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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES
HIV/HCV COINFECTION
COMPLEMENTARY AND ALTERNATIVE MEDICINE
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS
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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Results of sofosbuvir-based combination therapy for chronic hepatitis C cohort of Indian patients in real-life clinical practice. Sood A1, Midha V2, Mahajan R1, et al. J Gastroenterol Hepatol. 2017 Apr;32(4):894-900. doi: 10.1111/jgh.13628.
BACKGROUND AND AIM: The introduction of sofosbuvir has revolutionized the treatment of chronic hepatitis C. This study was planned to observe whether the efficacy and tolerability of sofosbuvir-based regimens demonstrated in phase 3 clinical trial results translate into real-life clinical practice. **METHODS:** This prospective, non-randomized observational study conducted in Dayanand Medical College and Hospital, Punjab, included all consecutive treatment-naïve patients with chronic hepatitis C (genotypes 1-5) who were treated with sofosbuvir-based regimens. Response to therapy was assessed at week 4 (rapid virological response), week 12 or 24 (end of treatment response), and 12 weeks after cessation of therapy (sustained virological response [SVR]). **RESULTS:** Of 947 patients diagnosed with chronic hepatitis C virus and considered for treatment with direct-acting antivirals, 736 patients (77.1%) opted for treatment (age 45.1 ± 10.1 years, 64% men, genotype 3 [80%], genotype 1 [14.7%], and genotype 4 [4.9%]). Viral load was high (>600 000 IU/mL) in 361/736 (49%); 330 patients (44.8%) had cirrhosis (80 [14.3%] were decompensated). Patients with genotypes 1, 4, and 5 (n = 135) were treated with triple drug regime (pegylated interferon, ribavirin, and sofosbuvir) for 12 weeks. Patients with genotype 3 (n = 589) were treated either with dual therapy (sofosbuvir and ribavirin) for 24 weeks (n = 405) or triple therapy for 12 weeks (n = 184). SVR was achieved in 453/473 (95.8%). SVR rates did not differ among different genotypes but were higher in non-cirrhotics. **CONCLUSION:** Sofosbuvir-based treatment regimens achieve high SVR rates in real-life cohort of Indian patients with chronic hepatitis C infection (including those with cirrhosis).

Real-world efficacy and safety of ritonavir-boosted paritaprevir, ombitasvir, dasabuvir ± ribavirin for hepatitis C genotype 1 - final results of the REV1TAL study. Lubel J1,2, Strasser S3, Stuart KA4, et al. Antivir Ther. 2017 Apr 19. doi: 10.3851/IMP3168. [Epub ahead of print]
BACKGROUND: Limited data exist on the outcomes of ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (PrOD) ± ribavirin in a real-world setting. The aim of this study was to compare the efficacy and safety of PrOD-based therapy in hepatitis C genotype 1 patients with

and without cirrhosis, and to explore pre-treatment factors predictive of sustained viral response (SVR) and serious adverse events (SAEs) on treatment. **METHODS:** 451 patients with hepatitis C genotype 1 treated in 20 centres across Australia were included. Baseline demographic, clinical and laboratory information, on-treatment biochemical, virological and haematological indices and details on serious adverse events were collected locally. **RESULTS:** Cirrhosis was present in 340 patients (75.4%). Overall SVR was 95.1% with no differences in SVR between the cirrhosis and non-cirrhosis groups (94.7% vs. 96.4%). SVR in subgenotypes 1a and 1b was 93.1% and 99.2%, respectively. On multivariate analysis, baseline bilirubin level and early treatment cessation predicted SVR. SAEs occurred in 10.9% of patients including hepatic decompensation (2.7%) and hepatocellular carcinoma (1.8%). On multivariate analysis of factors predictive of SAEs in the overall group, Child-Turcotte-Pugh (CTP) B was the only significant factor, while in those with cirrhosis, baseline albumin and creatinine levels were significant. **CONCLUSIONS:** In this large real-world cohort of HCV genotype 1 subjects, treatment with PrOD was highly effective and similar to clinical trials. Important determinants of reduced SVR include early cessation of therapy and baseline bilirubin concentration. SAEs were not infrequent with CTP B patients being at greatest risk.

[Dual treatment with sofosbuvir plus ribavirin is as effective as triple therapy with pegylated interferon plus sofosbuvir plus ribavirin in predominant genotype 3 patients with chronic hepatitis C.](#) Satsangi S1, Mehta M1, Duseja A1, Taneja S1, Dhiman RK1, Chawla Y1. Gastroenterol Hepatol. 2017 Apr;32(4):859-863. doi: 10.1111/jgh.13595.
BACKGROUND AND AIM: Sofosbuvir (SOF) was the first directly acting antiviral made available for chronic hepatitis C (CHC) in India. We describe our "real life" experience of using SOF with ribavirin (RBV) with or without pegylated interferon (Peg-IFN) in predominant genotype 3 patients with CHC. **METHODS:** A total of 158 patients (men 99 [62.6%], mean age 40.3 ± 12.8 years) with CHC treated with dual therapy (SOF + RBV) for 24 weeks or triple therapy (Peg-IFN + SOF + RBV) for 12 weeks were included prospectively. Patients with co-infection, decompensated liver disease, and post-organ transplantation were excluded. Data were analysed for the preference of treatment regimen, end of treatment response (ETR), sustained virological response at 12 weeks, and side effects. **RESULTS:** Genotype 3 was the predominant genotype (105 [66.4%]) followed by genotype 1 (40 [25.3%]) and genotype 4 (13[8.2%]). Forty-eight (30.37%) patients had cirrhosis (LSM $\geq$ 13 kPa), and 30 (19%) were treatment experienced with Peg-IFN + RBV. A total of 103 (65.18%) patients received dual therapy, and 55 (34.81%) received triple therapy. Resentment to receive injections, inaccessibility to a facility, fear of injection or its side effects, and financial constraints were the reasons to refuse triple therapy. All patients in triple therapy group and all but two patients (98%) in the dual therapy group attained ETR. All those who achieved ETR achieved sustained virological response at 12 weeks in both groups. But for anemia in three patients (two in triple, one in dual therapy), there were no major side effects. **CONCLUSIONS:** Most patients with CHC prefer an oral treatment with directly acting antivirals. Both oral and interferon-based regimens achieve high response rate.

[Safety of oral direct acting antiviral regimens for chronic hepatitis C in real life conditions.](#) Juanbeltz R1,2,3, Goñi Esarte S4, Úriz-Otano JI3,4, et al. Postgrad Med. 2017 May;129(4):476-483. doi: 10.1080/00325481.2017.1311197. Epub 2017 Apr 10.
OBJECTIVES: Direct acting antivirals (DAA) are extremely effective to treat chronic hepatitis C. The aim of this study was to evaluate, by using objective variables, the safety of DAA

combinations under clinical practice conditions. **METHODS:** A retrospective study was carried out in mono-infected patients with chronic hepatitis C treated with DAA between January and December 2015 in our centre. Discontinuations, treatment modifications, deaths and laboratory parameters were studied (liver function tests, hemoglobin, creatinine and lipid profile at baseline, weeks 4, 8 and post 12). Temporal variation of laboratory parameters was analyzed by t-test for paired data, and comparison between groups was made by t-test for independent samples and ANOVA. **RESULTS:** 227 patients were included (40.5% cirrhotic). Sustained virological response (SVR) was achieved in 97.3% of patients. In only one case was the antiviral medication suspended due to toxicity, and there were no voluntary treatment discontinuations. The use of ribavirin (RBV) was associated with mild transient hyperbilirubinemia (41.2%) and anemia (32.6%, with RBV dose reduction in 7.9% of cases). There was an elevation in total cholesterol and LDL-cholesterol (LDL-C) during and after treatment: mean increase of 23 mg/dL (0.59 mmol/L) and 22 mg/dL (0.57 mmol/L), respectively in post 12 (p < .0001). An increment of 20% of patients with cholesterol levels over optimal figures was observed after DAA completion. **CONCLUSION:** DAA have an optimum safety profile in real life conditions, with infrequent discontinuation and minor laboratory alterations.

Effectiveness of triple therapy with direct-acting antivirals for hepatitis C genotype 1 infection: application of propensity score matching in a national HCV treatment registry.
Gray E1, Pasta DJ2, Norris S3,4, O'Leary A5,6; Irish Hepatitis C Outcomes and Research Network (ICORN). BMC Health Serv Res. 2017 Apr 19;17(1):288. doi: 10.1186/s12913-017-2188-1.
BACKGROUND: Observational studies are used to measure the effectiveness of an intervention in non-experimental, real world scenarios at the population level and are recognised as an important component of the evidence pyramid. Such data can be accrued through prospective cohort studies and a patient registry is a proven method for this type of study. The national hepatitis C (HCV) registry was established in Ireland in 2012 with the aim of monitoring the clinical and economic outcomes from new, high cost regimens for the treatment of HCV infection. A sustained virological response (SVR) 24 weeks following completion of therapy with interferon-containing regimens is considered a cure. Non-randomisation in these studies can result in confounding or selection bias. Propensity score (PS) matching is one of a number of statistical tools that can be used to mitigate the effects of confounding in observational studies. **METHODS:** We analysed the data of 309 patients who underwent triple therapy treatment with telaprevir (TPV) in combination with pegylated-interferon and ribavirin (PR) or boceprevir (BOC)/PR between June 2012 and December 2014. The decision to initiate treatment and the selection of the treatment regimen was at the discretion of the physician. To adjust for confounding, three approaches to propensity score matching were assessed Adjusted sustained-virological response rates (SVR), odds ratios, p-values and 95% confidence intervals were calculated from the three PS matched dataset. **RESULTS:** Prior to matching, the unadjusted sustained virological response rates 24 weeks after treatment complete (SVR24) were 74% (n = 158/215) and 61% (n = 57/94) for telaprevir/PR and boceprevir/PR, respectively. After matching, adjusted SVR24 rates were between 73-74% and 60-61% for telaprevir/PR and boceprevir/PR, respectively. **CONCLUSION:** Efficacy rates were comparable with those reported in pivotal clinical trials and real world studies. After adjusting for confounding, we conclude that there was no difference in treatment effect after PS matching. The small sample size limits the conclusions that can be made about the effect of PS matching. Propensity score

adjustment remains a tool that can be applied to future analysis, however, we suggest, where possible, using a larger sample size in order to reduce the uncertainty around the outcomes.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Hepatitis C virus impairs natural killer cell activity via viral serine protease NS3.

Yang CM1, Yoon JC2, Park JH1, Lee JM1. PLoS One. 2017 Apr 14;12(4):e0175793. doi: 10.1371/journal.pone.0175793. eCollection 2017.

Hepatitis C virus (HCV) infection is characterized by a high frequency of chronic cases owing to the impairment of innate and adaptive immune responses. The modulation of natural killer (NK) cell functions by HCV leads to an impaired innate immune response. However, the underling mechanisms and roles of HCV proteins in this immune evasion are controversial, especially in the early phase of HCV infection. To investigate the role of HCV nonstructural proteins especially NS3 in the impairment of NK functions, NK cells were isolated from the PBMCs by negative selection. To assess the direct cytotoxicity and IFN-γ production capability of NK cells, co-cultured with uninfected, HCV-infected, HCV-NS3 DNA-transfected Huh-7.5, or HCV-NS replicon cells. To determine the effect of an NS3 serine protease inhibitor, HCV-infected Huh-7.5 cells were treated with BILN-2061. Then, NK cells were harvested and further co-cultured with K-562 target cells. NK cell functions were analyzed by flow cytometry and enzyme-linked immunosorbent assay. When co-cultured with HCV-infected Huh-7.5 cells, the natural cytotoxicity and IFN-γ production capability of NK cells were significantly reduced. NK cell functions were inhibited to similar levels upon co-culture with HCV-NS replicon cells, NS3-transfected cells, and HCV-infected Huh-7.5 cells. These reductions were restored by BILN-2061-treatment. Furthermore, BILN-2061-treatment significantly increased degranulation against K-562 target cells and IFN-γ productivity in NK cells. Consistent with these findings, the expression levels of activating NK cell receptors, such as NKp46 and NKp30, were also increased. In HCV-infected cells, the serine protease NS3 may play a role in the abrogation of NK cell functions in the early phase of infection through downregulation of NKp46 and NKp30 receptors on NK cells. Together, these results suggest that NS3 represents a novel drug target for the treatment of HCV infections.

Hepatitis C Virus Indirectly Disrupts DNA Damage-Induced p53 Responses by Activating Protein Kinase R.

Mitchell JK1, Midkiff BR2, Israelow B3, Evans MJ3, Lanford RE4, Walker CM5, Lemon SM6,7,8, McGivern DR6,8. MBio. 2017 Apr 25;8(2). pii: e00121-17. doi: 10.1128/mBio.00121-17.

Many DNA tumor viruses promote cellular transformation by inactivating the critically important tumor suppressor protein p53. In contrast, it is not known whether p53 function is disrupted by hepatitis C virus (HCV), a unique, oncogenic RNA virus that is the leading infectious cause of liver cancer in many regions of the world. Here we show that HCV-permissive, liver-derived HepG2 cells engineered to constitutively express microRNA-122 (HepG2/miR-122 cells) have normal p53-mediated responses to DNA damage and that HCV replication in these cells potently suppresses p53 responses to etoposide, an inducer of DNA damage, or nutlin-3, an inhibitor of p53 degradation pathways. Upregulation of p53-dependent targets is consequently repressed within HCV-infected cells, with potential consequences for cell survival. Despite this, p53 function is not disrupted by overexpression of the complete HCV

polyprotein, suggesting that altered p53 function may result from the host response to viral RNA replication intermediates. Clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9-mediated ablation of double-stranded RNA (dsRNA)-activated protein kinase R (PKR) restored p53 responses while boosting HCV replication, showing that p53 inhibition results directly from viral activation of PKR. The hepatocellular abundance of phosphorylated PKR is elevated in HCV-infected chimpanzees, suggesting that PKR activation and consequent p53 inhibition accompany HCV infection in vivo These findings reveal a feature of the host response to HCV infection that may contribute to hepatocellular carcinogenesis.IMPORTANCE Chronic infection with hepatitis C virus (HCV) is the leading cause of liver cancer in most developed nations. However, the mechanisms whereby HCV infection promotes carcinogenesis remain unclear. Here, we demonstrate that HCV infection inhibits the activation of p53 following DNA damage. Contrary to previous reports, HCV protein expression is insufficient to inhibit p53. Rather, p53 inhibition is mediated by cellular protein kinase R (PKR), which is activated by HCV RNA replication and subsequently suppresses global protein synthesis. These results redefine our understanding of how HCV infection influences p53 function. We speculate that persistent disruption of p53-mediated DNA damage responses may contribute to hepatocellular carcinogenesis in chronically infected individuals.

Functional Analysis of Hepatitis C Virus (HCV) Envelope Protein E1 Using a trans-Complementation System Reveals a Dual Role of a Putative Fusion Peptide of E1 in both HCV Entry and Morphogenesis. Tong Y1, Chi X2, Yang W2, Zhong J3. J Virol. 2017 Mar 13;91(7). pii: e02468-16. doi: 10.1128/JVI.02468-16. Print 2017 Apr 1.
Hepatitis C virus (HCV) is an enveloped RNA virus belonging to the Flaviviridae family. It infects mainly human hepatocytes and causes chronic liver diseases, including cirrhosis and cancer. HCV encodes two envelope proteins, E1 and E2, that form a heterodimer and mediate virus entry. While E2 has been extensively studied, less has been done so for E1, and its role in the HCV life cycle still needs to be elucidated. Here we developed a new cell culture model for HCV infection based on the trans-complementation of E1. Virus production of the HCV genome lacking the E1-encoding sequence can be efficiently rescued by the ectopic expression of E1 in trans The resulting virus, designated HCVΔE1, can propagate in packaging cells expressing E1 but results in only single-cycle infection in naive cells. By using the HCVΔE1 system, we explored the role of a putative fusion peptide (FP) of E1 in HCV infection. Interestingly, we found that the FP not only contributes to HCV entry, as previously reported, but also may be involved in virus morphogenesis. Finally, we identified amino acid residues in FP that are critical for biological functions of E1. In summary, our work not only provides a new cell culture model for studying HCV but also provides some insights into understanding the role of E1 in the HCV life cycle.IMPORTANCE Hepatitis C virus (HCV), an enveloped RNA virus, encodes two envelope proteins, E1 and E2, that form a heterodimeric complex to mediate virus entry. Compared to E2, the biological functions of E1 in the virus life cycle are not adequately investigated. Here we developed a new cell culture model for single-cycle HCV infection based on the trans-complementation of E1. The HCV genome lacking the E1-encoding sequence can be efficiently rescued for virus production by the ectopic expression of E1 in trans This new model renders a unique system to dissect functional domains and motifs in E1. Using this system, we found that a putative fusion peptide in E1 is a multifunctional structural element contributing to both HCV entry and morphogenesis. Our work has provided a new cell culture model to study HCV and provides insights into understanding the biological roles of E1 in the HCV life cycle.

Both Hepatitis C Virus-Specific T Cell Responses and IL28B rs12979860 Single-Nucleotide Polymorphism Genotype Influence Antihepatitis C Virus Treatment Outcome in Patients with Chronic Hepatitis C. Benito JM1,2, García-Samaniego J3,4, García M1,2, et al. J Interferon Cytokine Res. 2017 Apr 25. doi: 10.1089/jir.2016.0078. [Epub ahead of print]

Despite new treatments for hepatitis C virus (HCV) infection, IFNα-based regimens still have clinical relevance in special populations of patients and remain the only therapeutic option for many patients. We sought to elucidate the interplay between two relevant factors (IL28B polymorphism and T cell immune responses) involved in the outcome of this therapy in HCV-infected patients. We evaluated 38 patients infected with HCV genotype 1-17 coinfected with HIV-who were undergoing a full course of pegIFNα/RBV therapy. The interdependence and roles of T cell-mediated immune responses and IL28B rs12979860 single-nucleotide polymorphism genotype as predictors of virological response to anti-HCV treatment in patients with chronic hepatitis C were evaluated using nonparametric tests. Factors associated with rapid virological response (RVR) in univariate analysis were presence of CD4 T cell response against NS3 HCV protein, low baseline HCV-RNA, and IL28B CC genotype. Factors associated with sustained virological response (SVR) in univariate analysis were IL28B CC genotype, low baseline HCV-RNA, and presence of CD4 response against NS2. In the multivariate analysis, low baseline HCV-RNA and NS3-specific CD4 response showed a clear trend toward association with RVR (P = 0.09 and P = 0.07, respectively). Regarding SVR, IL28B CC genotype was the strongest predictor (P = 0.02), with presence of NS2-specific CD4 response showing a clear trend (P = 0.09). HCV-specific T cell response influences the outcome of pegIFNα/RBV therapy regardless of IL28B genotype. HCV-specific T cell responses (adaptive immunity) seem to influence viral clearance both in the short and long term during therapy (RVR and SVR), whereas the influence of the IL28B genotype (innate immunity) may be more relevant to the long-lasting therapeutic effect (SVR).

Notch Signaling Regulates Circulating T Helper 22 Cells in Patients with Chronic Hepatitis C. Jiang BC1, Liu X1, Liu XH2, Li ZS3, Zhu GZ1. Viral Immunol. 2017 Apr 14. doi: 10.1089/vim.2017.0007. [Epub ahead of print]

Notch signaling enhanced the response of interleukin (IL)-22-producing CD4+ T cells that were defined as T helper 22 (Th22) cells, and Notch-aryl hydrocarbon receptor (AhR)-IL-22 axis fine-tuned inflammatory response. Previous studies have demonstrated that both Notch signaling and Th22 cells took part in the pathogenesis of chronic hepatitis C virus (HCV) infection. Thus, in this study, we aimed at examining the regulatory role of Notch signaling in Th22 cells in HCV infection. A total of 59 patients with chronic hepatitis C and 22 normal controls (NCs) were enrolled in this study. The percentage of Th22 cells and mRNA expression of related transcriptional factors and cytokines were analyzed in response to γ-secretase inhibitor. Th22 cell frequency was significantly elevated in chronic hepatitis C in comparison with that in NCs. Inhibition of Notch signaling downregulated HCV-specific Th22 cells and IL-22 production, which was accompanied by the reduction of AhR and modulatory cytokines (IL-6 and tumor necrosis factor-α). Moreover, the suppression of Notch signaling also decreased the IL-22-mediated antimicrobial response in both normal and HCV-infected HepG2 cells/Huh7.5 cells. This process was also accompanied by the depression of signal transducers and activators of transcription 3 signaling. In conclusion, the current results suggested that Notch signaling acted

as a critical pathway in determining the response to IL-22 in chronic hepatitis C. Thus, Notch-Th22 axis might be considered a new therapeutic target for HCV-infected patients.

HIV/HCV COINFECTION

[Sofosbuvir Plus Ribavirin Without Interferon for Treatment of Acute Hepatitis C Virus Infection in HIV-1-Infected Individuals: SWIFT-C.](#) Naggie S1, Marks KM2, Hughes M3, et al. Clin Infect Dis. 2017 Apr 15;64(8):1035-1042. doi: 10.1093/cid/cix025.
BACKGROUND: Historically, acute hepatitis C virus (HCV) infection was treated with shorter durations of interferon-containing therapies. In the era of direct-acting antivirals (DAAs), it is unclear whether the efficacy of treatment achieved in chronic infection can be maintained with abbreviated courses of therapy during the acute phase. **METHODS:** The sofosbuvir-containing regimens without interferon for treatment of acute HCV in HIV-1 infected individuals (SWIFT-C) is an open-label, 2-cohort clinical trial in which the first cohort assessed for the safety and efficacy of 12 weeks of sofosbuvir plus ribavirin for the treatment of acute HCV infection in participants with chronic human immunodeficiency virus type 1 (HIV-1) infection. This is a preplanned analysis of the first cohort, which had a planned accrual of 17 participants.
RESULTS: Seventeen men (11 Hispanic, 6 white, median age 45 years) were enrolled. Most (88%) had HCV genotype-1 infection and few (24%) had the favorable IL28B CC genotype. Median baseline HCV RNA was 2 280 000 IU/mL (interquartile range, 272 000-4 230 000). Ten participants (59%) achieved the primary outcome of SVR12 (90% confidence interval, 36%-78%), failing to establish noninferiority. All treatment failures were due to viral relapse (41%). There were no premature treatment discontinuations. The only factor that differed between participants who achieved SVR vs those who relapsed was ribavirin concentration at the end of treatment. **CONCLUSION:** Sofosbuvir-ribavirin for 12 weeks for the treatment of acute HCV genotype-1 infection in HIV-1-infected persons results in a high relapse rate. Preliminary studies of DAA combination therapies suggest improved response rates, although the adequate duration of therapy remains unclear.

[Lack of decline in Hepatitis C Virus incidence among HIV-positive men who have sex with men during 1990-2014.](#) Van Santen DK1, Van Der Helm JJ2, Del Amo J3, et al. J Hepatol. 2017 Apr 12. pii: S0168-8278(17)30209-X. doi: 10.1016/j.jhep.2017.03.038. [Epub ahead of print]
BACKGROUND AND AIMS: Hepatitis C virus (HCV) incidence among HIV-positive men who have sex with men (MSM) has increased since 2000, though regional differences have been documented in recent years. We aimed to 1) estimate trends in HCV incidence among HIV-positive MSM, 2) assess the association between incidence and geographical region, age and HIV-related measurements and, 3) assess temporal changes in time from HIV seroconversion to HCV infection. **METHODS:** We used data from MSM with well-estimated dates of HIV seroconversion from the CASCADE Collaboration (1990-2014). We allowed for smoothly varying trends in HCV incidence over calendar time using restricted cubic splines. We assessed the association of calendar year, age, CD4 count (lagged), HIV RNA (lagged), geographical region and HIV infection stage (recent vs. chronic) with HCV incidence using Poisson regression. **RESULTS:** Of 5,941 MSM, 337 acquired HCV during follow-up. HCV incidence significantly increased from 0.7/1000 person-years (py) in 1990 to 18/1000 py in 2014. Recent calendar years, younger age, recent HIV infection and higher HIV RNA levels were significantly

associated with HCV incidence, while CD4 count was not. Trends differed by geographical region; while incidence appears to have stabilized in Western Europe and remained stable in Southern Europe, it continued to increase in Northern Europe in recent years. Time from HIV to HCV infection significantly decreased over calendar time (p<0.001). **CONCLUSIONS:** HCV has continued to spread among HIV-positive MSM in recent years, but trends differ by geographical region. Interventions to decrease the risk of HCV acquisition and increase early diagnosis are warranted. **LAY SUMMARY:** Hepatitis C virus infection continues to spread among HIV-positive men who have sex with men, especially among younger individuals. However, trends seem to differ by European region in recent years. Furthermore, men who have sex with men with a higher HIV RNA load were more likely to get infected with the hepatitis C virus. During recent HIV infection, MSM appear to be at higher risk of acquiring hepatitis C.

[Hepatitis C co-infection is associated with an increased risk of incident chronic kidney disease in HIV-infected patients initiating combination antiretroviral therapy.](#) Rossi C1, Raboud J2,3, Walmsley S3, et al. BMC Infect Dis. 2017 Apr 4;17(1):246. doi: 10.1186/s12879-017-2350-8.
BACKGROUND: Combination antiretroviral therapy (cART) has reduced mortality from AIDS-related illnesses and chronic comorbidities have become prevalent among HIV-infected patients. We examined the association between hepatitis C virus (HCV) co-infection and chronic kidney disease (CKD) among patients initiating modern antiretroviral therapy. **METHODS:** Data were obtained from the Canadian HIV Observational Cohort for individuals initiating cART from 2000 to 2012. Incident CKD was defined as two consecutive serum creatinine-based estimated glomerular filtration (eGFR) measurements <60 mL/min/1.73m2 obtained ≥3 months apart. CKD incidence rates after cART initiation were compared between HCV co-infected and HIV mono-infected patients. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox regression. **RESULTS:** We included 2595 HIV-infected patients with eGFR >60 mL/min/1.73m2 at cART initiation, of which 19% were HCV co-infected. One hundred and fifty patients developed CKD during 10,903 person-years of follow-up (PYFU). The CKD incidence rate was higher among co-infected than HIV mono-infected patients (26.0 per 1000 PYFU vs. 10.7 per 1000 PYFU). After adjusting for demographics, virologic parameters and traditional CKD risk factors, HCV co-infection was associated with a significantly shorter time to incident CKD (HR 1.97; 95% CI: 1.33, 2.90). Additional factors associated with incident CKD were female sex, increasing age after 40 years, lower baseline eGFR below 100 mL/min/1.73m2, increasing HIV viral load and cumulative exposure to tenofovir and lopinavir. **CONCLUSIONS:** HCV co-infection was associated with an increased risk of incident CKD among HIV-infected patients initiating cART. HCV-HIV co-infected patients should be monitored for kidney disease and may benefit from available HCV treatments.

[Significant reductions in alcohol use after Hepatitis C treatment: Results from the French ANRS CO13-HEPAVIH cohort.](#) Knight R1,2, Roux P3,4, Vilotitch A3,4, et al. Addiction. 2017 Apr 21. doi: 10.1111/add.13851. [Epub ahead of print]
BACKGROUND AND AIMS: Few data exist on changes to substance use patterns before and after hepatitis C virus (HCV) treatment. We used longitudinal data of HIV-HCV co-infected individuals to examine whether receiving Peg-interferon (Peg-IFN)-based therapy irrespective of HCV clearance could modify tobacco, cannabis and alcohol use. **DESIGN:** A prospective cohort of HIV-HCV co-infected individuals was enrolled from 2006. Participants' clinical data were

retrieved from medical records and socio-demographic and behavioral characteristics were collected by yearly self-administered questionnaires. **SETTING:** Data were collected across seventeen hospitals in France. **PARTICIPANTS:** All HIV-HCV co-infected patients who initiated HCV treatment during follow-up and answered items regarding substance use in at least one yearly questionnaire (258 patients, 671 visits). **INTERVENTION:** HCV treatment consisted of Peg-IFN based regimens. **MEASUREMENTS:** Four time-varying outcomes: hazardous alcohol use (AUDIT-C > 3/4 for women/men), number of alcohol units/month, binge drinking, cannabis and tobacco use. Mixed models assessed the effect of HCV treatment status (not yet treated, treated and HCV-cleared, treated and HCV-chronic) on each outcome. **FINDINGS:** A significant decrease (over 60% reduction) in both hazardous alcohol use and binge drinking and a reduction of 10 alcohol units/month were observed after HCV treatment (whatever the outcome). No significant effect of HCV treatment status was found on tobacco use and regular cannabis use but HCV 'clearers' reported less non-regular use of cannabis. **CONCLUSIONS:** Hepatitis C virus (HCV) treatment appears to help HIV-HCV co-infected patients reduce alcohol use.

[**Anger and quality of life in patients co-infected with HIV and hepatitis C virus: a cross-sectional study (ANRS CO13-HEPAVIH).**](#) Marcellin F1, Protopopescu C, Esterle L, et al. Eur J Gastroenterol Hepatol. 2017 Apr 17. doi: 10.1097/MEG.0000000000000883. [Epub ahead of print]
OBJECTIVE: The aim of this study is to document the relationship between anger dimensions (state, trait, expression, and control) and quality of life (QoL) in patients co-infected with HIV and hepatitis C virus (HCV). **PATIENTS AND METHODS:** This is a cross-sectional study nested in the ANRS CO13-HEPAVIH French national cohort. Anger and QoL were assessed using self-administered questionnaires in 536 HIV-HCV-co-infected patients. Correlations between anger scores (STAXI-2 scale) and QoL scores (WHOQOL-HIV BREF scale) were assessed using Spearman's coefficients. Multiple linear regression models were then used to test the relationship between the different dimensions of anger and QoL after adjustment for statistically significant psychosocial, sociobehavioral, and clinical characteristics. **RESULTS:** Patients with excessive alcohol use or history of injecting drug use had higher levels of anger. All dimensions of anger were significantly correlated with impaired QoL for all six dimensions of the WHOQOL-HIV BREF scale. Greater internal experience of anger and impaired anger control were confirmed as independent correlates of impaired QoL related to psychological health, social relationships, and patients' beliefs after adjustment for depressive symptoms, functional impact of fatigue, socioeconomic status, and HIV-related characteristics. **CONCLUSION:** Anger issues need close monitoring in HIV-HCV-co-infected patients, especially in patients with addictive behaviors. Screening for problems in anger management and implementing individualized psychotherapeutic strategies may help improve QoL in this population.

[**HCV Cure and Reinfection Among People With HIV/HCV Coinfection and People Who Inject Drugs.**](#) Martinello M1, Hajarizadeh B2, Grebely J2, Dore GJ2,3, Matthews GV2,3. Curr HIV/AIDS Rep. 2017 Apr 21. doi: 10.1007/s11904-017-0358-8. [Epub ahead of print]
PURPOSE OF REVIEW: Highly effective, well-tolerated interferon-free direct-acting antivirals (DAA) have revolutionised hepatitis C virus (HCV) therapeutics, with the opportunity for broad treatment scale-up among marginalised or "high-risk" populations, including people

who inject drugs (PWID) and people with HIV/HCV coinfection. **RECENT FINDINGS:** Concern that HCV reinfection may compromise HCV treatment outcomes is sometimes cited as a reason for not offering treatment to current and former PWID. However, the incidence of reinfection following interferon-based treatment for chronic HCV is low among PWID. Reinfection rates in HIV-positive men-who-have-sex-with-men (MSM) are varied, with high incidence reported in some cohorts. Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence could be achieved with targeted DAA therapy among those at the highest risk of ongoing transmission. This review will summarise the recent literature on DAA efficacy in PWID and people with HIV/HCV coinfection, discuss the individual- and population-level impact of DAA treatment scale-up and reinfection, and highlight ongoing and future research questions in expanding HCV care and treatment to those populations at high risk of ongoing HCV transmission.

[**HCV viremia associates with NK cell activation and dysfunction in anti retroviral HIV/HCV co-infected subjects.**](#) Papasavvas E1, Azzoni L1, Yin X1, et al. J Viral Hepat. 2017 Apr 17. doi: 10.1111/jvh.12714. [Epub ahead of print]
The impact of Hepatitis C virus (HCV) RNA levels on immune status in chronically HCV mono-infected when compared to HIV/HCV co-infected on antiretroviral therapy (ART) remains poorly understood. A total of 78 African American subjects HCV viremic/naïve to HCV treatment (33 HCV genotype 1 mono-infected, 45 HCV genotype 1/HIV co-infected on ART) were studied. Clinical and liver enzymes measurements were performed. Whole blood was analyzed for immune subset changes by flow-cytometry. Peripheral blood mononuclear cells (PBMC) were used for same-day constitutive and in vitro Interferon (IFN)-α-induced Signal Transducer and Activator of Transcription (STAT) phosphorylation, K562 target cell lysis and K562 target cell recognition-mediated IFN-γ production. Statistical analysis was done using R (2.5.1) or JMP Pro 11. While both groups did not differ in the level of liver enzymes, HIV/HCV had higher T cell activation/exhaustion, and constitutive STAT-1 phosphorylation compared to HCV. In contrast, CD4+ FoxP3+ CD25+ frequency, IFN-αR expression on NK cells, as well as constitutive and IFN-α-induced direct cytotoxicity were lower in HIV/HCV. Linear regression models further supported these results. Finally, increase in HCV viral load (vl) and CD4+ T cell count had an opposite effect between the two groups on NK cell activity, and T cell activation respectively. HCV viraemia in antiretroviral -treated HIV/HCV co-infection was associated with greater immune activation/exhaustion and NK dysfunction than HCV viral load alone in HCV mono-infection. The more pronounced immune modulation noted in antiretroviral treated HIV co-infected / untreated HCV viremic subjects may impact HCV disease progression and/or response to immunotherapy. This article is protected by copyright. All rights reserved.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

[**Influence of camel milk on the hepatitis C virus burden of infected patients.**](#)
El-Fakharany EM1, El-Baky NA1, Linjawi MH2, Aljaddawi AA3, Saleem TH4, Nassar AY4, Osman A5, Redwan EM1,3. Exp Ther Med. 2017 Apr;13(4):1313-1320. doi: 10.3892/etm.2017.4159. Epub 2017 Feb 22.
Hepatitis C virus (HCV) infection represents a world health problem and no protective vaccine or effective drug currently exists. For economic reasons, many patients use traditional medicines to control the infection. In Egypt, camel milk is one of the traditional medicines widely

consumed by patients infected with HCV. The present study aimed to evaluate the efficacy of camel milk in the treatment of patients infected with HCV. Whole camel milk from a local farm was administered to patients for 4 months (250 ml/day/patient). Patient sera were collected prior to and following camel milk drinking, and three markers were set-up for sera-evaluation. The three markers indicating the effect of camel milk on HCV infection were: Liver function assays [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]; a viral load assay; and anti-HCV antibodies profile and isotyping against synthetic HCV epitopes. Camel milk demonstrated the ability to improve general fatigue, health and liver function (ALT and AST levels); ALT was reduced in ~88% of patients and AST was reduced in all patients subsequent to drinking camel milk for four months. The majority of patients responded positively to camel milk treatment; RNA viral load decreased in 13 out of the 17 patients (76.47%) and one patient exhibited undetected viremia following camel milk treatment. The anti-HCV antibodies profile and isotyping were significantly decreased (P<0.05) in immunoglobulin (Ig)G1 following treatment in 70-76% of patients. However, the treatment was ineffective in 23.53% of patients who experienced no reduction in RNA viral load following treatment with camel milk. In conclusion, whole camel milk treatment demonstrated efficacy in vivo; the viral load in the majority of patient sera was reduced and the IgG isotype profile was converted to Th1 immunity.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

The cobas® HCV GT is a new tool that accurately identifies Hepatitis C virus genotypes for clinical practice. Fernández-Caballero JA1, Alvarez M1, Chueca N1, Pérez AB1, García F1. PLoS One. 2017 Apr 14;12(4):e0175564. doi: 10.1371/journal.pone.0175564. eCollection 2017. **OBJECTIVE:** We aimed to evaluate the correct assignment of HCV genotype/subtypes 1a and 1b by cobas® HCV genotyping (GT) assay (Roche Molecular Diagnostics) compared with nonstructural protein 5B (NS5B) sequencing. **PATIENTS AND METHODS:** Clinical samples from 153 patients submitted for HCV genotyping were studied. After genotyping with the cobas® HCV GT, sequencing of a 387 bp fragment in the NS5B gene and phylogenetic analysis was employed to compare genotyping results. Major discrepancies were defined as differences in the assigned genotype by cobas® HCV GT and NS5B sequencing (including genotype 1 subtypes 1a and 1b misclassification). **RESULTS:** Overall agreement between the cobas® HCV GT and NS5B sequencing was 98%; all the 1a, 1b, 2, 3 and 4 genotypes identified by cobas® HCV GT were concordant with NS5B sequencing. Three samples tested "indetermined" by cobas® HCV GT assay and were genotyped as 1a, 3a, and 4d by NS5B sequencing. **CONCLUSSION:** These results indicate that the cobas® HCV GT assay correctly identifies HCV genotypes, and points out the importance of additional methods based on DNA sequencing for resolving indeterminate results.

Geographic disparities in access to syringe services programs among young people with hepatitis C virus infection in the U.S. Canary L1, Hariri S1, Campbell C1, Young R2, Whitcomb J3, Kaufman H4, Vellozzi C1. Clin Infect Dis. 2017 Apr 11. doi: 10.1093/cid/cix333. [Epub ahead of print]
Using commercial laboratory data, we found 80% of 29,382 young people currently infected with hepatitis C lived >10 miles from a syringe services program. The median distance was 37 miles, with greater distances in rural areas and Southern and Midwestern states. Strategies to improve access to preventive services are warranted.

[Engagement in Care of High-Risk Hepatitis C Patients with Interferon-Free Direct-Acting Antiviral Therapies.](#) Dever JB1,2, Ducom JH1, Ma A1, Nguyen J1, Liu L2, Herrin A1, Groessl EJ1,2, Ho SB3,4. Dig Dis Sci. 2017 Apr 4. doi: 10.1007/s10620-017-4548-4. [Epub ahead of print]

BACKGROUND AND AIMS: The extent to which hepatitis C (HCV) treatment uptake is improved following introduction of interferon-free direct-acting antiviral (DAA) treatments is unknown. The purpose of this study was to determine HCV patient engagement and barriers to care for accessing DAA treatments in a real-world setting. **METHODS:** Patients with HCV viremia at high risk for fibrosis were identified using the Veterans Affairs (VA) registry within San Diego's VA in October 2014. Patients not enrolled in HCV clinic were systematically contacted by letter and phone. Logistic regression was used to examine patient factors associated with subsequent engagement in care over 12-20 months. **RESULTS:** In the local registry of 2089 patients, 481 were identified with high-risk fibrosis scores. Of those, 380 (79%) were eligible for antiviral treatment, and 178/380 (47%) patients were actively followed in clinic. The remaining 202/380 (53%) patients were never seen by a HCV clinic provider or lost to follow-up. Of these, 114/380 (30%) of the treatment-eligible cohort remained non-engaged in care following outreach. Compared with patients engaged in care, non-engaged patients were significantly more likely to have homelessness, COPD comorbidity, or active alcohol or/and drug use. Overall 74.4% of patients engaged in HCV clinic received antiviral treatment. **CONCLUSIONS:** A significant portion of eligible HCV patients could not be engaged in treatment after a programmatic outreach effort. These data indicate that more sustained or innovative outreach efforts are needed in order to maximize treatment access, with specific interventions targeting those with unstable housing and active alcohol/substance use disorders.

[Geographic Differences in Temporal Incidence Trends of Hepatitis C Virus Infection Among People Who Inject Drugs: The InC3 Collaboration.](#) Morris MD1, Shiboski S1, Bruneau J2, et al. Clin Infect Dis. 2017 Apr 1;64(7):860-869. doi: 10.1093/cid/ciw869.

BACKGROUND: We determined temporal trends (1985-2011) in hepatitis C virus (HCV) incidence and associated behavioral exposures for people who inject drugs (PWID) from the United States (Boston, Baltimore, and San Francisco), Canada (Montreal), the Netherlands (Amsterdam), and Australia (Sydney and Melbourne). **METHODS:** Using population-based cohort data from HCV-negative PWID, we calculated overall and within-city HCV incidence trends, HCV rates by study enrollment period (1985-2011), and temporal trends in exposure behaviors. Poisson regression models estimated trends in HCV incidence over calendar-time. Survival models identified risk factors for HCV incidence across cities and estimated independent effects of city and calendar period on HCV infection risk. **RESULTS:** Among 1391 initially HCV-negative participants followed prospectively (1644.5 person-years of observation [PYO]), 371 HCV incident infections resulted in an overall incidence of 22.6 per 100 PYO (95% confidence interval [CI], 20.4-25.0). Incidence was highest and remained elevated in Baltimore (32.6/100 PYO), San Francisco (24.7/100 PYO), and Montreal (23.5/100 PYO), lowest in Melbourne and Amsterdam (7.5/100 PYO and 13.1/100 PYO, respectively), and moderate (21.4/100 PYO) in Sydney. Higher rates of syringe and equipment sharing and lower prevalence of opioid agonist therapy were associated with HCV incidence in cities with the highest incidence. Risk for infection dropped by 18% for every 3-year increase in calendar-time (adjusted hazard ratio, 0.8 [95% CI, .8-.9]) in the multivariable model. **CONCLUSIONS:**

Differences in prevention strategies and injecting contexts may explain the ongoing high HCV incidence in these North American cities and emphasize the need for scale-up of opioid agonist therapy and increased coverage of needle and syringe programs in North America.

[Cost-effectiveness of combination daclatasvir-sofosbuvir for treatment of genotype 3 chronic hepatitis C infection in the United States.](#) Saint-Laurent Thibault C1, Moorjaney D2, Ganz ML3, Sill B4, Hede S5, Yuan Y5, Gorsh B6. J Med Econ. 2017 Apr 20:1-11. doi: 10.1080/13696998.2017.1307204. [Epub ahead of print]
BACKGROUND: A phase III trial evaluated the efficacy and safety of Daklinza (daclatasvir or DCV) in combination with sofosbuvir (SOF) for treatment of genotype (GT) 3 hepatitis C virus (HCV) patients. **AIM:** This study evaluated the cost-effectiveness of DCV + SOF vs SOF in combination with ribavirin (RBV) over a 20-year time horizon from the perspective of a United States (US) payer. **METHODS:** A published Markov model was adapted to reflect US demographic characteristics, treatment patterns, costs of drug acquisition, monitoring, disease and adverse event management, and mortality risks. Clinical inputs came from the ALLY-3 and VALENCE trials. The primary outcome was the incremental cost-utility ratio. Life-years, incidence of complications, number of patients achieving sustained virological response (SVR), and the total cost per SVR were secondary outcomes. Costs (2014 USD) and quality-adjusted life years (QALYs) were discounted at 3% per year. Deterministic, probabilistic, and scenario sensitivity analyses were conducted. **RESULTS:** DCV + SOF was associated with lower costs and better effectiveness than SOF + RBV in the base case and in almost all scenarios (i.e. treatment-experienced, non-cirrhotic, time horizons of 5, 10, and 80 years). DCV + SOF was less costly, but also slightly less effective than SOF + RBV in the cirrhotic and treatment-naïve population scenarios. Results were sensitive to variations in the probability of achieving SVR for both treatment arms. DCV + SOF costs less than $50,000 per QALY gained in 79% of all probabilistic iterations compared with SOF + RBV. **CONCLUSION:** DCV + SOF is a dominant option compared with SOF + RBV in the US for the overall GT 3 HCV patient population.

[Spontaneous remission of hepatitis B virus reactivation during direct-acting antiviral agent-based therapy for chronic hepatitis C.](#) Sato K1,2, Kobayashi T1,2, Yamazaki Y1,2, et al. Hepatol Res. 2017 Apr 19. doi: 10.1111/hepr.12905. [Epub ahead of print]
The administration of direct-acting antiviral agents (DAAs) to treat hepatitis C virus (HCV) infection has been reported to cause hepatitis B virus (HBV) reactivation. However, the actual conditions of HBV reactivation and the ideal timing of medical intervention have not been fully evaluated. We reported the cases of two female patients dually infected with HBV and HCV. Both patients were inactive HBV carriers. Although the serum HCV RNA levels promptly decreased after the initiation of DAA-based therapy, the serum HBV DNA levels gradually increased during DAA-based therapy, with the peak serum HBV DNA levels observed at 16 weeks after the initiation of DAA-based therapy in both cases. Subsequently, we checked the serum HBV DNA levels closely every week several times. Fortunately, the serum HBV DNA levels began to gradually decrease without medical intervention. Neither case developed an alanine aminotransferase flare-up. The HCV genotypes were 2a and 1b, and the DAA-based therapies of Cases 1 and 2 were 12 weeks of sofosbuvir/ribavirin and ombitasvir/paritaprevir/ritonavir, respectively. The significance of our case reports is the demonstration of the existence of spontaneous remission of HBV reactivation developed during DAA-based therapy and the avoidance of intervention of nucleot(s)ide analogs by frequent

monitoring of serum HBV DNA levels, and development of HBV reactivation regardless of the viral genotype or the class of DAAs. In conclusion, the close monitoring of the serum HBV DNA levels during and after DAA-based therapy is essential and medical intervention for HBV reactivation should be carefully considered on an individual basis.

Seroconversion rates among health care workers exposed to hepatitis C virus-contaminated body fluids: The University of Pittsburgh 13-year experience. Egro FM1, Nwaiwu CA2, Smith S3, Harper JD3, Spiess AM4. Am J Infect Control. 2017 Apr 24. pii: S0196-6553(17)30209-2. doi: 10.1016/j.ajic.2017.03.011. [Epub ahead of print]
BACKGROUND: Hepatitis C virus (HCV) transmission to health care personnel (HCP) after exposure to a HCV-positive source has been reported to occur at an average rate of 1.8% (range, 0%-10%). We aimed to determine the seroconversion rate after exposure to HCV-contaminated body fluid in a major U.S. academic medical center. **METHODS:** A longitudinal analysis of a prospectively maintained database of reported occupational injuries occurring between 2002 and 2015 at the University of Pittsburgh Medical Center was performed. Data collected include type of injury and fluid, injured body part, contamination of sharps, resident physicians' involvement, and patients' hepatitis B virus (HBV), HCV, and HIV status. **RESULTS:** A total of 1,361 cases were included in the study. Most exposures were caused by percutaneous injuries (65.0%), followed by mucocutaneous injuries (33.7%). Most (63.3%) were injuries to the hand, followed by the face and neck (27.6%). Blood exposure accounted for 72.7%, and blood-containing saliva accounted for 3.4%. A total of 6.9% and 3.7% of source patients were coinfected with HIV and HBV, respectively. The HCV seroconversion rate was 0.1% (n = 2) because of blood exposure secondary to percutaneous injuries. **CONCLUSIONS:** This study provides the largest and most recent cohort from a major U.S. academic medical center. The seroconversion rates among HCP exposed to HCV-contaminated body fluids was found to be lower than most of the data found in the literature.

The Role of e-Health in Optimizing Task-Shifting in the Delivery of Antiviral Therapy for Chronic Hepatitis C. Yoo ER1, Perumpail RB2, Cholankeril G3, Jayasekera CR2,4, Ahmed A2. Telemed J E Health. 2017 Apr 4. doi: 10.1089/tmj.2016.0189. [Epub ahead of print]
PURPOSE: Recently, we reported the successful application of task-shifting to improve the management of patients with chronic hepatitis C virus (HCV) infection receiving treatment with direct-acting antiviral (DAA) agents in underserved areas of California. We assessed the impact of e-health on task-shifting in our treatment model. **METHODS:** In a retrospective analysis, we reviewed the impact of e-health on optimizing the delivery of DAA-based regimen to HCV-infected patients in outreach clinics in medically underserved areas of California. A nonphysician healthcare provider worked in close conjunction with a hepatologist to monitor the patients during the course of antiviral therapy. We exclusively used our institution-based, secured e-health portal as the means of communication with the local staff and patients in outreach clinics. **RESULTS:** From January 2015 to June 2016, we treated over 100 HCV-infected patients with DAA-based regimens using the task-shifting model. During the study period, we did not experience any delay in the care of our patients undergoing treatment with DAA agents. Communication with the patient and staff using e-health was prompt, secured, and documented in electronic medical records. Due to the optimization of task-shifting by e-health and safety/tolerability of DAA, 95% patients did not need a follow-up clinic visit during the treatment. Return clinic visits during the treatment were unrelated to DAA use or associated with

ribavirin-related anemia. In addition, we noted improvement in access and capacity of our outreach clinic. **CONCLUSIONS:** We report a positive impact of e-health in optimizing task-shifting for DAA in HCV-infected patients in underserved outreach clinics. More importantly, a secondary improvement in access and capacity of our clinic was noted.

[Prevalence of HIV, HCV and HBV among Homeless and Non-homeless United States Veterans.](#) Noska AJ1, Belperio PS2, Loomis TP2, O'Toole TP3, Backus LI2. Clin Infect Dis. 2017 Apr 1. doi: 10.1093/cid/cix295. [Epub ahead of print]
BACKGROUND: Veterans are disproportionately affected by HIV, hepatitis C (HCV) and hepatitis B (HBV). Homeless veterans are at particularly high risk for HIV, HCV and HBV due to a variety of overlapping risk factors, including high rates of mental health disorders and substance use disorders. The prevalence of HIV, HCV and HBV among homeless veterans nationally is currently unknown. This study describes national testing rates and prevalence of HIV, HCV and HBV among homeless veterans. **METHODS:** Using data from the VA's Corporate Warehouse Data from 2015, we evaluated HIV, HCV, and HBV laboratory testing and infection confirmation rates and diagnoses on the Problem List for non-homeless veterans and for veterans utilizing homeless services in 2015. **RESULTS:** Among 242,740 homeless veterans in VA care in 2015, HIV, HCV and HBV testing occurred in 63.8% (n=154,812), 78.1% (n=189,508), and 52.8% (n=128,262), respectively. The HIV population prevalence was 1.52% (3,684/242,740) among homeless veterans, compared to 0.44% (23,797/5,424,685) among non-homeless veterans. The HCV population prevalence among homeless veterans was 12.1% (29,311/242,740), compared to 2.7% (148,079/5,424,685) among non-homeless veterans, while the HBV population prevalence was 0.99% (2,395/242,740) for homeless veterans, and 0.40% (21,611/5,424,685) among non-homeless veterans. **CONCLUSIONS:** To our knowledge this work represents the most comprehensive tested prevalence and population prevalence estimates of HIV, HCV and HBV among homeless veterans nationally. The data demonstrate high prevalence of HIV, HCV and HBV among homeless veterans, and reinforce the need for integrated healthcare services along with homeless programming.

[Estimation of State-Level Prevalence of Hepatitis C Virus Infection, US States and District of Columbia, 2010.](#)
Rosenberg ES1, Hall EW1, Sullivan PS1, Sanchez TH1, Workowski KA2, Ward JW3, Holtzman D3. Clin Infect Dis. 2017 Apr 26. doi: 10.1093/cid/cix202. [Epub ahead of print]
BACKGROUND: Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States and a leading cause of morbidity and mortality. Previous analyses of the US National Health and Nutrition Examination Survey (NHANES) indicated approximately 3.6 million noninstitutionalized persons with antibody to HCV (anti-HCV). However, state-level prevalence remains less understood and cannot be estimated reliably from NHANES alone. **METHODS:** We used 3 publicly available government data sources to estimate anti-HCV prevalence in each US state among noninstitutionalized persons aged ≥18 years. A small-area estimation model combined indirect standardization of NHANES-based prevalence with logistic regression modeling of mortality data, listing acute or chronic HCV infection as a cause of death, from the National Vital Statistics System during 1999-2012. Model results were combined with US Census population sizes to estimate total number and prevalence of persons with antibody to HCV in 2010. **RESULTS:** National anti-HCV prevalence was 1.67% (95% confidence interval [CI], 1.53-1.90), or 3 911 800 (95% CI, 3 589 400- 4 447 500)

adults in 2010. State-specific prevalence ranged from 0.71% (Illinois) to 3.34% (Oklahoma). The West census region had the highest region-specific prevalence (2.14% [95% CI, 1.96-2.48]); 10 of 13 states had rates above the national average. The South had the highest number of persons with anti-HCV (n = 1561600 [95% CI, 1 427 700-1 768 900]). The Midwest had the lowest region-specific prevalence (1.14% [95% CI, 1.04%-1.30%]). **CONCLUSIONS:** States in the US West and South have been most impacted by hepatitis C. Estimates of HCV infection burden are essential to guide policy and programs to optimally prevent, detect, and cure infection.

HEPATOCELLULAR (LIVER) CANCER

Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. Bang CS1, Song IH2. BMC Gastroenterol. 2017 Apr 4;17(1):46. doi: 10.1186/s12876-017-0606-9.
BACKGROUND: The long-term clinical outcomes of antiviral therapy for patients with chronic hepatitis C are uncertain in terms of hepatitis C virus (HCV)-related morbidity and mortality according to the response to antiviral therapy. This study aimed to assess the impact of antiviral treatment on the development of HCC and mortality in patients with chronic HCV infection. **METHODS:** A systematic review was conducted for studies that evaluated the antiviral efficacy for patients with chronic hepatitis C or assessed the development of HCC or mortality between SVR (sustained virologic response) and non-SVR patients. The methodological quality of the enrolled publications was evaluated using Risk of Bias table or Newcastle-Ottawa scale. Random-effect model meta-analyses and meta-regression were performed. Publication bias was assessed. **RESULTS:** In total, 59 studies (4 RCTs, 15 prospective and 40 retrospective cohort studies) were included. Antiviral treatment was associated with reduced development of HCC (vs. no treatment; OR 0.392, 95% CI 0.275-0.557), and this effect was intensified when SVR was achieved (vs. no SVR, OR: 0.203, 95% CI 0.164-0.251). Antiviral treatment was associated with lower all-cause mortality (vs. no treatment; OR 0.380, 95% CI 0.295-0.489) and liver-specific mortality (OR 0.363, 95% CI 0.260-0.508). This rate was also intensified when SVR was achieved [all-cause mortality (vs. no SVR, OR 0.255, 95% CI 0.199-0.326), liver-specific mortality (OR 0.126, 95% CI 0.094-0.169)]. Sensitivity analyses revealed robust results, and a small study effect was minimal. **CONCLUSIONS:** In patients with chronic hepatitis C, antiviral therapy can reduce the development of HCC and mortality, especially when SVR is achieved.

Outcome of All-Oral Direct-Acting Antiviral Regimens on the Rate of Development of Hepatocellular Carcinoma in Patients with Hepatitis C Virus Genotype 1-Related Chronic Liver Disease. Ogata F1, Kobayashi M, Akuta N, et al. Oncology. 2017 Apr 28. doi: 10.1159/000470910. [Epub ahead of print]
OBJECTIVES: There is little information on the risk factors for hepatocellular carcinoma (HCC) and outcome of treatment with an all-oral combination of direct-acting antiviral regimens following eradication of hepatitis C virus (HCV) RNA. **METHODS:** The study subjects were 1,170 patients with HCV genotype 1-related chronic liver disease treated with either NS5A inhibitor plus NS3/4A protease inhibitor (n = 707), NS5A inhibitor plus NS5B polymerase inhibitor (n = 345), or NS5A inhibitor, NS3/4A protease inhibitor plus ritonavir (n = 118), for 12-24 weeks. All patients were free of HCC before and during therapy. **RESULTS:** In this retrospective study, 22 patients developed HCC during the follow-up (time from the end of antiviral therapy until the last visit: 1.3 years). At 1 and 2 years after completion of the treatment,

the cumulative HCC rates for the whole group were 1.8 and 2.3%, respectively, and 1.4 and 1.8%, respectively, for 1,065 patients who showed sustained virological response (SVR). The risk factors for HCC identified by multivariate analysis were hypoalbuminemia, thrombo-cytopenia, a high α-fetoprotein level, and non-SVR for all patients, and hypoalbuminemia and a high α-fetoprotein level for patients with SVR. **CONCLUSION:** Eradication of HCV RNA by direct-acting antiviral regimens might reduce the risk of HCC. Albumin and α-fetoprotein levels are significant risk factors for HCC.

[Direct-acting antiviral therapy decreases hepatocellular carcinoma recurrence rate in cirrhotic patients with chronic hepatitis C.](#) Virlogeux V1,2, Pradat P1,2, Hartig-Lavie K1,2, et al. Liver Int. 2017 Apr 19. doi: 10.1111/liv.13456. [Epub ahead of print]
BACKGROUND AND AIMS: Arrival of direct-acting antiviral (DAA) agents against hepatitis C virus (HCV) with high-sustained virological response (SVR) rates and very few side effects has drastically changed the management of HCV infection. The impact of DAA exposure on hepatocellular carcinoma (HCC) recurrence after a first remission in patients with advanced fibrosis remains to be clarified. **METHODS:** 68 consecutive HCV patients with a first HCC diagnosis and under remission, subsequently treated or not with a DAA combination, were included. Clinical, biological, and virological data were collected at first HCC diagnosis, at remission and during the surveillance period. **RESULTS:** All patients were cirrhotic. Median age was 62 years and 76% of patients were male. Twenty-three patients (34%) were treated with DAAs and 96% of them achieved SVR. Median time between HCC remission and DAA initiation was 7.2 months (IQR: 3.6 - 13.5; range: 0.3 - 71.4) and median time between DAA start and HCC recurrence was 13.0 months (IQR: 9.2 - 19.6; range: 3.0 - 24.7). Recurrence rate was 1.7/100 person-months among treated patients vs 4.2/100 person-months among untreated patients (p=0.008). In multivariate survival analysis, the hazard ratio for HCC recurrence after DAA exposure was 0.24 (95% confidence interval: 0.10-0.55; p<0.001). **CONCLUSIONS:** HCC recurrence rate was significantly lower among patients treated with DAA compared with untreated patients. Given the potential impact of our observation, large-scale prospective cohort studies are needed to confirm these results. This article is protected by copyright. All rights reserved.

[Indoleamine 2,3-dioxygenase: As a potential prognostic marker and immunotherapeutic target for hepatocellular carcinoma.](#) Asghar K1, Farooq A1, Zulfiqar B1, Rashid MU1. World J Gastroenterol. 2017 Apr 7;23(13):2286-2293. doi: 10.3748/wjg.v23.i13.2286.
Tumor cells induce an immunosuppressive microenvironment which leads towards tumor immune escape. Understanding the intricacy of immunomodulation by tumor cells is essential for immunotherapy. Indoleamine 2,3-dioxygenase (IDO) is an immunosuppressive enzyme which mediates tumor immune escape in various cancers including hepatocellular carcinoma (HCC). IDO up-regulation in HCC may lead to recruitment of regulatory T-cells into tumor microenvironment and therefore inhibit local immune responses and promote metastasis. HCC associated fibroblasts stimulate natural killer cells dysfunction through prostaglandin E2 and subsequently IDO promotes favorable condition for tumor metastasis. IDO up-regulation induces immunosuppression and may enhance the risk of hepatitis C virus and hepatitis B virus induced HCC. Therefore, IDO inhibitors as adjuvant therapeutic agents may have clinical implications in HCC. This review proposes future prospects of IDO not only as a therapeutic target but also as a prognostic marker for HCC.

Occurrence of hepatocellular carcinoma in HIV/HCV co-infected patients treated with direct-acting antivirals. Hasson H1, Merli M2, Messina E2, et al. J Hepatol. 2017 Apr 11. pii: S0168-8278(17)30203-9. doi: 10.1016/j.jhep.2017.03.032. [Epub ahead of print] Controversial data on high incidence of hepatocellular carcinoma (HCC) in patients with HCV-related liver disease treated with interferon-free anti-HCV direct-acting antivirals has been reported Even higher risk of de novo HCC has been envisaged in the subpopulation of HIV/HCV co-infected patients in whom cancer immune-surveillance might be decreased. We present 118 consecutive HIV/HCV co-infected patients undergoing DAAs-based treatment, in which the observed de novo HCC incidence was 2.5% after a median follow-up of 85 weeks, therefore non-significantly increased compared to HIV-negative subjects.

HCV Genotype 6 Increased the Risk for Hepatocellular Carcinoma Among Asian Patients With Liver Cirrhosis. Lee MH1, Hsiao TI2,3, Subramaniam SR4, et al. Am J Gastroenterol. 2017 Apr 25. doi: 10.1038/ajg.2017.123. [Epub ahead of print] **OBJECTIVES:** Hepatitis C virus (HCV) infection is a well-documented risk factor for hepatocellular carcinoma (HCC). Seven HCV genotypes have been classified, and the genotypes show a great variety of geographic distribution. HCV genotype 6 is prevalent in Southeast Asia and has been less studied than the other genotypes. **METHODS:** This follow-up study was designed to evaluate the natural history of HCV genotype 6. The cohort enrolled 851 Asian patients consisting of 222 with HCV genotype 6 and 629 with other genotypes. The incidence of HCC per 1,000 person-years of various HCV genotypes was estimated by dividing the new HCC cases to the person-years of follow-up. The adjusted hazards ratios (HRs) with 95% confidence intervals (CIs) were estimated by Cox's proportional hazards models. **RESULTS:** After 4072 person-years of follow-up, there were 96 newly-developed HCC cases, confirming an incidence of 23.6 per 1000 person-years. By stratifying cirrhosis at study entry, the cumulative risk of HCC among HCV genotype 6 vs. non-6 was 2.9 vs. 2.2% for those without cirrhosis (P=0.45) and 76.2% (95% CI: 55.6-96.8%) vs. 36.2% (95% CI: 28.7-39.1%) for those with cirrhosis (P<0.05), respectively. Among patients with cirrhosis, HCV genotype 6 was significantly associated with HCC compared to patients with non-6 genotypes, with the adjusted HR=2.12 (1.33-3.39), P<0.05. In a model treating patients with genotypes other than 1 or 6 as the reference, the adjusted HR for HCC for HCV genotypes 1 and 6 were 1.13 (0.56-2.27) and 2.34 (1.12-4.86), respectively. **CONCLUSIONS:** Among patients with cirrhosis, those with HCV genotype 6 infection should be given high priority for antiviral therapy to decrease HCC risk and for vigilant adherence to HCC surveillance.Am J Gastroenterol advance online publication, 25 April 2017; doi:10.1038/ajg.2017.123.

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. El-Khoueiry AB1, Sangro B2, Yau T3, et al. Lancet. 2017 Apr 20. pii: S0140-6736(17)31046-2. doi: 10.1016/S0140-6736(17)31046-2. [Epub ahead of print] **BACKGROUND:** For patients with advanced hepatocellular carcinoma, sorafenib is the only approved drug worldwide, and outcomes remain poor. We aimed to assess the safety and efficacy of nivolumab, a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor, in patients with advanced hepatocellular carcinoma with or without chronic viral hepatitis.

METHODS: We did a phase 1/2, open-label, non-comparative, dose escalation and expansion trial (CheckMate 040) of nivolumab in adults (≥18 years) with histologically confirmed advanced hepatocellular carcinoma with or without hepatitis C or B (HCV or HBV) infection. Previous sorafenib treatment was allowed. A dose-escalation phase was conducted at seven hospitals or academic centres in four countries or territories (USA, Spain, Hong Kong, and Singapore) and a dose-expansion phase was conducted at an additional 39 sites in 11 countries (Canada, UK, Germany, Italy, Japan, South Korea, Taiwan). At screening, eligible patients had Child-Pugh scores of 7 or less (Child-Pugh A or B7) for the dose-escalation phase and 6 or less (Child-Pugh A) for the dose-expansion phase, and an Eastern Cooperative Oncology Group performance status of 1 or less. Patients with HBV infection had to be receiving effective antiviral therapy (viral load <100 IU/mL); antiviral therapy was not required for patients with HCV infection. We excluded patients previously treated with an agent targeting T-cell costimulation or checkpoint pathways. Patients received intravenous nivolumab 0·1-10 mg/kg every 2 weeks in the dose-escalation phase (3+3 design). Nivolumab 3 mg/kg was given every 2 weeks in the dose-expansion phase to patients in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressor without viral hepatitis, HCV infected, and HBV infected. Primary endpoints were safety and tolerability for the escalation phase and objective response rate (Response Evaluation Criteria In Solid Tumors version 1.1) for the expansion phase. This study is registered with ClinicalTrials.gov, number NCT01658878. **FINDINGS:** Between Nov 26, 2012, and Aug 8, 2016, 262 eligible patients were treated (48 patients in the dose-escalation phase and 214 in the dose-expansion phase). 202 (77%) of 262 patients have completed treatment and follow-up is ongoing. During dose escalation, nivolumab showed a manageable safety profile, including acceptable tolerability. In this phase, 46 (96%) of 48 patients discontinued treatment, 42 (88%) due to disease progression. Incidence of treatment-related adverse events did not seem to be associated with dose and no maximum tolerated dose was reached. 12 (25%) of 48 patients had grade 3/4 treatment-related adverse events. Three (6%) patients had treatment-related serious adverse events (pemphigoid, adrenal insufficiency, liver disorder). 30 (63%) of 48 patients in the dose-escalation phase died (not determined to be related to nivolumab therapy). Nivolumab 3 mg/kg was chosen for dose expansion. The objective response rate was 20% (95% CI 15-26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6-28) in the dose-escalation phase. **INTERPRETATION:** Nivolumab had a manageable safety profile and no new signals were observed in patients with advanced hepatocellular carcinoma. Durable objective responses show the potential of nivolumab for treatment of advanced hepatocellular carcinoma. **FUNDING:** Bristol-Myers Squibb.