
INTRODUCTION: In the era of direct-acting antivirals, hepatitis C virus (HCV) genotype (GT) 3 remains as the most difficult-to-treat HCV-GT. Currently, data on the efficacy of ledipasvir/sofosbuvir plus ribavirin (SOF/LDV+RBV) in GT3-infected patients are limited. We investigated the efficacy of this regimen in a real-life cohort from Austria. PATIENTS AND METHODS: A total of 55 patients with HCV-GT3 and compensated liver disease (20% treatment-experienced, 33% with cirrhosis, 7% with HIV coinfection) from four Austrian hepatitis centers received treatment with SOF/LDV+RBV for 12 weeks. The primary endpoint was sustained virological response 12 weeks after end of therapy (SVR12). RESULTS: In the modified intention-to-treat analysis - excluding patients lost to follow-up - the overall SVR12 rate was 94% (95% confidence interval: 84-99%). In treatment-naive and treatment-experienced patients, SVR12 rates were 95 and 89%, respectively. SVR12 rate was 91% in patients without cirrhosis and 100% in patients with cirrhosis. There were no serious adverse events. Viral sequencing did not show the presence of any resistance-associated substitutions in any of the three relapsed patients. CONCLUSION: Despite a very weak antiviral activity of ledipasvir against HCV-GT3 in vitro, a 12-week course of SOF/LDV+RBV was highly effective, with a 94% SVR12 rate in our cohort of compensated HCV-GT3-infected patients. Thus, if pangenotypic NS5A inhibitors are not available or not reimbursed by insurances, SOF/LDV+RBV seems to be an effective alternative in patients with HCV-GT3 infection.


Interactions between simeprevir (hepatitis C virus [HCV] NS3/4A protease inhibitor) and ledipasvir (HCV NS5A replication complex inhibitor) were investigated in treatment-naive HCV genotype 1-infected patients without cirrhosis, treated with simeprevir-sofosbuvir-ledipasvir in a
two-panel, phase 2, open-label study. Patients had stable background treatment with sofosbuvir (400 mg once daily [QD]). In panel 1 (n = 20), the effect of ledipasvir (90 mg QD) on simeprevir (150 mg QD) was studied. Patients received simeprevir and sofosbuvir from days 1 to 14; steady-state pharmacokinetics (PK) of simeprevir was assessed (day 14). On day 15, ledipasvir was added and steady-state PK of simeprevir in the combination was evaluated (day 28). In panel 2 (n = 20), the effect of simeprevir on ledipasvir was investigated. From days 1 to 14, patients received ledipasvir and sofosbuvir and steady-state PK of ledipasvir was assessed (day 14). On day 15, simeprevir was added and a full PK profile was obtained (day 28). The least-squares mean maximum plasma concentration and area under the concentration-time curve (90% confidence interval) increased 2.3-fold (2.0- to 2.8-fold) and 3.1-fold (2.4- to 3.8-fold) for simeprevir, respectively (panel 1), and 1.6-fold (1.4- to 1.9-fold) and 1.7-fold (1.6- to 2.0-fold) for ledipasvir, respectively (panel 2), in the presence versus the absence of the other drug. All patients achieved sustained virologic responses 12 weeks after treatment end. Adverse events, mainly grade 1/2, occurred in 80% of patients; the most common was photosensitivity (45%). Due to the magnitude of interaction and the limited amount of safety data available, the use of this treatment combination is not recommended.


**OBJECTIVE:** Direct acting antivirals (DAAs) have overcome many long-standing medical barriers to hepatitis C virus (HCV) treatment (i.e. host characteristics and medical contraindications) and treatment outcome disparities that were associated with interferon regimens. The public health and clinical benefit of current and forthcoming DAA discoveries will be limited if efforts are not made to examine racial, psychological, and socioeconomic factors associated with being treated with DAAs. This study examined racial, psychological, and socioeconomic factors that facilitate and inhibit patients receiving DAAs for HCV.

**PATIENTS AND METHODS:** This was a single-center retrospective cohort study at a large urban tertiary center of patients (n=747) who were referred for evaluation and treatment of HCV. **RESULTS:** Sixty-eight percent of patients were non-Hispanic White, 31% were African American, and 1% were of other ethnicities. The majority of patients received treatment, but 29% (218/747) did not. Patients who were older [odds ratio (OR)=1.02, 95% confidence interval (CI): 1.01-1.04] and insured (OR=2.73, 95% CI: 1.12-6.97) were more likely to receive HCV treatment. Patients who were African American (OR=0.46, 95% CI: 0.46-1.06), used drugs (OR=0.09, 95% CI: 0.04-0.17), smoked (OR=0.55, 95% CI: 0.37-0.81), and used alcohol (OR=0.11, 95% CI: 0.06-0.20) were less likely to receive HCV treatment. **CONCLUSION:** Though DAAs have eliminated many historically, long-standing medical barriers to HCV treatment, several racial, psychological and socioeconomic barriers, and disparities remain. Consequently, patients who are African American, uninsured, and actively use drugs and alcohol will suffer from increased HCV-related morbidity and mortality in the coming years if deliberate public health and clinical efforts are not made to facilitate access to DAAs.

**Patient-Reported Outcomes Following Treatment of Chronic Hepatitis C Virus Infection With Sofosbuvir and Velpatasvir, With or Without Voxilaprevir.** Younossi ZM1, Stepanova
BACKGROUND & AIMS: Chronic infection with hepatitis C virus (HCV) has many hepatic and extrahepatic manifestations, measured by patient-reported outcomes (PROs). We measured changes in PROs during HCV treatment with recently developed pangenotypic regimens and from a sustained virologic response 12 weeks after treatment ended (SVR12).

METHODS: We collected PRO data from 2 multi-center, blinded, international phase 3 trials of sofosbuvir, velpatasvir, and voxilaprevir, from 748 patients previously treated with direct-acting antivirals for chronic infection with HCV of any genotype (59% HCV genotype 1, 43% with compensated cirrhosis) (POLARIS-1 and POLARIS-4). The combination of sofosbuvir, velpatasvir, and voxilaprevir was given to 445 patients, the combination of sofosbuvir and velpatasvir to 151 patients, and placebo to 152 patients. Patients completed the SF-36, FACIT-F, CLDQ-HCV, and WPAI:SHP questionnaires at baseline, during treatment, and during the follow-up period.

RESULTS: There was no difference in baseline clinical or demographic features or PRO scores among the groups (all P>.05). The group that received the combination of sofosbuvir, velpatasvir, and voxilaprevir had more gastrointestinal symptoms than the groups that received sofosbuvir and velpatasvir or placebo (P=.0001). An SVR12 was achieved by 90.1% of patients who received sofosbuvir and velpatasvir vs 96.9% of patients who received sofosbuvir, velpatasvir, and voxilaprevir (P=.0008). After 12 weeks of treatment, some PRO scores improved in both treatment groups (by 2.5 or by 9.1 points, on a 0-100 scale; P<.05) but not in the placebo group. All increases in PRO scores were sustained or increased after treatment ended (an increase of up to 11.1 points at 12 weeks after treatment and an increase of up to 16.6 points at 24 weeks after treatment ended) (P<.05 for all but 2 PROs). There were no differences in PROs between the sofosbuvir and velpatasvir group vs the sofosbuvir, velpatasvir, and voxilaprevir group (all P>.05). In multivariate analysis, after adjustment for clinical and demographic factors and baseline PRO scores, receiving treatment was associated with higher PROs scores than receiving placebo (beta as high as 5.1) (P<.05). CONCLUSION: In an analysis of data from 2 phase 3 clinical trials of patients with chronic HCV infection of any genotype, we found the combination of sofosbuvir, velpatasvir, with or without voxilaprevir, to increase PRO scores compared with placebo. These findings indicate the comprehensive benefit of these regimens during treatment and after SVR.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES


Hepatitis C virus (HCV) RNA replication occurs in tight association with remodeled host cell membranes, presenting as cytoplasmic accumulations of single, double and multi membrane vesicles in infected cells. Formation of these so-called replication organelles is mediated by a complex interplay of host cell factors and viral replicase proteins. Of these, nonstructural protein 4B (NS4B), an integral transmembrane protein, appears to play a key role, but little is known about the molecular mechanisms how this protein contributes to organelle biogenesis. Using forward and reverse genetics we identified glycine-zipper motifs within transmembrane helices 2 and 3 of NS4B that are critically involved in viral RNA replication. Foerster resonance energy
transfer analysis revealed the importance of the glycine-zippers in NS4B homo and heterotypic self-interactions. Additionally, ultrastructural analysis using electron microscopy unraveled a prominent role of glycine-zipper residues for the subcellular distribution and the morphology of HCV-induced double membrane vesicles. Notably, loss-of-function NS4B glycine-zipper mutants prominently induced single membrane vesicles with secondary invaginations that might represent an arrested intermediate state in double membrane vesicle formation. These findings highlight a so far unknown role of glycine residues within the membrane integral core domain for NS4B self-interaction and functional as well as structural integrity of HCV replication organelles. **IMPORTANCE:** Remodeling of the cellular endomembrane system leading to the establishment of replication organelles is a hallmark of positive-strand RNA viruses. In the case of hepatitis C virus (HCV), expression of the nonstructural proteins induces the accumulation of double membrane vesicles that likely arise from a concerted action of viral and co-opted cellular factors. However, the underlying molecular mechanisms are incompletely understood. Here, we identify glycine-zipper motifs within HCV nonstructural protein 4B (NS4B) transmembrane segments 2 and 3 that are crucial for the protein’s self-interaction. Moreover, glycine residues within NS4B transmembrane helices critically contribute to the biogenesis of functional replication organelles and thus, efficient viral RNA replication. These results reveal how glycine-zipper motifs in NS4B contribute to structural and functional integrity of the HCV replication organelles and thus, viral RNA replication.

**Authentic Patient-Derived Hepatitis C Virus Infects and Productively Replicates in Primary CD4+ and CD8+ T Lymphocytes In Vitro.** Skardasi G1, Chen AY1, Michalak TI2. J Virol. 2017 Nov 22. pii: JVI.01790-17. doi: 10.1128/JVI.01790-17. [Epub ahead of print] Accumulated evidence indicates that immune cells can support replication of hepatitis C virus (HCV) in infected patients and in culture. However, there is a scarcity of data on the degree to which individual immune cell types support HCV propagation and on characteristics of virus assembled. We investigated the ability of authentic, patient-derived HCV to infect in vitro two closely related but functionally distinct immune cell types, CD4+ and CD8+ T lymphocytes, and assessed properties of virus produced by these cells. The HCV replication system in intermittently mitogen-stimulated T cells was adapted to infect primary human CD4+ or CD8+ T lymphocytes. HCV replicated in both cell types, although at significantly higher levels in CD4+ than CD8+ T cells. Thus, HCV RNA replicative (negative) strand was detected in CD4+ and CD8+ cells at estimated mean levels of 6.7 x 10^2 ± SEM 3.8 x 10^2 and 1.2 x 10^2 ± SEM 0.8 x 10^2 copies/μg RNA, respectively (P<0.0001). Intracellular HCV NS5a and/or core proteins were identified in 0.9% of CD4+ and 1.2% of CD8+ T cells. Double staining for NS5a and T cell type-specific markers confirmed that transcriptionally competent virus replicated in both cell types. Further, an HCV-specific protease inhibitor, telaprevir, inhibited infection in both CD4+ and CD8+ cells. Emergence of unique HCV variants and release of HCV RNA-reactive particles with biophysical properties different from those of virions in plasma inocula suggested that distinct viral particles were assembled and, therefore, they may contribute to the pool of circulating virus in infected patients. **IMPORTANCE** Although the liver is the main site of HCV replication, infection of the immune system is an intrinsic characteristic of this virus independent of whether infection is symptomatic or clinically silent. Many fundamental aspects of HCV lymphotropism remain uncertain, including degree to which different immune cells support infection and contribute to virus diversity. We show that authentic, patient-derived HCV productively replicates in vitro in two closely related but functionally distinct types of T

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lymphocytes, CD4+ and CD8+ cells. The display of viral proteins and unique variants, production of virions with biophysical properties distinct from those in plasma serving as inocula, and inhibition of replication by an antiviral agent ascertained that both T cell subtypes supported virus propagation. Infection of CD4+ and CD8+ T cells, which are central to the adaptive antiviral immune responses, can directly affect HCV clearance, favor virus persistence and decisively influence development and progression of hepatitis C.


**AIM:** Management of low skeletal muscle mass (LSM) is a very important topic since LSM affects patient mortality in liver diseases. Changes in body composition are unexplored in chronic hepatitis C virus (HCV) patients, including those with liver cirrhosis, who receive direct-acting antiviral (DAA) therapy. Body composition measurements and liver function tests were performed before and after DAA therapy. **METHODS:** Blood examination, visceral fat area (VFA) and extremity skeletal muscle mass were measured using the multi-frequency bioelectrical impedance analysis method: i) at 24 weeks pre DAA therapy; ii) at the start of DAA therapy; iii) at the end of DAA therapy; iv) at 24 weeks post DAA therapy; and v) at 48 weeks post DAA therapy. **RESULTS:** Serum albumin (Alb) levels were significantly increased at 48 weeks post DAA therapy, especially in patients with LSM. Skeletal muscle mass index (SMI) was significantly increased after DAA therapy (at 24 weeks and 48 weeks post DAA therapy) in patients with LSM (p<0.05). An increase in SMI was associated with an increase in body weight or a decrease in VFA. **CONCLUSIONS:** We continuously measured body composition in HCV infected patients who received DAA therapy and found that skeletal muscle mass was significantly increased, associated with an elevation of serum Alb levels and/or body weight or reduction in VFA, but only in patients who presented with LSM before DAA therapy.


Host cells harbor various intrinsic mechanisms to restrict viral infections as a first line of antiviral defense. Viruses have evolved various countermeasures against these antiviral mechanisms. Here we show that N-Myc Downstream-Regulated Gene 1 (NDRG1) limits productive HCV infection by inhibiting viral assembly. Interestingly, HCV infection down-regulates NDRG1 protein and mRNA expression. Loss of NDRG1 increases the size and number of lipid droplets, which are the sites of HCV assembly. HCV suppresses NDRG1 expression by up-regulating MYC, which directly inhibits the transcription of NDRG1 Up-regulation of MYC also leads to reduced expression of NDRG1-specific kinase SGK1, resulting in markedly diminished phosphorylation of NDRG1. Knockdown of MYC during HCV infection rescues NDRG1 expression and phosphorylation, suggesting that MYC regulates NDRG1 at both transcriptional and post-translational levels. Overall, our results suggest that NDRG1 restricts HCV assembly by limiting lipid droplet formation. HCV counteracts this intrinsic antiviral mechanism by down-regulating NDRG1 via a MYC-dependent mechanism.**IMPORTANCE** Hepatitis C virus (HCV) is an enveloped single-stranded RNA virus that targets hepatocytes in the liver. HCV is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular
carcinoma and estimates suggest a global prevalence of 2.35%. Up to 80% of acutely infected individuals will develop chronic infection and as many as 5% eventually progress to liver cancer. Understanding of the mechanisms behind virus-host interaction and viral carcinogenesis is still lacking. The significance of our research is that it identifies a previously unknown relationship between HCV and a known tumor-associated gene. Further our data point to a new role for this gene in the liver and lipid metabolism. Thus HCV infection serves as a great biological model to advance our knowledge of liver functions and the development of liver cancer.

PMID: 29118118

HIV/HCV Coinfection

Food insecurity may lead to incomplete HIV viral suppression and less immune reconstitution among HIV/hepatitis C virus-coinfected people. Aibibula W1, Cox J1,2, Hamelin AM1, Moodie E1, Naimi AI3, McLinden T1, Klein MB1,2, Brassard P1,2,4. HIV Med. 2017 Nov 2. doi: 10.1111/hiv.12561. [Epub ahead of print]

OBJECTIVES: The aim of this study was to determine the impact of food insecurity (FI) on HIV viral load and CD4 count among people coinfected with HIV and hepatitis C virus (HCV).

METHODS: This study was conducted using data from the Food Security & HIV-HCV Sub-Study of the Canadian Co-Infection Cohort study. FI was measured using the adult scale of Health Canada's Household Food Security Survey Module and was classified into three categories: food security, moderate food insecurity and severe food insecurity. The association between FI, HIV viral load, and CD4 count was assessed using a stabilized inverse probability weighted marginal structural model. RESULTS: A total of 725 HIV/HCV-coinfected people with 1973 person-visits over 3 years of follow-up contributed to this study. At baseline, 23% of participants experienced moderate food insecurity and 34% experienced severe food insecurity. The proportion of people with undetectable HIV viral load was 75% and the median CD4 count was 460 [interquartile range (IQR): 300-665] cells/μL. People experiencing severe food insecurity had 1.47 times [95% confidence interval (CI): 1.14, 1.88] the risk of having detectable HIV viral load and a 0.91-fold (95% CI: 0.84, 0.98) increase in CD4 count compared with people who were food secure.

CONCLUSIONS: These findings provide evidence of the negative impact of food insecurity on HIV viral load and CD4 count among HIV/HCV-coinfected people.


BACKGROUND: Direct acting antivirals (DAAs) have revolutionized hepatitis C (HCV) treatment with >90% cure rates even in real-world studies, giving hope that HCV can be eliminated. However, for DAAs to have a population-level impact on the burden of HCV disease, treatment uptake needs to be expanded. We investigated temporal trends in HCV treatment uptake and evaluated factors associated with second-generation DAA initiation and efficacy among key HIV-HCV co-infected populations in Canada.

METHODS: The Canadian HIV-HCV Co-Infection Cohort Study prospectively follows 1699 participants from 18 centres. Among HCV RNA+ participants, we determined the incidence of HCV treatment initiation per year overall and by key populations between 2007 and 2015. Key populations were based on World Health Organization (WHO) guidelines including: people who actively inject drugs (PWID) (reporting injection drug use, last 6 months); Indigenous people; women and men who
have sex with men (MSM). Multivariate Cox models were used to estimate adjusted hazard ratios (aHR) and 2-year probability of initiating second-generation DAAs for each of the key populations. **RESULTS:** Overall, HCV treatment initiation rates increased from 8 (95% CI, 6-11) /100 person-years in 2013 to 28 (95% CI, 23-33) /100 person-years in 2015. Among 911 HCV RNA + participants, there were 202 second-generation DAA initiations (93% with interferon-free regimens). After adjustment (aHR, 95% CI), active PWID (0.60, 0.38-0.94 compared to people not injecting drugs) and more generally, people with lower income (<$18 000 CAD/year) (0.50, 0.35, 0.71) were less likely to initiate treatment. Conversely, MSM were more likely to initiate 1.95 (1.33, 2.86) compared to heterosexual men. In our cohort, the population profile with the lowest 2-year probability of initiating DAAs was Indigenous, women who inject drugs (5%, 95% CI 3-8%). Not having any of these risk factors resulted in a 35% (95% CI 32-38%) probability of initiating DAA treatment. Sustained virologic response (SVR) rates were >82% in all key populations. **CONCLUSION:** While treatment uptake has increased with the availability of second-generation DAAs, marginalized populations, already engaged in care, are still failing to access treatment. Targeted strategies to address barriers are needed to avoid further health inequities and to maximize the public health impact of DAAs.


The incidence of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection has been increasing with over 10 million people affected globally. The role biomarkers play as predictors of cardiovascular disease (CVD) risk among coinfected individuals is not well defined. We aimed to systematically review current evidence describing CVD biomarkers among individuals with HIV/HCV coinfection. We searched EMBASE, CINAHL, Google Scholar, PubMed, and Web of Science from inception to June 2017. MeSH terms and keywords were used to identify studies with information on HIV/HCV coinfection and CVD biomarkers (structural, functional, and serological) such as carotid intima-media thickness (CIMT), endothelial markers, C-reactive protein (CRP), homocysteine, and lipids. Among 332 articles screened, 28 were included (39,498 participants). Study designs varied: 18 cross-sectional, 9 cohort, and 1 clinical trial. Compared with healthy controls and people with HIV or HCV monoinfection, individuals with HIV/HCV coinfection had statistically significant lower levels of lipids and CRP and higher levels of endothelial markers (sICAM-1 and sVCAM-1), CIMT, homocysteine, and IL-6. One study found the odds of carotid plaque in coinfected individuals was 1.64 (0.91-2.94) compared with healthy controls, and another study showed the prevalence of vascular plaques (carotid and femoral) in coinfected individuals was higher compared with HIV monoinfected individuals (44% vs 14%, P = 0.04). Biomarkers of CVD have different patterns of association with HIV/HCV coinfection compared with monoinfection and healthy controls. Prospective studies are needed to confirm the predictive value of these biomarkers for clinical CVD risk among coinfected individuals. PMID: 29135056

OBJECTIVE: To examine factors associated with hepatitis C virus (HCV) infection among a national sample of Indigenous and non-Indigenous people who inject drugs (PWID) in Australia.

METHODS: Respondents were recruited from Australia's Needle Syringe Program Survey; an annual bio-behavioural surveillance project that monitors HCV antibody prevalence among PWID. Data from 2006-2015 were de-duplicated to retain only one record where individuals participated in >1 survey round. Univariate and multivariable logistic regression examined demographic characteristics and injection-related behaviours associated with exposure to HCV.

RESULTS: Among 17,413 respondents, 2,215 (13%) were Indigenous Australians. Compared to their non-Indigenous counterparts, Indigenous respondents were significantly more likely to be exposed to HCV infection (53% vs. 60% respectively, p<0.001). Among Indigenous respondents, HCV antibody positivity was independently associated with a history of imprisonment (Adjusted Odd Ratio [AOR] 2.13, 95%CI 1.73-2.64), opioid injection (AOR 1.53, 95%CI 1.14-2.16), recruitment in a metropolitan location (AOR 1.27, 95%CI 1.02-1.59), engagement in opioid substitution therapy (AOR 2.83, 95%CI 2.23-3.59) and length of time since first injection (p<0.001).

CONCLUSION: Indigenous PWID are more likely to be exposed to HCV infection than their non-Indigenous counterparts. Implications for public health: Increased access to culturally sensitive harm reduction programs is required to prevent primary HCV infection and reinfection among Indigenous PWID. Given recent advances in HCV treatment, promotion of treatment uptake among Indigenous PWID may reduce future HCV-related morbidity and mortality.


AIM: To assess the real-world effectiveness and cost of simeprevir (SMV), and/or sofosbuvir (SOF)-based therapy for chronic hepatitis C virus (HCV) infection. METHODS: The real-world performance of patients treated with SMV/SOF ± ribavirin (RBV), SOF/RBV, and SOF/RBV with pegylated-interferon (PEG) were analyzed in a consecutive series of 508 patients with chronic HCV infection treated at a single academic medical center. Patients with genotypes 1 through 4 were included. Rates of sustained virological response - the absence of a detectable serum HCV RNA 12 wk after the end of treatment [sustained virological response (SVR) 12] - were calculated on an intention-to-treat basis. Costs were calculated from the payer's perspective using Medicare/Medicaid fees and Redbook Wholesale Acquisition Costs. Patient-related factors associated with SVR12 were identified using multivariable logistic regression. RESULTS: SVR12 rates were as follows: 86% (95%CI: 80%-91%) among 178 patients on SMV/SOF ± RBV; 62% (95%CI: 55%-68%) among 234 patients on SOF/RBV; and 78% (95%CI: 68%-86%) among 96 patients on SOF/PEG/RBV. Mean costs-per-SVR12 were $174442 (standard deviation: ± $18588) for SMV/SOF ± RBV; $223003 (± $77946) for SOF/RBV; and $126496 (±
Among patients on SMV/SOF ± RBV, SVR12 was less likely in patients previously treated with a protease inhibitor [odds ratio (OR): 0.20, 95%CI: 0.06-0.56]. Higher bilirubin (OR: 0.47, 95%CI: 0.30-0.69) reduced the likelihood of SVR12 among patients on SOF/RBV, while FIB-4 score ≥ 3.25 reduced the likelihood of SVR12 (OR: 0.18, 95%CI: 0.05-0.59) among those on SOF/PEG/RBV. **CONCLUSION:** SVR12 rates for SMV and/or SOF-based regimens in a diverse real-world population are comparable to those in clinical trials. Treatment failure accounts for 27% of costs.

**A Risk Score to Predict the Development of Hepatic Encephalopathy in a Population-Based Cohort of Patients with Cirrhosis.** Tapper EB1,2, Parikh N1,2, Sengupta N3, Mellinger J1, Ratz D4, Lok AS1, Su GL1,2. Hepatology. 2017 Nov 1. doi: 10.1002/hep.29628. [Epub ahead of print]

Over 40% of patients with cirrhosis will develop hepatic encephalopathy (HE). HE is associated with decreased survival, falls, motor vehicle accidents, and frequent hospitalization. Accordingly, we aimed to develop a tool to risk-stratify patients for HE development. We studied a population-based cohort of all patients with cirrhosis without baseline HE (N=1,979) from the Veterans Administration from Michigan, Indiana, and Ohio (1/1/2005-12/31/10) using demographic, clinical, laboratory, and pharmacy data. The primary outcome was the development of HE. Risk-scores were constructed with both baseline and longitudinal data (annually updated parameters) and validated using bootstrapping. The cohort had mean age of 58.0±8.3 years, 36% had hepatitis C, 17% had ascites. Opiates, benzodiazepines, statins, and nonselective beta-blockers were taken at baseline by 24%, 13%, 17%, and 12%. Overall, 863(43.7%) developed HE within 5 years. In multivariable models, risk factors (HR, 95%CI) for HE included higher bilirubin (1.07, 1.05-1.09) and nonselective beta-blocker use (1.34, 1.09-1.64), while higher albumin (0.54, 0.48-0.59) and statin use (0.80, 0.65-0.98) were protective. Other clinical factors, including opiate and benzodiazepine use were not predictive. The AUROC for HE using the 4 significant variables in baseline and longitudinal models were 0.68 (0.66-0.70) and 0.73 (0.71-0.75), respectively. Model effects were validated and converted into a risk score. A score ≤0 in our longitudinal model assigns a 6% 1-year probability of HE while a score >20 assigns a 38% 1-year risk. **CONCLUSION:** Patients with cirrhosis can be stratified by a simple risk-score for HE that accounts for changing clinical data. Our data also highlight a role for statins in reducing cirrhosis complications including HE. This article is protected by copyright. All rights reserved.


Approximately three quarters of acute hepatitis C (HCV) infections evolve to a chronic state, while one quarter are spontaneously cleared. Genetic predispositions strongly contribute to the development of chronicity. We have conducted a genome-wide association study to identify genomic variants underlying HCV spontaneous clearance using ImmunoChip in European and African ancestries. We confirmed two previously reported significant associations, in the IL28B/IFNL4 and the major histocompatibility complex (MHC) regions, with spontaneous clearance in the European population. We further fine-mapped the association in the MHC to a region of about 50 kilo base pairs, down from 1 mega base pairs in the previous study.
Additional analyses suggested that the association in MHC is stronger in samples from North America than those from Europe.

**Economic evaluation of HCV testing approaches in low and middle income countries.**

**BACKGROUND:** Hepatitis C virus (HCV) infection represents a major public health burden with diverse epidemics worldwide, but at present, only a minority of infected persons have been tested and are aware of their diagnosis. The advent of highly effective direct acting antiviral (DAA) therapy, which is becoming available at increasingly lower costs in low and middle income countries (LMICs), represents a major opportunity to expand access to testing and treatment. However, there is uncertainty as to the optimal testing approaches and who to prioritize for testing. We undertook a narrative review of the cost-effectiveness literature on different testing approaches for chronic hepatitis C infection to inform decision-making and formulation of recommendations in the 2017 World Health Organization (WHO) viral hepatitis testing guidelines.

**METHODS:** We undertook a focused search and narrative review of the literature for cost effectiveness studies of testing approaches in three main groups:- 1) focused testing of specific high-risk groups (defined as those who are part of a population with higher seroprevalence or who have a history of exposure or high-risk behaviours); 2) "birth cohort" testing among easily identified age groups (i.e. specific birth cohorts) known to have a high prevalence of HCV infection; and 3) routine testing in the general population. Articles included were those published in PubMed, written in English and published after 2000.

**RESULTS:** We identified 26 eligible studies. Twenty-four of them were from Europe (n = 14) or the United States (n = 10). There was only one study from a LMIC (Egypt) and this evaluated general population testing. Thirteen studies evaluated focused testing among specific groups at high risk for HCV infection, including nine in persons who inject drugs (PWID); five among people in prison, and one among HIV-infected men who have sex with men (MSM). Eight studies evaluated birth cohort testing, and five evaluated testing in the general population. Most studies were based on a one-time testing intervention, but in one study testing was undertaken every 5 years and in another among HIV-infected MSM there was more frequent testing. Comparators were generally either: 1) no testing, 2) the status quo, or 3) multiple different strategies. Overall, we found broad agreement that focused testing of high risk groups such as persons who inject drugs and men who have sex with men was cost-effective, as was birth cohort testing. Key drivers of cost-effectiveness were the prevalence of HCV infection in these groups, efficacy and cost of treatment, stage of disease and linkage to care. The evidence for routine population testing was mixed, and the cost-effectiveness depends largely on the prevalence of HCV.

**CONCLUSIONS:** The evidence base for different HCV testing approaches in LMICs is limited, minimizing the contribution of cost-effectiveness data alone to decision-making and recommendations on testing approaches in the 2017 WHO viral hepatitis testing guidelines. Overall, the guidelines recommended focused testing in high risk-groups, particularly PWID, prisoners, and men who have sex with men; with consideration of two other approaches:- birth cohort testing in those countries with epidemiological evidence of a significant birth cohort effect; and routine access to testing across the general population in those countries with a high HCV seroprevalence above 2% - 5% in the general population. Further implementation research on different testing approaches is needed in order to help guide national policy planning.

**OBJECTIVES:** Sexually transmitted and blood-borne infections (STBBIs) are associated with stigmatizing attitudes and beliefs, which can affect the quality of and access to health care, as well as mental health and quality of life. The current study describes the adaptation from an HIV-related stigma scale and pilot testing of a new STBBI Stigma Scale, assessing the stigmatizing attitudes and beliefs of health and social service providers in Canada. **METHODS:** 144 health and social service providers from across Canada completed the newly adapted scale assessing stigma associated with HIV, hepatitis C, other viral STBBIs and bacterial STBBIs, as well as demographic information, a scale of social desirability and measures of convergent and divergent validity. Participants were recruited through listervs and completed the scale online. **RESULTS:** The new scale, consisting of 21 items for each category, demonstrated excellent internal consistency, reliability, and convergent and divergent validity. The factor structure of the scale supports a tripartite model of stigma consisting of stereotyping, prejudice and discrimination. Stereotyping had the highest relative scores on the subscales, and attitudes regarding other viral STBBIs differed significantly from the other STBBI categories. **CONCLUSION:** The new scale provides a contextually relevant and applicable psychometrically valid tool to assess STBBI-related stigma among health and social service providers in Canada. The tool can be used to assess attitudes and beliefs, as well as guide self-assessment and possible trainings for providers.


**BACKGROUND:** The current low access to virological testing to confirm chronic viraemic HCV infection in low- and middle-income countries (LMIC) is limiting the rollout of hepatitis C (HCV) care. Existing tests are complex, costly and require sophisticated laboratory infrastructure. Diagnostic manufacturers need guidance on the optimal characteristics a virological test needs to have to ensure the greatest impact on HCV diagnosis and treatment in LMIC. Our objective was to develop a target product profile (TPP) for diagnosis of HCV viraemia using a global stakeholder consensus-based approach. **METHODS:** Based on the standardised process established to develop consensus-based TPPs, we followed five key steps. (i) Identifying key potential global stakeholders for consultation and input into the TPP development process. (ii) Informal priority-setting exercise with key experts to identify the needs that should be the highest priority for the TPP development; (iii) Defining the key TPP domains (scope, performance and operational characteristics and price). (iv) Delphi-like process with larger group of key stakeholder to facilitate feedback on the key TPP criteria and consensus building based on pre-defined consensus criteria. (v) A final consensus-gathering meeting for discussions around disputed criteria. A complementary values and preferences survey helped to assess trade-offs between different key characteristics. **RESULTS:** The following key attributes for the TPP for a test to confirm HCV viraemic infection were identified: The scope defined is for both HCV detection as well as confirmation of cure. The timeline of development for tests envisioned in the TPP is 5 years. The test should be developed for use by health-care workers or laboratory technicians with limited training in countries with a medium to high prevalence of HCV (1.5-3.5% and >3.5%) and in high-risk populations in low prevalence settings (<1.5%).
clinical sensitivity at a minimum of 90% is considered sufficient (analytical sensitivity of the equivalent of 3000 IU/ml), particularly if the test increases access to testing through an affordable price, increase ease-of-use and feasibility on capillary blood. Polyvalency would be optimal (i.e. ability to test for HIV and others). The only characteristic that full agreement could not be achieved on was the price for a virological test. Discussants felt that to reach the optimal target price substantial trade-offs had to be made (e.g. in regards to sensitivity and integration).

**CONCLUSION:** The TPP and V&P survey results define the need for an easy-to-use, low cost test to increase access to diagnosis and linkage to care in LMIC.

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**Hepatocellular (Liver) Cancer**

**Levels of Cytokines in Serum Associate With Development of Hepatocellular Carcinoma in Patients With HCV Infection Treated With Direct-acting Antivirals.**

Concern has arisen about development of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) infection treated with direct-acting antivirals (DAAs). To identify patients at risk for HCC, we evaluated serum levels of immune mediators before, during, and after DAA treatment of HCV infection. Our study included 13 patients who developed HCC within 18 months after treatment (3 with HCC recurrence and 10 with new HCC) and 10 patients who did not develop HCC (controls), within at least 24 months of treatment (median, 26 months). We identified a set of 12 immune mediators (cytokines, growth factors, and apoptosis markers) whose levels were significantly higher in serum before DAA treatment of patients who eventually developed de novo HCC compared to controls. A panel of 9 cytokines, measured in serum before treatment (MIG, IL22, TRAIL, APRIL, VEGF, IL3, TWEAK, SCF, IL21), identified patients who developed de novo HCC with an area under the receiver operating characteristic curve value higher than 0.8. Further analyses of changes in levels of inflammatory cytokines during DAA treatment also provides important information about HCV-induced carcinogenesis and the effects of DAAs.


**BACKGROUND:** Hepatitis C (HCV) infection is an increasingly common cause of hepatocellular carcinoma (HCC) in China. **AIMS:** We aimed to determine differences in demographic and behavioral profiles associated with HCC in HCV+ patients in China and the USA. **METHODS:** Consecutive HCV+ patients were recruited from centers in China and the USA. Clinical data and lifestyle profiles were obtained through standardized questionnaires. Multivariable analysis was conducted to determine factors associated with HCC diagnosis within groups. **RESULTS:** We included 41 HCC patients from China and 71 from the USA, and 931 non-HCC patients in China and 859 in China. Chinese patients with HCC were significantly younger, less likely to be male and to be obese than US patients with HCC (all p < 0.001). Chinese patients with HCC had a significantly lower rate of cirrhosis diagnosis (36.6 vs. 78.9%,
p < 0.001); however, they also had a higher rate of hepatitis B core antibody positivity (63.4 vs. 36.8%, p = 0.007). In a multivariable analysis of the entire Chinese cohort, age > 55, male sex, the presence of diabetes, and time from maximum weight were associated with HCC, while tea consumption was associated with a decreased HCC risk (OR 0.37, 95% CI 0.16-0.88). In the US cohort, age > 55, male sex, and cirrhosis were associated with HCC on multivariable analysis.

**CONCLUSIONS:** With the aging Chinese population and increasing rates of diabetes, there will likely be continued increase in the incidence of HCV-related HCC in China. The protective effect of tea consumption on HCC development deserves further validation.


**BACKGROUND:** Prognosis in patients with hepatocellular carcinoma (HCC) is not only influenced by tumor-related factors but also by the background liver functions. The maximal removal rate of technetium-99m-galactosyl human serum albumin (GSA-Rmax) of the remnant liver (rGSA-Rmax) is a useful candidate for predicting the liver function and clarifying the relationship between the remnant liver functional reserve and tumor-free survival in patients who have undergone hepatectomy. **PATIENTS AND METHODS:** One hundred and sixty-five patients with HCC who underwent curative hepatectomy were divided into three groups of hepatitis B virus (B-HCC; n=42), hepatitis C virus (C-HCC, n=58), and non-B, non-C (NBNC-HCC, n=65). The relationship between rGSA-Rmax and survival was examined by univariate and multivariate analyses. **RESULTS:** In the C-HCC group, the albumin, or LHL15, level was significantly lower, and alanine aminotransferase, ICGR15, and the prevalence of grade B liver damage were significantly higher than other two groups (P<0.05). GSA-Rmax or rGSA-Rmax was not different between the three groups. Lower GSA-Rmax and rGSA-Rmax were only significantly associated with lower tumor-free survival in the C-HCC group by the univariate analysis (P<0.05) but not significantly by the multivariate analysis. **CONCLUSION:** GSA-Rmax and rGSA-Rmax reflect the severity of liver dysfunction and furthermore, the lower rGSA-Rmax is useful as a complementary factor to predict the early HCC recurrence after hepatectomy.

**Proton pump inhibitors are associated with accelerated development of cirrhosis, hepatic decompensation and hepatocellular carcinoma in noncirrhotic patients with chronic hepatitis C infection: results from ERCHIVES,** Li DK1, Yan P2, Abou-Samra AB3, Chung RT1,4, Butt AA2,3,5,6. Aliment Pharmacol Ther. 2017 Nov 3. doi: 10.1111/apt.14391. [Epub ahead of print]

**BACKGROUND:** Proton pump inhibitors are among the most commonly prescribed medications in the United States. Their safety in cirrhosis has recently been questioned, but their overall effect on disease progression in noncirrhotic patients with chronic liver disease remains unclear. **AIM:** To determine the impact of proton pump inhibitors on the progression of liver disease in noncirrhotic patients with hepatitis C virus (HCV) infection. **METHODS:** Using the electronically retrieved cohort of HCV-infected veterans (ERCHIVES) database, we identified all subjects who received HCV treatment and all incident cases of cirrhosis, hepatic decompensation and hepatocellular carcinoma. Proton pump inhibitor use was measured using...
cumulative defined daily dose. Multivariate Cox regression analysis was performed after adjusting univariate predictors of cirrhosis and various indications for proton pump inhibitor use. **RESULTS:** Among 11,526 eligible individuals, we found that exposure to proton pump inhibitors was independently associated with an increased risk of developing cirrhosis (hazard ratio [HR]: 1.32; 95% confidence interval: [1.17, 1.49]). This association remained robust to sensitivity analysis in which only patients who achieved sustained virologic response were analysed as well as analysis excluding those with alcohol abuse/dependence. Proton pump inhibitor exposure was also independently associated with an increased risk of hepatic decompensation (HR: 3.79 [2.58, 5.57]) and hepatocellular carcinoma (HR: 2.01 [1.50, 2.70]). **CONCLUSIONS:** In patients with chronic HCV infection, increasing proton pump inhibitor use is associated with a dose-dependent risk of progression of chronic liver disease to cirrhosis, as well as an increased risk of hepatic decompensation and hepatocellular carcinoma.


**BACKGROUND AND AIMS:** Diabetes mellitus (DM) has been found to be strongly associated with an increased risk of hepatocellular carcinoma (HCC) among chronic hepatitis C (CHC) patients. Several studies have also found an association between metabolic steatosis and the risk of HCC in CHC patients, whether this latter association has been accounted for by the known relationship between DM and HCC is still unknown. **METHODS:** A cohort consisting of 976 non-genotype 3 patients histologically proven to have CHC and treated with interferon and ribavirin was studied. Cumulative incidence and HCC risk were analyzed using the Kaplan-Meier method and Cox proportional hazard analysis. **RESULTS:** HCC developed in 140 subjects over a median follow-up period of 97.3 months, while 699 patients achieved sustained virological response (SVR). According to multivariate analyses, age ≥ 60 years, advanced fibrosis, and genotype 1 were identified as independent factors significantly associated with HCC development in SVR patients. Furthermore, using the absence of steatosis and absence of DM as references, the presence of steatosis without DM (HR=2.09, 95% CI=1.12-3.9, P=0.021), the presence of DM without steatosis (HR=2.78, 95% CI=1.3-5.92, P=0.008), and the combined presence of steatosis and DM (HR=3.25, 95% CI=1.44-7.33, P = 0.004) were identified as independent factors significantly associated with HCC development in the SVR patients. In contrast, steatosis alone, DM alone, and the combined presence of steatosis and DM were not associated with HCC development in non-SVR patients. **CONCLUSIONS:** Steatosis and DM may be associated with HCC development in non-genotype 3 CHC patients with SVR.