to optimize tribal communities' responsiveness to reduce health disparities. **STUDY DESIGN:** Semi-structured qualitative interviews. **METHODS:** Interviews were guided by community-based participatory research (CBPR) principles to create programs, projects, and policy recommendations meaningful to American Indian and Alaska Native (AI/AN) people. **RESULTS:** The study generated a formative understanding of the context of AI/AN people who inject drugs (PWID) in three distinct AI/AN communities as well as developed local capacity for future programming, projects, and policy. **CONCLUSIONS:** This study confirms CBPR methods should be part of an iterative cycle to inform policy and programs. CBPR has helped strengthen local research capacity and has formed ongoing relationships between study investigators, local liaisons, and the community that will be essential for next phases of program design and policy implementation. This cycle of CBPR could be replicated in other tribal communities to bring awareness of the opioid epidemic and its effects and to prioritize local indigenous and community-led responses.

[A Transitioning Epidemic: How The Opioid Crisis Is Driving The Rise In Hepatitis C.](#)

Powell D1, Alpert A2, Pacula RL3. Health Aff (Millwood). 2019 Feb;38(2):287-294. doi: 10.1377/hlthaff.2018.05232.

The hepatitis C virus is responsible for more deaths in the United States than any other infectious disease, and hepatitis C infections have been rising at an alarming rate since 2010. We evaluated the role of the opioid epidemic and, in particular, the 2010 introduction of an abuse-deterrent version of OxyContin. The OxyContin reformulation led some users of the drug to switch to heroin, which could have exposed them to the hepatitis C virus. We used difference-in-differences methods, using data for the period 2004-15, to assess whether states with higher rates of OxyContin misuse prior to reformulation-states where the reformulation had more impact-experienced faster growth in infections after the reformulation. States with above-median OxyContin misuse before the reformulation experienced a 222 percent increase in hepatitis C infection rates in the post-reformulation period, while states with below-median misuse experienced only a 75 percent increase. These results suggest that interventions to deter opioid misuse can have unintended long-term public health consequences.

[Experiences with interferon-free hepatitis C therapies: addressing barriers to adherence and optimizing treatment outcomes.](#)

Skolnik AA1,2,3, Noska A4,5, Yakovchenko V1, Tsai J6,7, Jones N6,7, Gifford AL1,2, McInnes DK8,9. BMC Health Serv Res. 2019 Feb 1;19(1):91. doi: 10.1186/s12913-019-3904-9.

BACKGROUND: Millions of Americans are living with hepatitis C, the leading cause of liver disease in the United States. Medication treatment can cure hepatitis C. We sought to understand factors that contribute to hepatitis C treatment completion from the perspectives of patients and providers. **METHODS:** We conducted semi-structured interviews at three Veterans Affairs Medical Centers. Patients were asked about their experiences with hepatitis C treatments and perspectives on care. Providers were asked about observations regarding patient responses to

medications and perspectives about factors resulting in treatment completion. Transcripts were analyzed using a grounded thematic approach—an inductive analysis that lets themes emerge from the data. **RESULTS:** Contributors to treatment completion included Experience with Older Treatments, Hope for Improvement, Symptom Relief, Tailored Organized Routines, and Positive Patient-Provider Relationship. Corresponding barriers also emerged, including pill burden and skepticism about treatment effectiveness and safety. **CONCLUSION:** Despite the improved side-effect profile of newer HCV medications, multiple barriers to treatment completion remain. However, providers and patients were able to identify avenues for addressing such barriers.

Sofosbuvir-Based Regimens for Chronic Hepatitis C in a Well-Insured U.S. Population: Patient Characteristics, Treatment Adherence, Effectiveness, and Health Care Costs, 2013-2015. Yin S1, Barker L1, White JZ1, Jiles RB1. *J Manag Care Spec Pharm.* 2019 Feb;25(2):195-210. doi: 10.18553/jmcp.2019.25.2.195.

BACKGROUND: Chronic hepatitis C (CHC) is a leading cause of morbidity and mortality and has imposed a high health care burden in the United States. Direct-acting antiviral (DAA) regimens are well tolerated and highly effective for CHC therapy but were initially marketed at a high price. Studies of their real-world use with a nationwide population are limited.

OBJECTIVE: To examine patient characteristics, treatment adherence, effectiveness, and health care costs in a large U.S. population with commercial and Medicare supplemental insurance plans who received simeprevir (SIM), sofosbuvir (SOF), or ledipasvir/sofosbuvir (LED/SOF) during the years 2013-2015. **METHODS:** Patients with at least 1 diagnosis code for CHC and at least 1 claim for SIM, SOF, or LED/SOF prescriptions were selected. The date of the first claim for SIM, SOF, or LED/SOF was defined as the index date. Analyses were stratified by 4 regimens: SOF + SIM ± ribavirin (RBV), SOF + peginterferon alpha-2a or 2b (PEG) + RBV, SOF + RBV, and LED/SOF ± RBV. Adherence was defined by the proportion of days covered (PDC) ≥ 80%. Sustained virologic response (SVR12) was defined as a hepatitis C virus (HCV) RNA load of ≤ 25 IU/mL measured at ≥ 12 weeks following the end of the days supply of the last DAA refill. Health care costs such as DAA drug costs and medical costs (inpatient costs plus outpatient costs) were described. **RESULTS:** Of 10,808 CHC patients, approximately two thirds were male, and mean age was 55 years. The proportion of patients with compensated cirrhosis among each regimen ranged from 7.4% in LED/SOF ± RBV to 13.8% in SOF + SIM ± RBV, and the proportion of patients with decompensated cirrhosis ranged from 3.9% in LED/SOF ± RBV to 10.7% in SOF + SIM ± RBV. The majority of patients (89.0%) used the newer regimen LED/SOF ± RBV in 2015. Adherence rates were estimated at 80.5%, 81.5%, 85.7%, and 91.4% for SOF + SIM ± RBV (n = 1,761); SOF + PEG + RBV (n = 1,314); SOF + RBV (n = 1,994); and LED/SOF ± RBV (n = 5,739), respectively. Regimen-specific adherence predictors included sex, age group, payer type, health plan, and treatment option with RBV. Being born during 1945-1965, liver disease severity, and Charlson Comorbidity Index levels did not predict adherence in any regimen. Overall SVR12 was 92.6% in 203 patients with available HCV RNA results: 100% (41/41) in SOF + SIM ± RBV; 83.3% (25/30) in SOF + PEG + RBV; 90.6% (29/32) in SOF + RBV; and 93% (93/100) in LED/SOF ± RBV. While the drug costs for these DAA regimens were initially high, they had decreased 18.9% (P < 0.001) during 2013-2015. Medical costs decreased 9.2% (P < 0.001) 1 year after the index dates. **CONCLUSIONS:** These results indicate that DAA drug costs decreased steadily during 2013-2015 and that 89% of patients on SOF-based DAA regimens took newer, lower-cost regimens with adherence rates above 80%. Available data show that SVR12 rates were close to those obtained in clinical studies. Medical

costs also significantly decreased 1 year after the index dates. **DISCLOSURES:** No outside funding supported this study. All authors are U.S. federal employees of the Centers for Disease Control and Prevention. The authors declare that they have no competing interests. The findings and conclusions in this research are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

[New Face of Hepatitis C.](#) Wu T1, Konyon PG2, Cattaneo AW2, Saab S3,4,5. Dig Dis Sci. 2019 Feb 13. doi: 10.1007/s10620-019-05511-y. [Epub ahead of print]

Chronic hepatitis C viral (HCV) infection continues to carry a high burden of disease despite recent and emerging advancements in treatment. The persistently high prevalence of HCV is attributed to the rising opioid epidemic, with a history of injection drug use as the primary risk factor for infection. As a result, the epidemiology of HCV-infected individuals is changing. Previously a disease of "Baby Boomers," males, and non-Hispanic blacks, the new generation of patients with HCV includes younger adults from 20 to 39 years of age, both men and women similarly represented, and non-Hispanic whites. Shifting trends in these demographics may be attributed to the use of injection drugs, which also has suggested impact on fibrosis progression in infected individuals. Awareness of the changing face of HCV is necessary to expand and revise recommendations regarding screening, outreach, and care engagement of infected individuals, in order to best identify patients at-risk for infection.

[Evidence-based and guideline-concurrent responses to narratives deferring HCV treatment among people who inject drugs.](#) Childs E1, Assoumou SA2, Biello KB3,4,5, et al. Harm Reduct J. 2019 Feb 11;16(1):14. doi: 10.1186/s12954-019-0286-6.

BACKGROUND: Hepatitis C virus (HCV) infection is increasingly prevalent among people who inject drugs (PWID) in the context of the current US opioid crisis. Although curative therapy is available and recommended as a public health strategy, few PWID have been treated. We explore PWID narratives that explain why they have not sought HCV treatment or decided against starting it. We then compare these narratives to evidence-based and guideline-concordant information to better enable health, social service, harm reduction providers, PWID, and other stakeholders to dispel misconceptions and improve HCV treatment uptake in this vulnerable population. **METHODS:** We recruited HIV-uninfected PWID (n = 33) through community-based organizations (CBOs) to participate in semi-structured, in-depth qualitative interviews on topics related to overall health, access to care, and knowledge and interest in specific HIV prevention methods. **RESULTS:** In interviews, HCV transmission and delaying or forgoing HCV treatment emerged as important themes. We identified three predominant narratives relating to delaying or deferring HCV treatment among PWID: (1) lacking concern about HCV being serious or urgent enough to require treatment, (2) recognizing the importance of treatment but nevertheless deciding to delay treatment, and (3) perceiving that clinicians and insurance companies recommend that patients who currently use or inject drugs should delay treatment. **CONCLUSIONS:** Our findings highlight persistent beliefs among PWID that hinder HCV treatment utilization. Given the strong evidence that treatment improves individual health regardless of substance use status while also decreasing HCV transmission in the population, efforts are urgently needed to counter the predominant narratives identified in our study. We provide evidence-based, guideline-adherent information that counters the identified narratives in order to help individuals working with PWID to motivate and facilitate treatment access and uptake. An important strategy to improve HCV treatment initiation among PWID could involve

disseminating guideline-concordant counternarratives to PWID and the providers who work with and are trusted by this population.

[Impact of hepatitis C virus and insurance coverage on mortality.](#) Bush H, Paik J, Golabi P, de Avila L, Escheik C, Younossi ZM1. Am J Manag Care. 2019 Feb;25(2):61-67.

OBJECTIVES: To assess the association of payer status and mortality in hepatitis C virus (HCV)-infected patients. **STUDY DESIGN:** For this retrospective observational study, we used the National Health and Nutrition Examination Survey from 2000 to 2010. Adults with complete data on medical questionnaires, HCV RNA, insurance types, and mortality follow-ups were included. **METHODS:** We used Cox proportional hazards models to evaluate independent associations of insurance type with mortality in HCV-infected individuals. These models were rerun in the subset of HCV-positive subjects to determine the association of insurance type with mortality. The data used in this study predated the implementation of the Affordable Care Act. **RESULTS:** Among 19,452 eligible participants, 311 (1.4%) were HCV positive. HCV-positive patients were older, were more likely to be non-Hispanic black and male, and had higher prevalence of hypertension (all $P < .001$). HCV-positive patients were also less likely to have private insurance and more likely to be covered by Medicaid or be uninsured relative to HCV-negative patients ($P < .001$). Among HCV-positive patients, after adjustment for confounders, those with Medicaid coverage had an increased risk of mortality compared with those with private insurance (hazard ratio [HR], 6.31; 95% CI, 1.22-29.94) and uninsured individuals (HR, 8.83; 95% CI, 1.56-49.99). **CONCLUSIONS:** Patients who have HCV are more likely to be uninsured or covered by Medicaid. HCV-positive patients with Medicaid have an increased mortality risk compared with those with private insurance. Given the high burden of HCV infection and adverse prognosis among individuals covered by Medicaid, policy makers must prioritize funding and supporting Medicaid programs.

[Hepatitis C virus and the kidney.](#) Pol S1, Parlati L2, Jadoul M3. Nat Rev Nephrol. 2019 Feb;15(2):73-86. doi: 10.1038/s41581-018-0081-8.

Hepatitis C virus (HCV) infection is more prevalent and is associated with higher mortality in patients receiving dialysis and in kidney transplant recipients than in the general population. Kidney transplant recipients who are HCV-positive are also at higher risk of allograft and liver failure than are HCV-negative recipients. Moreover, HCV infection is associated with a higher incidence and faster progression of diabetes mellitus and chronic kidney disease (CKD), as well as a higher incidence of systemic (especially cardiovascular) complications. The finding that these complications of HCV infection are attenuated in patients who achieve a sustained virologic response (SVR) emphasizes the need to treat patients with CKD who are HCV-positive with oral antiviral therapies. Fortunately, the available evidence suggests that a SVR can be achieved in >95% of patients with late-stage CKD and in kidney transplant recipients. According to international guidelines, all patients with CKD and HCV infection should be considered for treatment with direct acting antivirals (DAAs), prioritizing those with symptomatic cryoglobulinaemic vasculitis, extensive liver fibrosis and stage 4-5 CKD. DAA treatment can be delayed until after transplantation in recipients whose waiting time is markedly reduced by accepting an HCV-positive organ. An emerging issue is the long-term renal safety of DAAs, which requires a re-appraisal. Overall, the elimination of HCV from patients with CKD now seems to be achievable, provided that DAA treatment is coupled with reinforced hygienic precautions to prevent reinfections in dialysis units.

Successful Implementation of a Shared Medical Appointment Model for Hepatitis C Treatment at a Community Health Center.

Hodges J1, Reyes J2, Campbell J3, Klein W3, Wurcel A2,4. J Community Health. 2019 Feb;44(1):169-171. doi: 10.1007/s10900-018-0568-z. Highly efficacious direct acting antiviral (DAA) therapy for treatment of Hepatitis C Virus (HCV) infection is largely inaccessible to communities facing a shortage of available specialist providers. Though less demanding than previous interferon regimens, DAA therapy requires patients to adhere to 8-12 weeks of daily treatment, which can be challenging for some patient populations. Duffy Health Center, located on Cape Cod, Massachusetts, provides integrated medical, mental health and case management services to people who are homeless or at risk for homelessness. The goal of this manuscript is to evaluate the outcomes of treatment of HCV infection with a shared medical appointment (SMA) model. The primary outcome was sustained virologic response (SVR-12), or HCV RNA \leq 15 IU/mL at 12 weeks post-treatment. There were 102 patients recruited, with a total of 104 treatments administered. Over three-fourths of patients who attended one SMA visit (78 of 102) continued in SMA for the duration of treatment. Of these patients opting for SMA, 99% (77 of 78) completed the full treatment course, and 91% (71 of 78) of SMA patients achieved SVR-12. DAA therapy provided by non-specialist providers using the SMA model yielded comparable response rates to those achieved by specialist providers, and has the potential to substantially increase access to HCV treatment for patient populations within high-risk communities.

Trends in Treatment Uptake and Provider Specialty for Hepatitis C Virus (HCV) Infection in the Veterans Affairs Healthcare System: Results From the Electronically Retrieved Cohort of HCV-Infected Veterans (ERCHIVES).

Butt AA1,2, Yan P1, Lo Re Iii V3, Shaikh OS1, Ross DB4. Clin Infect Dis. 2019 Feb 15;68(5):857-859. doi: 10.1093/cid/ciy697. Between 2001 and 2017, 108133 persons (45.7% of diagnosed cases) were initiated on anti-hepatitis C virus treatment in the Veterans Affairs healthcare system. In 2017, nonphysician clinicians accounted for 22.2% of prescriptions, infectious diseases specialists for 14.9%, and gastroenterologists/hepatologists for 10.3%. In the pre-direct-acting antiviral era, they accounted for 7.2%, 26.7%, and 11.6%, respectively.

Marijuana is not associated with progression of hepatic fibrosis in liver disease: a systematic review and meta-analysis.

Farooqui MT1, Khan MA2, Cholankeril G3, et al. Eur J Gastroenterol Hepatol. 2019 Feb;31(2):149-156. doi: 10.1097/MEG.0000000000001263.

BACKGROUND: An estimated 22 million adults use marijuana in the USA. The role of marijuana in the progression of hepatic fibrosis remains unclear. **AIMS:** We carried out a systematic review and meta-analysis to evaluate the impact of marijuana on prevalence and progression of hepatic fibrosis in chronic liver disease. **PATIENTS AND METHODS:** We searched several databases from inception through 10 November 2017 to identify studies evaluating the role of marijuana in chronic liver disease. Our main outcome of interest was prevalence/progression of hepatic fibrosis. Adjusted odds ratios (ORs) and hazards ratios (HRs) were pooled and analyzed using random-effects model. **RESULTS:** Nine studies with 5 976 026 patients were included in this meta-analysis. Prevalence of hepatic fibrosis was evaluated in nonalcoholic fatty liver disease (NAFLD), hepatitis C virus (HCV), and hepatitis C and HIV coinfection by two, four, and one studies. Progression of hepatic fibrosis was evaluated by two studies. Pooled OR for prevalence of fibrosis was 0.91 (0.72-1.15), I=75%. On subgroup

analysis, pooled OR among NAFLD patients was 0.80 (0.75-0.86), I=0% and pooled OR among HCV patients was 1.96 (0.78-4.92), I=77%. Among studies evaluating HR, pooled HR for progression of fibrosis in HCV-HIV co-infected patients was 1.03 (0.96-1.11), I=0%.

CONCLUSION: Marijuana use did not increase the prevalence or progression of hepatic fibrosis in HCV and HCV-HIV-coinfected patients. On the contrary, we noted a reduction in the prevalence of NAFLD in marijuana users. Future studies are needed to further understand the therapeutic impact of cannabidiol-based formulations in the management of NAFLD.

[HCV-Associated Nephropathies in the Era of Direct Acting Antiviral Agents.](#) Angeletti A1, Cantarelli C2, Cravedi P2. *Front Med (Lausanne)*. 2019 Feb 8;6:20. doi: 10.3389/fmed.2019.00020. eCollection 2019.

Hepatitis C virus (HCV) infection is a systemic disorder that frequently associates with extrahepatic manifestations, including nephropathies. Cryoglobulinemia is a typical extrahepatic manifestation of HCV infection that often involves kidneys with a histological pattern of membranoproliferative glomerulonephritis. Other, less common renal diseases related to HCV infection include membranous nephropathy, focal segmental glomerulosclerosis, IgA nephropathy, fibrillary and immunotactoid glomerulopathy. Over the last decades, the advent of direct-acting antiviral therapies has revolutionized treatment of HCV infection, dramatically increasing the rates of viral clearance. In patients where antiviral therapy alone fails to induce renal disease remission add-on B-cell depleting agents represent an alternative to counteract the synthesis of pathogenic antibodies. Immunosuppressive therapies, such as steroids, alkylating agents, and plasma exchanges, may still represent an effective option to inhibit immune-complex driven inflammatory response, but the potentially associated increase of HCV replication and worsening of liver disease represent a serious limitation to their use.

[Characterization of Early Hepatic Injury in HCV-Negative Recipients of HCV-Infected Kidneys.](#) Mazur RD1, Abt PL2, Blumberg EA3, Bloom RD4, Reddy KR1, Reese PP4,5, Goldberg DS1,5. *Clin Transplant*. 2019 Feb 19:e13494. doi: 10.1111/ctr.13494. [Epub ahead of print]

Recent data demonstrate that transplanting kidneys from hepatitis C virus (HCV)-infected donors could increase the number of kidney transplants (KT) by 500-1,000 per year with durable cure rates and excellent 1-year renal function.¹ However, data on the risks of acute donor-derived HCV are limited, hampering our ability to inform patients and providers. We sought to examine data from a trial of transplanting HCV-negative patients with kidneys from HCV-infected donors (THINKER, NCT #02743897) to determine whether these recipients had a greater likelihood of having early alanine aminotransferase (ALT) elevations versus comparator recipients of kidneys from HCV-negative donors.

[Cost Effectiveness of Early Treatment with Direct-Acting Antiviral Therapy in Adolescent Patients with Hepatitis C Virus Infection.](#) Nguyen J1, Barritt Iv AS2, Jhaveri R3. *J Pediatr*. 2019 Feb 6. pii: S0022-3476(18)31729-3. doi: 10.1016/j.jpeds.2018.12.012. [Epub ahead of print]

OBJECTIVE: To evaluate the cost effectiveness of early treatment with direct-acting antiviral therapy in adolescent patients with chronic hepatitis C virus (HCV) infection compared with treatment deferral. **STUDY DESIGN:** We constructed a Markov model to assess the cost effectiveness of treating a hypothetical cohort of 30 000 adolescent patients with chronic HCV at

age 12 years compared with deferring treatment until adulthood from a societal perspective. Model inputs for transition probabilities, HCV treatment and medical care costs, and quality-adjusted life-year (QALY) utilities were derived from the literature and wholesale acquisition estimates. Deterministic sensitivity analyses varied parameters for non-HCV medical care and treatment cost, reinfection rates, treatment uptake, disease progression, liver transplant survival, and treatment with recently approved pangenotypic direct-acting antiviral agents. Discounted costs and total QALYs per person were quantified after 30 years. Cost effectiveness was evaluated as the incremental change in total medical costs per QALY gained. **RESULTS:** The incremental cost effectiveness of early treatment initiation compared with deferred treatment was approximately \$27 000 per QALY gained after 30 years and considered cost effective. In a scenario analysis, hypothetical treatment initiation with currently available pangenotypic agents would be even more cost effective, ranging from \$10 000 to \$21 000 per QALY gained. Cost-effectiveness estimates were sensitive to variations in decompensated cirrhosis progression in adolescence, adult reinfection, and treatment uptake in adults. **CONCLUSIONS:** Early treatment in adolescent patients with chronic HCV infection with currently available direct-acting antivirals seems to be cost effective compared with deferred treatment. Future efforts to control the HCV epidemic should include increasing the number of children treated.

HEPATOCELLULAR (LIVER) CANCER

[PPPDE1 promotes hepatocellular carcinoma development by negatively regulate p53 and apoptosis.](#) Xie X1,2, Wang X2, Liao W3, et al. Apoptosis. 2019 Feb;24(1-2):135-144. doi: 10.1007/s10495-018-1491-6.

We have previously identified that PPPDE1 is a deubiquitinase (DUB) belonging to a cysteine isopeptidase family. Here we sought to explore the biological significance of PPPDE1 in hepatocellular carcinoma and its underlying molecular mechanism. In the present study, we found that amplification and overexpression of PPPDE1 were associated with poor prognosis in hepatocellular carcinoma (HCC). We also demonstrated that knocking down of PPPDE1 could significantly block the clonal growth and tumorigenicity of human HCC cells, which revealed a critical role for PPPDE1 in HCC development. Furthermore, we proved that PPPDE1 is a key modulator of p53 protein level and its down stream apoptosis pathway. Taken together, these results suggested that PPPDE1 is a putative HCC driver gene and extensive studies should be conducted in the future to investigate the role of PPPDE1 in HCC and other tumors.

[High incidence of hepatocellular carcinoma and postoperative complications in patients with nonalcoholic steatohepatitis as a primary indication for deceased liver transplantation.](#) Kern B1,2, Feurstein B1, Fritz J3, et al. Eur J Gastroenterol Hepatol. 2019 Feb;31(2):205-210. doi: 10.1097/MEG.0000000000001270.

BACKGROUND AND AIMS: Nonalcoholic steatohepatitis (NASH) is an increasingly prevalent indication for liver transplantation (LT) across the world. The relative outcomes following transplantation are poorly described in this cohort. We aimed to analyze the incidence and outcome of LT for NASH as compared with other indications. **PATIENTS AND METHODS:** This is a retrospective analysis of 513 patients who underwent deceased-donor, adult LT between 2002 and 2012 as recorded at the Medical University of Innsbruck, Austria. **RESULTS:** The prevalence of NASH cirrhosis as indication for liver transplantation was 12.7% (65/513). Patient survival in patients with NASH was comparable to other indications, including

alcohol-induced liver steatosis (ALD) and hepatitis C virus (HCV) ($P=0.208$). Patients with NASH were older, had a higher model of end-stage liver disease score and a higher BMI, but patient survival and graft survival were equivalent to other indications. Patients with hepatocellular carcinoma (HCC) as primary indication for liver transplantation showed significantly inferior overall survival as compared with the other indications ($P=0.003$). Patients with NASH had coexisting HCC in 53.7% of cases, whereas HCC in ALD, HCV and other indications was prevalent in 31.2, 47.7, and 34.5%, respectively ($P<0.0001$). Patients with NASH had a higher incidence of advanced HCCs (outside the Milan criteria) than patients with ALD, HCV, and other indications ($P=0.034$). Postoperative complications were significantly higher in the NASH cohort ($P=0.048$). **CONCLUSION:** In this single-center LT database analysis, patients with NASH have a higher incidence and a more rapid progression of HCC as well as an increased incidence of postoperative complications. Our findings warrant confirmation by others.

Inadequate Hepatocellular Carcinoma Screening in Patients With Nonalcoholic Steatohepatitis Cirrhosis. Aby E1, Phan J1, Truong E1, Grotts J1, Saab S1,2. J Clin Gastroenterol. 2019 Feb;53(2):142-146. doi: 10.1097/MCG.0000000000001075.

BACKGROUND: Nonalcoholic steatohepatitis (NASH) is a common cause of liver disease which can progress to cirrhosis and hepatocellular carcinoma (HCC). American Association for the Study of Liver Diseases (AASLD) guidelines recommend abdominal ultrasound, with or without serum alpha-fetoprotein, every 6 months for HCC surveillance in cirrhotic patients.

GOALS: Describe HCC surveillance rates in NASH cirrhosis compared with hepatitis C (HCV) cirrhosis and the impact of surveillance on tumor size, treatment, and mortality. **STUDY:** Adults with NASH and HCV cirrhosis diagnosed with HCC from 2009 to 2016 were retrospectively evaluated. Patients were categorized into 3 mutually exclusive disease screening groups based on abdominal imaging with or without serum alpha-fetoprotein testing before HCC diagnosis.

RESULTS: In total, 99 patients with NASH cirrhosis and 162 patients with HCV cirrhosis were evaluated. In total, 51.5% of NASH cirrhosis patients and 25.9% of HCV cirrhosis patients had no screening before HCC diagnosis. Patients with HCV cirrhosis were significantly more likely to undergo surveillance compared with patients with NASH cirrhosis ($P=0.002$). NASH cirrhosis patients who underwent complete screening had smaller tumors compared with those with incomplete screening and no screening ($P=0.006$). There were no differences in number of tumors at diagnosis or mortality between screening groups in patients with NASH cirrhosis ($P=0.281$ and 0.468 , respectively). **CONCLUSIONS:** There is suboptimal HCC surveillance in NASH and HCV cirrhotic patients, with a greater proportion of patients with NASH cirrhosis not undergoing surveillance. Patients with NASH cirrhosis who had complete surveillance had smaller tumors at diagnosis, but there were no differences in treatment outcomes or mortality.

Serum MicroRNAs as Biomarkers in Hepatitis C: Preliminary Evidence of a MicroRNA Panel for the Diagnosis of Hepatocellular Carcinoma. Weis A1,2, Marquart L3, Calvopina DA4,5, Genz B6,7, Ramm GA8,9, Skoien R10,11,12. Int J Mol Sci. 2019 Feb 17;20(4). pii: E864. doi: 10.3390/ijms20040864.

Early diagnosis of cirrhosis and hepatocellular carcinoma (HCC) due to chronic Hepatitis C (CHC) remain clinical priorities. In this pilot study, we assessed serum microRNA (miRNA) expression to distinguish cirrhosis and HCC, alone and in combination with the aminotransferase-to-platelet ratio (APRI), Fibrosis 4 (FIB-4), and alpha-fetoprotein (AFP). Sixty

CHC patients were subdivided into 3 cohorts: Mild disease (fibrosis stage F0-2; n = 20); cirrhosis (n = 20); and cirrhosis with HCC (n = 20). Circulating miRNA signatures were determined using a liver-specific real-time quantitative reverse transcription PCR (qRT-PCR) microarray assessing 372 miRNAs simultaneously. Differentially-expressed miRNA candidates were independently validated using qRT-PCR. Serum miRNA-409-3p was increased in cirrhosis versus mild disease. In HCC versus cirrhosis, miRNA-486-5p was increased, whereas miRNA-122-5p and miRNA-151a-5p were decreased. A logistic regression model-generated panel, consisting of miRNA-122-5p + miRNA-409-3p, distinguished cirrhosis from mild disease (area under the curve, AUC = 0.80; sensitivity = 85%, specificity = 70%; $p < 0.001$). When combined with FIB-4 or APRI, performance was improved with AUC = 0.89 ($p < 0.001$) and 0.87 ($p < 0.001$), respectively. A panel consisting of miRNA-122-5p + miRNA-486-5p + miRNA-142-3p distinguished HCC from cirrhosis (AUC = 0.94; sensitivity = 80%, specificity = 95%; $p < 0.001$), outperforming AFP (AUC = 0.64, $p = 0.065$). Serum miRNAs are differentially expressed across the spectrum of disease severity in CHC. MicroRNAs have great potential as diagnostic biomarkers in CHC, particularly in HCC where they outperform the only currently-used biomarker, AFP.

Identification of special key genes for alcohol-related hepatocellular carcinoma through bioinformatic analysis. Zhang X1, Kang C1, Li N1, Liu X2, Zhang J1, Gao F1, Dai L3. PeerJ. 2019 Feb 6;7:e6375. doi: 10.7717/peerj.6375. eCollection 2019.

BACKGROUND: Alcohol-related hepatocellular carcinoma (HCC) was reported to be diagnosed at a later stage, but the mechanism was unknown. This study aimed to identify special key genes (SKGs) during alcohol-related HCC development and progression. **METHODS:** The mRNA data of 369 HCC patients and the clinical information were downloaded from the Cancer Genome Atlas project (TCGA). The 310 patients with certain HCC-related risk factors were included for analysis and divided into seven groups according to the risk factors. Survival analyses were applied for the HCC patients of different groups. The patients with hepatitis B virus or hepatitis C virus infection only were combined into the HCC-V group for further analysis. The differentially expressed genes (DEGs) between the HCCs with alcohol consumption only (HCC-A) and HCC-V tumors were identified through limma package in R with cutoff criteria $|\log_2 \text{fold change} (\log_2 \text{FC})| > 1.0$ and $p < 0.05$. The DEGs between eight alcohol-related HCCs and their paired normal livers of GSE59259 from the Gene Expression Omnibus (GEO) were identified through GEO2R (a built-in tool in GEO database) with cutoff criteria $|\log_2 \text{FC}| > 2.0$ and $\text{adj.}p < 0.05$. The intersection of the two sets of DEGs was considered SKGs which were then investigated for their specificity through comparisons between HCC-A and other four HCC groups. The SKGs were analyzed for their correlations with HCC-A stage and grade and their prognostic power for HCC-A patients. The expressional differences of the SKGs in the HCCs in whole were also investigated through Gene Expression Profiling Interactive Analysis (GEPIA). The SKGs in HCC were validated through Oncomine database analysis. **RESULTS:** Pathological stage is an independent prognostic factor for HCC patients. HCC-A patients were diagnosed later than HCC patients with other risk factors. Ten SKGs were identified and nine of them were confirmed for their differences in paired samples of HCC-A patients. Three (SLC22A10, CD5L, and UROC1) and four (SLC22A10, UROC1, CSAG3, and CSMD1) confirmed genes were correlated with HCC-A stage and grade, respectively. SPP2 had a lower trend in HCC-A tumors and was negatively correlated with HCC-A stage and grade. The SKGs each was differentially expressed between HCC-A and at least one of other HCC groups.

CD5L was identified to be favorable prognostic factor for overall survival while CSMD1 unfavorable prognostic factor for disease-free survival for HCC-A patients and HCC patients in whole. Through Oncomine database, the dysregulations of the SKGs in HCC and their clinical significance were confirmed. **CONCLUSION:** The poor prognosis of HCC-A patients might be due to their later diagnosis. The SKGs, especially the four stage-correlated genes (CD5L, SLC22A10, UROC1, and SPP2) might play important roles in HCC development, especially alcohol-related HCC development and progression. CD5L might be useful for overall survival and CSMD1 for disease-free survival predication in HCC, especially alcohol-related HCC.

[Direct-acting antivirals response in hepatocellular carcinoma: Does the presence of hepatocellular carcinoma matter?](#) Huang CF^{1,2,3}, Yu ML^{1,2,4,5}. Clin Mol Hepatol. 2019 Feb 11. doi: 10.3350/cmh.2018.1014. [Epub ahead of print]

During the clinical trial development of directly acting antivirals (DAAs), evidence regarding the treatment efficacy in chronic hepatitis C patients with hepatocellular carcinoma (HCC) was scarce because these patients have always been excluded. Apart from the clinical trials, more HCC patients are currently being treated in daily practice, given that these treatments are highly effective and involve well-tolerated regimens. Large scale, real-world studies have demonstrated potentially suboptimal antiviral treatment efficacy in HCC patients who received DAAs. It is postulated that the impairment of the bioavailability of DAAs may account for the inferior treatment response. However, the results could not be generalized across all studies. The differing results were attributed to diverse patient characteristics, suboptimal regimens or imprecise definitions of active cancer statuses at the time of treatment initiation. Additional large-scale studies that utilize the treatment of choice in clearly defined HCC patients with different disease severities are warranted to clarify the issue.

[Low recurrence rate of hepatocellular carcinoma following ledipasvir and sofosbuvir treatment in a real-world chronic hepatitis C patients cohort.](#) Idilman R¹, Demir M¹, Aladag M¹, et al. J Viral Hepat. 2019 Feb 11. doi: 10.1111/jvh.13075. [Epub ahead of print]

The aims of the present study were to evaluate the efficacy and tolerability of ledipasvir/sofosbuvir (LDV/SOF) with or without ribavirin in the treatment of chronic hepatitis C (CHC) in patients with advanced liver disease and to analyze whether the use of LDV/SOF treatment is associated with a new occurrence of hepatocellular carcinoma (HCC) during and after LDV/SOF treatment. The Turkish Early Access Program provided LDV/SOF treatment to a total of 200 eligible CHC patients with advanced liver disease. The median follow-up period was 22 months. All patients were Caucasian, 84% were infected with genotype 1b, and 24% had a liver transplantation before treatment. The sustained virological response (SVR12) was 86.0% with ITT analysis. SVR12 was similar among patients with Child-Pugh class A, B, and C disease and transplant recipients. From baseline to SVR12, serum ALT level and MELD score were significantly improved ($p < 0.001$). LDV/SOF treatment was generally well tolerated. Only one patient developed a new diagnosed HCC. Seventeen of the 35 patients, who had a history of previous HCC developed HCC recurrence during the LDV/SOF treatment or by a median follow-up of six months after treatment. HCC recurrence was less commonly observed in patients who received curative treatment for HCC compared with those patients who received non-curative treatment ($p = 0.007$). In conclusion, LDV/SOF with or without ribavirin is an effective and tolerable treatment in CHC patients with advanced liver disease. Eradication is associated with improvements in liver function and a reduced risk of developing a new

occurrence of HCC. **LAY SUMMARY:** Ledipasvir and sofosbuvir with or without ribavirin is an effective and tolerable treatment in hepatitis C virus-infected patients with advanced liver disease. Eradication is associated with improvements of liver function and a reduces the risk of developing a new occurrence of hepatocellular carcinoma. This article is protected by copyright. All rights reserved.