ORAL ABSTRACTS

7TH CANADIAN SYMPOSIUM ON HCV – FRIDAY, FEBRUARY 9, 2018

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Nationwide estimates and risk factors of readmission in patients with cirrhosis in the United States
The impact of nursing volume on in-hospital mortality among patients with cirrhosis: A population-based study
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Characterization of exosomal microRNA content during HCV infection

Christopher Ablenas, University of Ottawa; John Pezacki, University of Ottawa; Curtis Cooper, University of Ottawa

BACKGROUND: Hepatitis C virus (HCV) treatments with high cure rates have reduced but not eliminated the elevated risk in HCV infected patients for developing hepatocellular carcinoma (HCC) (1). In the coming years, HCV-related HCC in the aging population is projected to increase (2). Despite progress in our understanding of viral pathogenesis, the mechanisms of viral-induced HCC remain elusive.

MicroRNAs (miRNAs) are important modulators of physiological processes. Dysregulation of miRNA expression has been documented in both HCV infection and many types of cancer, including HCC. An emerging area of miRNA study is in the context of exosomes.

Exosomes are membrane-enclosed vesicles that are actively packaged with RNAs, proteins, and lipids within cells, and released into the extracellular space. Exosomes participate in cell-to-cell communication, provide an indication of the physiological/pathological state of their cells of origin, and can play important roles in disease progression.

PURPOSE: To identify miRNAs that are differentially packaged into exosomes during HCV infection that may play a role in the development of HCC.

METHODS: Exosomes from cell culture supernatants of HCV JFH1 infected cells were isolated by differential ultracentrifugation and the miRNA content was profiled using Nanostring Technologies nCounter analysis system. The exosomal miRNA profile was compared to that of uninfected cells to identify exosomal miRNAs that are dysregulated during HCV infection. Computational target prediction algorithms were then used to identify putative mRNA targets for the altered miRNAs.

RESULTS: The miRNAs differentially packaged into exosomes in cell culture during HCV infection will be discussed, along with their putative mRNA targets and preliminary target validation.

CONCLUSIONS: This study provides a better understanding of the role of exosomal miRNAs in cell-to-cell signaling during HCV infection, and serves as a basis to screen for altered exosomal miRNAs in HCV-infected patient sera before and after treatment. This will provide a better understanding of the biological mechanism through which patients develop HCC.

REFERENCES

Investigating how miR-122 alters the secondary structure of the HCV genome

Jasmin Chahal, McGill University; Selena Sagan, McGill University

BACKGROUND: Hepatitis C virus (HCV) is a positive-sense single-stranded RNA virus and thus, its genomic RNA itself must act as a template for viral translation, replication, and packaging. To accommodate this, the 5’ and 3’ non-coding regions (NCRs) contain cis-acting RNA elements (CREs) that play key roles in the viral life cycle. These CREs are involved in interactions with RNA and proteins, one of which is with the liver-specific microRNA, miR-122. miR-122 binds to two sites on the 5’NCR and promotes HCV RNA accumulation, although the precise role of miR-122 in the HCV life cycle is unclear. Recent studies suggest that miR-122 may modulate the structure of the 5’ NCR and/or the viral internal ribosomal entry site (IRES).

PURPOSE: We are investigating how miR-122 binding alters the structure of the HCV genome.

METHODS: We have performed Selective 2’ Hydroxyl Acylation analyzed by Primer Extension (SHAPE) to analyze the structure of the HCV 5’ NCR in the presence and absence of miR-122 in vitro and in vivo, using the in vivo SHAPE reagent, methylnicotinic acid imidazolide azide (NAI-N3). SHAPE analysis was performed by both gel and
capillary electrophoresis and data was analyzed using SAFA or QuSHAPE, respectively. The secondary structural alterations of the two miR-122 bindings site on HCV RNA (the first 42 nts of the 5’ end) were analyzed using gel electrophoresis while SHAPE analysis of the entire HCV RNA 5’NCR was done by capillary electrophoresis. In addition, to further understand these interactions we are using Electrophoretic Mobility Shift Assays (EMSA) and isothermal titration calorimetry (ITC) to measure dissociation constants of miR-122 binding at site 1, site 2 or both sites.

RESULTS: Not surprisingly, our in vitro SHAPE results of the 5’ terminus (nts 1–42) of the HCV RNA +/- miR-122 suggest that in the single-stranded RNA stretch and SLI of the HCV genome become more constrained upon miR-122 binding. We are currently analyzing the entire 5’NCR (nts 1-370) of HCV RNA +/- miR-122 to determine whether miR-122 induces changes in the secondary structure in the IRES region. Our preliminary analysis suggests that nts at stem-loop IIIa and IV of the IRES are more constrained when miR-122 is bound.

CONCLUSIONS: We observed that miR-122 binding alters the secondary structure of the HCV 5’NCR. In addition to the miR-122 sites, regions in the IRES become more constrained when miR-122 is bound, suggesting that there may be cross-talk between miR-122 and the HCV IRES. We anticipate that these studies will uncover how miR-122 alters the structure of the HCV genome and will help to clarify the role of miR-122 in HCV RNA accumulation. We hope to identify new modes of RNA regulation and may uncover novel RNA-based targets for antiviral intervention.

Removal of an immune masking domain, hypervariable region 1 (HVR1) of HCV glycoprotein e2, does not enhance the immunogenicity of a glycoprotein-based HCV vaccine

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Current evidence points to a protective role for virus neutralizing antibodies and virus-specific cellular immune responses in immunity against HCV infection. Many cross-neutralizing monoclonal antibodies have been identified. These antibodies have been shown to protect or clear infection in animal models. We are developing a recombinant envelope glycoprotein vaccine containing the gpE1/gpE2 heterodimer along with a T cell antigen to broaden HCV-specific cellular immune responses. Previous clinical trials have shown a gpE1/gpE2 vaccine can induce antibodies that neutralize the in vitro infectivity of all the major HCVcc genotypes around the world. However, cross-neutralization appeared to favour certain genotypes with significant but lower neutralization against others. HCV may employ epitope masking to avoid immunoglobulin-mediated control. The HVR1 at the amino-terminus of glycoprotein E2 blocks access to many neutralizing antibodies. Consistent with this, other groups have reported that recombinant viruses lacking the HVR1 are hypersensitive to neutralization. It has been proposed that E1E2 lacking this domain could be a better vaccine antigen to induce broadly neutralizing antibodies. In this study, we examined the immunogenicity of recombinant E1E2 lacking the HVR1 (DHVR1). We found that WT and DHVR1 E1E2 can induce HCV specific antibodies equally well and both antigens induced antibodies targeting many well-characterized cross-genotype neutralizing epitopes. However, while antisera from DHVR1 immunized mice can effectively neutralize HCVpp lacking the HVR1, this antisera showed a reduction in neutralization activity against WT HCVpp. This data suggests DHVR1 E1E2 is not a superior vaccine antigen. Based on chimpanzee protection data reported previously using wt gpE1/gpE2 and our current findings, we are preparing a combination vaccine including a wild type recombinant gpE1/gpE2 for clinical testing in the near future.
The use of oncolytic measles-based vectors for targeted treatment of HCV-induced liver cancer

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BACKGROUND: While novel antiviral agents offer potential cure for hepatitis C, options for the treatment of hepatocellular carcinoma (HCC) resulting from HCV infection remain limited. Current approaches include surgical resection, radiofrequency ablation, embolization, liver transplantation, and chemotherapy, etc.; however, these therapies are ineffective in advanced HCC stage, and situations such as contraindications, lack of donor livers, risk of recurrence, and the varied responses lead to the poor prognosis of such disease. These issues highlight the importance of developing novel therapies for the treatment of HCV-induced HCC. Recently, the tumor marker nectin-4, which is found on many adenocarcinomas including HCC, was identified as one of the receptors for measles virus (MV). This discovery highlighted the potential of using oncolytic MV-based vectors for treating liver cancers, including the context of HCV-induced HCC.

PURPOSE: To explore the use of MV-based oncolytic viruses to target the tumor marker nectin-4 on HCV-induced HCC.

METHOD: We first examine the level of nectin-4 expression in clinical HCC specimens from the Oncomine online microarray/gene expression database (https://www.oncomine.org). Commercially available HCC cell lines are evaluated for nectin-4 expression in vitro. The targeting and oncolytic abilities of a recombinant wild type (wt) MV (strain IC323) are validated in the HCC cell lines and their derivatives containing HCV subgenomic RNA. The role of HCV NS3/4A protease and cell innate immunity in the scenario of oncolytic virus treatment will also be examined. We will subsequently determine the effect of MV-based vectors on tumor growth in HCC mouse tumor models.

RESULTS: Oncomine online dataset analysis reveals that nectin-4 is overexpressed in clinical HCC specimens, including those with HCV infection, compared to normal liver tissue. Preliminary results indicate that HCC cell lines including Huh-7, HepG2, and Hep3B, express nectin-4 and are susceptible to oncolytic MV infection. Additionally, Huh-7 cells harboring replicating HCV subgenomes (GT1b and GT2a) exhibit better MV infectivity and spread compared to the HCV-negative parental cells.

CONCLUSION: We have shown that nectin-4 is overexpressed in clinical HCC specimens, and that HCC cell lines expressing nectin-4 can be targeted by MV-based oncolytic vector. More importantly, enhanced MV infectivity and spread in the hepatoma cell lines with replicating HCV subgenomes suggest that suppressed cell innate immunity may have influenced the infectivity of oncolytic vector. We expect that oncolytic virus treatment will retard tumor growth, and a functional immune system should further enhance remission in these liver cancer models.

Exploring immunological restoration with second generation DAA in HCV-infected individuals

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BACKGROUND: HCV establishes a chronic infection causing liver fibrosis, cirrhosis and hepatocellular carcinoma. Liver macrophages (MF) originating in part from blood monocytes are involved in promoting HCV immunity but also cause tissue damage by their ability to create a pro-inflammatory environment. Although the ability of blood monocytes and liver MF to support productive HCV replication is still on debate, it is well established that their activation can be mediated by HCV RNA
and viral proteins, via specific Toll-like receptors engagement. Of note, HCV infection is associated with alterations in monocytes homeostasis, with higher frequency of pro-inflammatory CD16+ monocytes that may differentiate into pathogenic MF. Second generation direct-action antiviral therapy (DAA) is effective in clearing HCV infection; however, whether DAA reverses liver inflammation through the restoration of monocyte homeostasis remains unknown.

**PURPOSE:** This study aims to analyze changes in frequency and activation phenotype of blood monocyte subsets in chronically HCV-infected individuals undergoing DAA treatment.

**METHODS:** Individuals were enrolled in the Reference Center for Hepatitis Treatment (Brazil). Blood samples were collected before (T0) and 12 weeks after the end of therapy, corresponding to sustained virological response (SVR). Blood from uninfected individuals was used as controls. Peripheral blood mononuclear cells were isolated using Ficoll gradient centrifugation. Monocyte phenotype was analysed by flow cytometry upon staining with CD14, CD16, HLA-DR, and CCR2 Abs. Inflammatory molecules were quantified in serum by Luminex® Multiplex Assay.

**RESULTS:** Ninety participants were followed until SVR time. At baseline, this group exhibited a mean age of 59.6±9.3 years, 74.4% presented cirrhosis, and genotype 1 was found in 82.2%. Of note, 60% participants were treatment-experienced. The blood monocytes phenotypic analysis was performed on 20/90 HCV+ and 10 controls. The total monocytes frequency identified as CD14+HLA-DR+ cells, as well as the CD16- monocytes frequency, were significantly reduced in HCV+ individuals at T0 compared to controls, with no significant difference in CD16+ monocytes. DAA therapy resulted in a significant increase in total monocytes as well as CD16- monocytes frequencies that reached values similar to the controls. Regarding CCR2 expression on CD16+/CD16- monocyte subsets, no significant changes were observed between HCV+ and control groups and neither within HCV+ at T0 and SVR. The quantification of inflammatory molecules of 36 HCV+ individuals demonstrated a significant decrease in IP-10, CCL3, CCL4, IL-1β, IL-15, IFN-γ and TGF-β levels and a significant increase in IL-1ra levels at SVR time compared to T0.

**CONCLUSIONS:** These results demonstrate that DAA therapy was successful in mediating SVR in HCV+ individuals included in the study. They also reveal the capacity of DAA to promote the normalisation of CD16- monocyte frequency as well as the plasmatic inflammatory milieu. Future studies should address the capacity of DAA to restore liver function.

**Identification of host and viral proteins at the 5’ terminus of the HCV genome by BioID**

Alexander Southward, McGill University

**BACKGROUND:** Hepatitis C virus (HCV) is a positive-sense, single-stranded RNA virus belonging to the Flaviviridae family. The HCV genome consists of a single ORF that is flanked by highly structured 5’ and 3’ untranslated regions (UTRs). The 5’ UTR promotes several important protein and RNA interactions essential for protein synthesis and viral RNA replication. Among these interactions, the highly-abundant, liver-specific microRNA-122 (miR-122), interacts with two sites within the 5’ UTR. This interaction promotes viral RNA accumulation; however, the precise mechanism(s) of miR-122-mediated viral RNA accumulation remain unclear.

**PURPOSE:** The purpose of this study is to uncover novel proteins interacting with the 5’ UTR of the HCV genome. We hypothesize that host and/or viral proteins localize to the 5’ terminus of the HCV genome and play a role in HCV RNA replication, genome circularization, or in complex with miR-122.

**METHODS:** We aim to identify host and viral factors interacting with the 5’ terminus of HCV using a proximity-dependent biotin identification method (BioID). An essential component of the BioID strategy revolves around promiscuous biotinylation of nearby proteins by BirA, an E. coli derived biotin ligase. In this study, we exploit the high affinity interaction between the Bacteriophage λ BoxB stem-loop structure and the λN protein to localize a BirA fusion protein to the 5’ terminus of the HCV genome. Biotinylated proteins will be affinity purified and analyzed using mass spectrometry.
Mental health, risk behaviors and substance use profiling of patients infected or at-risk of acquiring hepatitis C seen in community and hospital care settings in New Brunswick

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BACKGROUND: In New Brunswick, care for those infected with Hepatitis C Virus (HCV) is provided in both hospital and community-based settings.

RESULTS: To date, we have demonstrated that HCV containing a BoxB stem-loop accumulates appropriately in cell culture and we have developed the λN-BirA fusion protein. We are currently in the process of expressing both the λN-BirA fusion protein and BoxB HCV RNA in cell culture. Subsequently, we will use BioID to identify vicinal proteins by mass spectrometry. Vicinal proteins will be investigated for their role in the HCV lifecycle using knockdown or overexpression studies in the presence or absence of miR-122.

CONCLUSIONS: The identification of proteins at the 5’ terminus of the HCV genome will reveal new host-virus interactions, will help elucidate the mechanisms of miR-122-mediated viral RNA accumulation, and may provide novel targets for antiviral therapy.

LIMITED PROVINCIAL DATA CURRENTLY EXISTS ABOUT DIFFERENCES BETWEEN PATIENTS SEEN IN THESE SETTINGS. THE HEPATITIS C POSITIVE AND AT-RISK (HEAR) DATABASE WAS CREATED IN 2014 TO CAPTURE INFORMATION ABOUT THIS POPULATION AS A WAY TO BETTER UNDERSTAND THE SOCIAL AND ENVIRONMENTAL FACTORS CONTRIBUTING TO THE BURDEN OF HCV IN THE PROVINCE. THE CURRENT STUDY UTILIZED DATA IN THE HEAR DATABASE TO ANALYZE DIFFERENCES OF SOCIOECONOMIC STATUS, HIGH RISK BEHAVIORS, MENTAL HEALTH AND PSYCHIATRIC COMORBIDITIES, AND PATTERNS OF SUBSTANCE ABUSE.

PURPOSE: The aim of this study is to characterize the socioeconomic and environmental factors affecting patients seen in two common care settings in New Brunswick.

METHOD: Personal health information was collected once informed consent was obtained both prospectively and retrospectively via self-reported questionnaires, by the patient’s clinician or via electronic medical records. Baseline characteristics for all patients enrolled in the database between April 2014 and April 2016 were included in the analysis. Univariate comparisons of hospital-based and community-based patients were conducted using chi-square or Fisher’s exact tests for nominal variables. Mann-Whitney or analysis of variance (ANOVA) was used for ordinal or interval data for non-normally and normally distributed data, respectively.

RESULTS: There were 374 patients included in the analysis. It was demonstrated that the community group had a greater proportion of unemployment (64%), social assistance (82%), past incarceration (70%) and mental illness treatment (72%). These patients also reported engaging in high risk activities including sexual behaviors (45%), tattoos (51%) and shared drug paraphernalia (75%). Notably, the community group demonstrated significantly higher rates of suffering abuse (47%) and positive family histories of addictions (72%) and psychiatric conditions (36%). Current substance use was more prevalent in the community group for all substances analyzed including tobacco (79%), alcohol (59%), cannabis (69%), benzodiazepines (47%), cocaine (40%), opiates (36%) and methamphetamine (10%). Substance abuse profiling of the cohort demonstrated a progression from tobacco, alcohol and cannabis use in early teens (age of
first use 13.5, 14, and 14 respectively) to benzodiazepines, cocaine, methamphetamine and opiate use in early 20’s (age of first use 20, 20, 21 and 22 respectively).

CONCLUSIONS: The current study provides a comprehensive snapshot on the NB population infected or at-risk of acquiring HCV which was not previously available. Findings confirm that distinct differences exist between the patients seen in each type of setting. Barriers associated with both settings may limit screening and treatment uptake but understanding the fundamental differences between patients treated in each care setting has the potential to aid in facilitating targeted screening practices, reduce barriers associated with the uptake of care and identify key areas of clinical need in the future.

The interface between sexual and injecting risk for hepatitis C virus infection among people who inject drugs in Montreal

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BACKGROUND: Although hepatitis C virus (HCV) infection is both preventable and curable, acquisition remains high among key affected populations, particularly people who inject drugs and men who have sex with men. Most studies examining HCV infection and acquisition have focused on injecting risk behaviours with few considering the contribution of sexual activity, particularly among sexual minorities. Considering the complex interplay between sexual behaviour and drug consumption, a better understanding of HCV seropositivity and incidence in sexual minorities is necessary and timely.

PURPOSE: In a cohort of people who inject drugs, this study aimed to examine the association of recent sexual activity with 1) HCV seropositivity at enrolment, and 2) HCV seroconversion among those HCV seronegative at enrolment.

METHODS: All participants enrolled in the HEPCO study (Nov 2004–Dec 2016) were eligible for the HCV seropositivity analysis, while those HCV seronegative at enrolment with >1 follow-up visit were eligible for the HCV seroconversion incidence analysis. Comprehensive behavioural and socio-demographic questionnaires and anti-HCV antibody testing was undertaken at enrolment and 3–6 month follow-up intervals. We assessed sexual activity in the past 3–6 months as a time-updating variable as follows: no sexual partner, opposite sex partner only, or same-sex (+/- opposite) partner. Associations between sexual activity and HCV infection at enrolment and time to HCV seroconversion were examined using logistic regression and Cox regression analysis, respectively.

RESULT: At baseline, of the 1518 participants enrolled (17% female), median age was 38 years (IQR: 29–46), and 65% (n=980) were anti-HCV antibody positive. Most participants recently injected cocaine (63%), 31% recently injected heroin and 34% prescription opioids. In unadjusted logistic regression, participants reporting recent opposite-sex partner only [odds ratio: 0.45, 95% CI: 0.35, 0.58], or same-sex partner (odds ratio: 0.50, 95% CI: 0.34, 0.73) were less likely to be HCV seropositive at baseline, compared to participants that reported no sexual partner. Within the HCV seroconversion incidence analysis, 153 of 432 participants had HCV seroconversion during 1229.29 years follow-up time: an incidence rate of 13.55/100py (11.53–15.82). In unadjusted Cox regression analysis, reporting recent same-sex partner (Hazard ratio: 2.06, 95% CI: 1.20, 3.54), but not opposite-sex partner only (Hazard ratio: 1.33, 95% CI: 0.91, 1.95), was associated with HCV seroconversion relative to reporting no sexual partner.

CONCLUSION: In this cohort of people who inject drugs, reporting recent same-sex partners was associated with reduced odds of HCV seropositivity at enrolment, but greater risk of HCV acquisition. These results suggest complicated interactions of risk behaviours, and the need for targeted prevention strategies for people who report same-sex activity.
Neighbourhood risk environments and Hepatitis C virus infection among persons who inject drugs in Montreal

Nanor Minoyan, L'Université de Montréal / CRCHUM; Andreea Adelina Artenie, l’Université de Montréal; Julie Bruneau, CRCHUM

BACKGROUND: Decades of research have elucidated the primary individual-level determinants of HCV infection among persons who inject drugs (PWID), the primary reservoir for the virus in high-income countries. Nevertheless, in Montreal, Canada, an estimated 72% of PWID will acquire HCV over the course of their lifetimes. The combined challenges of substance use, social vulnerability, and blood-borne-virus infection faced by this population imply a need to diversify harm-reduction strategies. According to the “risk environment” framework (1), harm reduction strategies must address the upstream social circumstances in which risk behaviours take place. Neighbourhoods have previously been used to represent exposures dictated by social vulnerability. However, few studies apply a longitudinal perspective to study the influence of neighbourhoods on HCV and drug-related harms among persons who inject drugs (PWID).

PURPOSE: We aimed to examine the relationship between neighborhood deprivation and HCV transmission among PWID in Montreal.

METHODS: We analysed data from the HEPCO prospective cohort study of Montreal PWID. Every 3 months, participants provide details on drug behaviours, sociodemographics, and dwelling postal codes. Blood samples are tested at baseline for presence of HCV RNA and antibody; RNA testing is performed at follow-up visits. Neighborhood deprivation was defined based on the Pampalon deprivation index, an aggregate census measure widely used in Quebec to represent social inequalities in health. Based on population quintiles of the index, participants were classified as residing in deprived (Q4–5) vs non-deprived areas (Q1–2–3). Descriptive analyses compared participant risk behaviours across deprivation categories. Cox proportional hazards regression was performed to estimate the association between neighbourhood deprivation and incident HCV infection (defined as a positive RNA test among RNA-participants).

RESULTS: 277 participants contributed 449 person-years of follow-up. 49 cases of incident HCV infection were observed among participants RNA-negative at baseline (IR: 11.0 cases 100 person-years). 543 postal codes were recorded throughout follow-up. Participants living in deprived neighborhoods (n=114, 47.5%) were less likely to report injecting heroin (32% vs 44.4%), sharing syringes (16.0% vs 23.0%), unstable housing (13.3% vs 23.0%) and employment (18% vs 31%) than those living in non-deprived areas. 84.8% of consecutive follow-up visits represented a move into or out of deprived neighborhoods. No association was found between neighborhood deprivation and rate of HCV infection (aHR: 1.1, 95% CI: 0.6–1.9, 76% of observations non-missing for deprivation).

CONCLUSION: Neighborhood deprivation was not associated with HCV transmission in analyses considering current neighbourhoods. Greater consideration of mobility across levels of deprivation in subsequent analyses may reveal a dynamic relationship between risk environments and HCV transmission, informing harm reduction strategies.

REFERENCE

Reinfection/Recurrence of hepatitis C virus infection in a prospective cohort study of people who inject drugs in Montreal: does viral clearance mechanism play a role?

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BACKGROUND: Hepatitis C viral transmission among people who inject drugs (PWID) remains high in Montreal, despite availability of harm reduction strategies. The recent introduction of highly efficient, direct-acting antiretroviral therapies may have significant potential in curbing the HCV epidemic in this high-risk group. A portion of the HCV disease burden is attributable to HCV reinfection/recurrence among PWID who have previously cleared the virus, though estimates differ across studies. It further remains unclear whether the rate of reinfection/recurrence following spontaneous resolution differs from the rate following treatment-induced SVR. Estimating rates of reinfection/recurrence among these specific groups could have important implications for treatment guidelines, as well as to inform treatment-as-prevention strategies.

PURPOSE: We sought to estimate the rate of HCV reinfection/recurrence among PWID in Montreal. We also sought to compare rates observed among PWID who cleared the virus spontaneously (SC) to those who achieved SVR through IFN- or DAA-based treatment (TX).

METHODS: We constructed an HCV reinfection/recurrence cohort using data from a prospective cohort study of PWID (Jan.2010–May 2017). Blood samples were tested at baseline for presence of HCV RNA and antibody, followed by tri-monthly follow-up visits to detect HCV RNA. Interviewer-administered questionnaires collected behavioural and sociodemographic data at each visit. Participants were eligible if they tested anti-HCV positive and negative for HCV RNA at baseline or over the course of follow-up. They were classified as SC or TX using a combination of self-report and clinical data. Participants began accruing follow-up time from baseline if they tested RNA-/Ab+. Those with active infection at baseline, as well as those who seroconverted over the course of the study, began contributing follow-up time once they became RNA-negative (SC group: ≥6 months after known infection date; TX group: following end-of-treatment SVR date). We defined HCV reinfection/recurrence as a positive HCV RNA test among individuals having previously cleared the virus, consistent with current clinical definitions. Kaplan-Meier survival curves were plotted, and time-to-event methods were used to calculate recurrence rates (overall and by clearance group).

RESULT: 269 individuals contributed 771.0 person-years of follow-up (median follow-up: 27 months). Overall, 53 participants tested positive for HCV-RNA during follow-up (IR: 6.88/100 person-years, 95% CI: 5.15–8.99). 25 cases were observed in the TX group (IRTX: 6.58/100 p-y); 28 were observed in the SC group (IRSC: 7.16/100 p-y). Reinfection rates did not differ according to viral clearance mechanism (K-M log-rank test p-value: 0.65).

CONCLUSION: HCV reinfection/recurrence rates did not differ according to viral clearance mechanism within this prospective cohort study with relatively long follow-up and frequent testing intervals. The estimated overall rate of HCV recurrence was comparable to current estimates of primary infection in the cohort. Preventive strategies must therefore be promulgated alongside treatment to reduce drug-related harms among PWID.

Evaluation of hepatitis C knowledge among medical and nursing students

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BACKGROUND: Early diagnosis of Hepatitis C and identification of asymptomatic patients is necessary for timely treatment to prevent progression to severe liver disease and death. Past studies have shown that one of the major barriers to early diagnosis is the fact Hepatitis awareness remains low in the general public as well as among healthcare professionals. While most primary healthcare professionals will not receive specialized training in Hepatitis C, they are often the ones involved in the initial diagnosis. The current suboptimal diagnostic rate highlights a need to increase awareness of Hepatitis C among healthcare professionals, and to help them have a better understanding of the disease. Advocacy for more training and education on Hepatitis C knowledge among healthcare trainees could be beneficial in improving the delivery of timely diagnosis and treatment to patients.

PURPOSE: The purpose of this study was to perform a knowledge evaluation of Hepatitis C among medical and nursing students at Memorial University to advocate for better Hepatitis C education among healthcare professional trainees.
METHOD: An electronic questionnaire containing 10 multiple choice questions assessing knowledge and awareness of Hepatitis C was distributed to all current medical and nursing students at Memorial University of Newfoundland for voluntary response.

RESULTS: A total of 88 students responded to the questionnaire with a ratio of 64% medical students and 35% nursing students. Results showed that 25% of respondents believe jaundice is the most common symptom of a chronic Hepatitis C infection, with additional 28% respondents answering with either cirrhosis or “I don’t know”. A shocking 39% of respondents believe that Hepatitis C is a vaccine-preventable disease. A question assessing their knowledge regarding current effective treatment of Hepatitis C infection showed that 24% of the students picked vaccination as the most effective treatment, while another 15% believe Hepatitis C cannot be cured.

CONCLUSION: While acknowledging the limited sample size of this study and appreciating the fact that 41% of the respondents were first year medical or nursing students, it is clearly evident that Hepatitis C knowledge and awareness is low among healthcare trainees. Healthcare professional trainees are expected to have a better knowledge base of Hepatitis C than the general population and increasing their awareness of this disease early in their education could have profound impact on improving the diagnostic rate of Hepatitis C later in their established career. This study shows that better educational efforts on this topic is warranted at the undergraduate level.

Toward taking account to provide care for Indigenous persons living with Hepatitis C virus (HCV) – identifying areas for future research and engagement

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BACKGROUND: Our existing understanding suggests that there are significant needs and opportunities to care for Indigenous persons living with HCV. Innovative strategies can address challenges related to providing care in remote regions, stigma and competing health and social demand to improve access for all. Work to improve the readiness of both individuals and communities will be foundational to working toward HCV elimination.

METHODS: We conducted a face-to-face interactive workshop at the Wise Practices, Skills Building and Annual General Meeting of the Canadian Aboriginal AIDS Network in Calgary 2017. A sharing circle in which individual safety was emphasized was used.

RESULTS: A number of themes were identified. These included 1) the need for wise practices for care cascades for Indigenous people in general which promote wholistic health and wellness; 2) the need for after-care again guided by wise practices; 3) the importance of the criminal justice system and the need for the development of improved linkages to care and support between correctional facility and community; 4) the need to support wise practices to reduce and combat stigma, particularly at the local small community level and in a variety of contexts and 5) the need for education and support of health care workers in the evolving field of HCV treatment.

DISCUSSION: Future research to support the development of a wise practice approach to HCV care for Indigenous people in Canada will need attention to linkage and after-care. A wholistic and two-eyed seeing approach will be the focus of our future work.

Exploring treatment adherence to direct acting antivirals among HCV positive individuals who use drugs in Bangladesh

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all were male and 93% were >30 years of age. Of the 55 patients on treatment, to date 39 have completed treatment: 36 (92.3%) adhered based on an 80% threshold set for compliance with DAA regimen, 3 non-adhered. SVR12 assessments are expected to be completed by January 2018. In-depth interviews revealed that close family ties, regular follow-ups and influence by peers enabled PWUD to adhere to treatment. However, barriers to adherence identified included lack of knowledge regarding HCV resulting in mistrust among some as to why they were receiving such extra attention.

CONCLUSION: Our findings suggest that overall adherence to DAA was good and facilitated by close follow up, support by family members and raising awareness amongst PWUD regarding HCV in the surrounding community. However, most of the PWUDs lead chaotic lifestyles, which were associated with mental and physical health problems, financial difficulties and lack of meaningful social relationships. Regular follow-up by outreach staff attenuated the impact of the preceding factors and contributed to improved adherence. The findings of the pilot study will help with developing strategies for effectively treating PWUD with HCV.

Substitution treatment for opioides is a key of success for HCV cure in injection drug users

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INTRODUCTION: In Canada, despite the universal health care system, access to HCV treatment remains limited for drug users (DU). Many physicians prefer to ensure abstinence before initiating treatment. However, Intravenous DU (IDU) consuming drugs are more at risk of transmission. The aim of this study was to assess our ability...
to cure HCV infection in IDU regardless of their consumption.

**METHODS:** All HCV-treated patients followed at Clinique Medicale du Quartier Latin (CMQL) were included in this retrospective study. Information on socio-demographics, medical history and treatment was collected from the electronic medical chart. At CMQL HCV-patients are followed by a multidisciplinary team (nurse, family doctor, hepatologist, social worker, community pharmacist) and have access to a low threshold opioid substitution therapy (OST) if they need so. Sustained virological response rate at 12 weeks after end of treatment (SVR12) was calculated by Intent-to-treat analysis (ITT). Determinants of SVR were analysed by multiple logistical regression using SPSS-24.

**RESULTS:** 104 HCV patients treated with INF-free-DAA were included in this study. 79% were men, with a mean age of 53 y (IQR: 48y - 59y). 46% were HIV-coinfected, 23% were active-IDU, 14% were on OST, 5% without housing, 46% with ROH-problem, 31% were cirrhotic, 77% were infected with genotype-1 and 70% were naïve at the INF-free-DAA treatment initiation. Over all, 85% achieved SVR12 while 2% discontinued treatment. Even if SVR seems higher in non-IDU, the difference was not statistically significant (SVR=90% for non IDU vs. 84% for previous-IDU and 78% for active-IDU; p=0.471). 100% of patients on OST achieved SVR. In multivariate analyses, after controlling for gender, age, drug and alcohol use, housing, depression, diabetes, HIV-coinfection, treatment history and genotype, cirrhosis was the only determinant who impacted SVR (aOR= 0.13; 95%CI= 0.04 - 0.46; p=0.002).

**CONCLUSION:** At CMQL, the SVR rate remained high and did not differ by IDU status. The «difficult-to-treat» IDU are manageable if we offer them adequate support. OST is one of the best opportunities for curing active-drug users for their HCV.

**Sofosbuvir plus ribavirine for 24 weeks in an HIV-infected, cirrhotic patient with chronic hepatitis E virus infection**

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**BACKGROUND:** Chronic Hepatitis E virus (HEV) infection as a cause of liver disease, including rapid progression to cirrhosis, has been well described in immuno-compromised patients. Treatment of this condition has included reduction of immunosuppression in transplant recipients, peg-interferon therapy, and ribavirin (RBV) monotherapy, all with suboptimal rates of sustained viral eradication. More recently, reports of in vitro activity of sofosbuvir (SOF) against HEV as well as transient suppression of viremia in a single patient have raised the question of whether SOF-based therapy could provide an effective treatment option.

**METHODS:** This is a case report of a 51 year old HIV-infected male with a history of AIDS, Kaposi’s sarcoma, lymphoma and chronic genotype 3 HEV resulting in cirrhosis had failed to clear HEV with 5 years of RBV monotherapy, despite ALT normalization. He was then treated and cured with sofosbuvir 400 mg daily plus RBV 1000 mg daily for 24 weeks.

**RESULTS:** Pretreatment HEV RNA was 1500 IU/mL for this patient and ALT was within normal limits. Six months after completing 24 weeks of treatment, HEV RNA remains negative and ALT and AST stay within normal limits. SOF+RBV was well tolerated with no adverse effects and no new laboratory abnormalities. The patient’s CD4 count which had been consistently around 80 cells/ml increased to 150 cells/ml at the end of treatment.

**CONCLUSIONS:** This is the first case report of chronic HEV treated with SOF+RBV for 24 weeks. The patient remains HEV negative 6 months after completing treatment. Further studies are needed to investigate the safety and efficacy of SOF+RBV as a treatment for chronic HEV infection.
HepCInfo updates: National hepatitis C research knowledge synthesis, evaluation

Suzanne Fish; Laurie Edmiston, CATIE; Laurel Challacombe, CATIE; Scott Anderson, CATIE; Tim Rogers, CATIE; Erica Lee, CATIE; David McLay, CATIE

BACKGROUND: HepCInfo Updates is CATIE’s bi-weekly e-newsletter covering the latest in hepatitis C research and news, including treatment, prevention, harm reduction and epidemiology information relevant to the Canadian context. Each newsletter contains two sections: “New and noteworthy” which summarizes 2–3 new developments in hepatitis C and “Straight to the source for new science” which provides links to recent research of interest.

HepCInfo Updates is available online through CATIE’s website and is emailed to subscribers. There are 3,062 HepCInfo Updates subscribers – including 2,605 English subscribers and 457 French subscribers.

In November 2016, CATIE launched an online survey in FluidSurveys to evaluate HepCInfo Updates.

PURPOSE: As one of CATIE’s key publications, HepCInfo Updates has two primary objectives: Objective 1: Increase knowledge and awareness of the nature of hepatitis C and ways to address them. Objective 2: Enhance individual and organizational capacity to plan and deliver programs and services.

METHODS: CATIE launched an online survey in FluidSurveys to evaluate HepCInfo Updates. The survey was promoted through the HepCInfo Updates subscribers list. Notice of the survey was included in the e-mail distribution of two HepCInfo Updates issues and an additional request to complete the survey was e-mailed to subscribers. The survey was available online for nine weeks.

Ninety-eight people started the survey with 90 people completing all questions in the survey (completion rate 91.8%). Frequency descriptives were compiled for all respondents.

RESULTS: The evaluation demonstrated that HepCInfo Updates is relevant to our stakeholders and effective at achieving our knowledge exchange objectives.

Is HepCInfo Updates relevant?

- 98% reported that at least ‘some’ of the content of HepCInfo Updates is relevant to them.
- 92% were ‘satisfied’ or ‘very satisfied’ with the publication.

Is HepCInfo Updates effective?

OBJECTIVE 1: Increased knowledge and awareness of the nature of hepatitis C and ways to address them.

- 95% agreed or strongly agreed that HepCInfo Updates made them aware of information that has increased their knowledge of hepatitis C.
- 94% agreed or strongly agreed that HepCInfo Updates made them aware of relevant, up-to-date information on developments in the treatment and prevention of hepatitis C.
- 87% have used the information they were made aware of through HepCInfo Updates to educate or inform clients, health professionals, colleagues or members of the public.

OBJECTIVE 2: Enhanced individual and organizational capacity to plan and deliver programs and services.

- 87% agreed or strongly agreed that they can use/apply the information they were made aware of through HepCInfo Updates in their work.
- 59% have used the information they were made aware of through HepCInfo Updates to change work practices and/or implement/change programming. Specifically.

CONCLUSIONS: Readership evaluation of HepCInfo Updates was overwhelmingly positive. HepCInfo Updates is meeting its objectives.
**Proteomics: The doctor is IN the Tardis**
Douglas Laird, HepC BC

**BACKGROUND:** The liver biopsy was the golden standard for liver fibrosis diagnosis. Advances in non-invasive techniques started with the Fibrosure, which was based on an algorithm of blood composition done in a laboratory. Then the ultrasound technique Fibroscan was developed and placed into wider practice by technicians and physicians.

The Fibrosure is compact and portable. It is expensive and requires recalibration, which is also very costly. The cost can be justified by quantity of scale, mainly inside of zones of urban populations. Rural populations are not serviced on a routine basis, and travel costs can be significant to do so.

**PURPOSE:** While not widely in use in Canada, proteomics offer a method of analytical detail and increase health comprehension enormously. Given the wide range of comorbidities involved in Hepatitis C virus, the technology would increase diagnostics using a sample of blood to give a profile of 210 proteins. The number of diagnostic tests for fibrosis and the potential for hepatic carcinoma would increase, with monitoring results post SVR giving critical information on a range of health concerns that could reduce mortality.

**METHOD:** Studies indicate that serum proteomics are useful for HCC diagnostics (Uto et al, 2010) while serum proteomics can predict hepatic fibrosis in HCV (Hannivoort, Hernandez-Gea, & Friedman, 2012).

**RESULTS:** There is an important need for HCC diagnostics with HCV and HBV clients that is unmet, especially for rural clients where travel costs to major centers take up a considerable proportion of health care budgets in the far north. Post SVR results for cirrhotic patients are critical to reduce cancer mortality. As baby boomer testing remains controversial in Canada, advancing the availability to proteomics would be an alternative request by advocacy groups that would extend protection against comorbidities such as stroke. Taken together, cost savings to the health care system could be substantial.

**CONCLUSIONS:** Having proteomic technology available would result divergent advantages, especially in the proper diagnostics of TIA or mimics involved in stroke diagnostics. Further studies are warranted to add proteomics to standard medical diagnostics as a benefit to decrease mortality due to HCC.

**REFERENCES**
virological cure even following years of chronic infection. Whether TEX in these cured subjects convert to recovered T cells (TRECOV) with better functional and durable memory profile remains unknown. Here, we aim to determine the cellular profiles, molecular mechanisms, and population dynamics of TRECOV, and to investigate whether TEX become “reprogrammed” into more functional T cells following non-immunological cure of chronic disease. For these aims, we are examining virus-specific T cells from chronic HCV patients cured by DAA treatment and from mice cured of chronic lymphocytic choriomeningitis virus clone 13 (LCMV-cl13) by adoptive transfer. Using this well-defined tractable mouse model we can dissect the molecular mechanisms underlying changes in TEX following the elimination of chronic antigen stimulation. Additionally, this mouse model enables the investigation of the recall and protective capacities of TRECOV upon re-exposure to the antigen compared to TEX and memory T cells (TMEM). Our data indicate that some markers of exhaustion (including PD-1) are downregulated on TRECOV, while some markers of TMEM may be recovered upon cure of infection. Nevertheless, other aspects of TEX biology do not appear to be corrected simply by eliminating chronic infection. Rechallenge studies indicate that TEX retain some recall capacity. Nevertheless, co-transfer of TEX and TMEM indicate that TEX are highly compromised in this recall capacity when compared to TMEM on a per cell basis. The expansion of TEX was associated with a specific subset of cells identified by intermediate expression of PD-1 and expression of the transcription factor TCF-1+ (PD-1 Int TCF-1+). TRECOV possess enhanced recall response compared to TEX indicating some improvement in this key memory T cell property. However, we are currently examining the recall capacity of TRECOV compared to Tmem, and the subset dynamics involved. We are also investigating whether the changes in TRECOV are linked to selective recovery of a specific subset of TEX, and/or changes in their transcriptional profiles and epigenetic landscapes. We expect these studies to enhance our understanding of the immunological and epigenetic mechanisms of TEX recovery. These studies could also identify candidate transcriptional circuits differentially regulated in readily-recovered T cells that could represent novel therapeutic targets for reversal of immune exhaustion.

**Participation of Argonaute isoforms and the TNRC6 family of proteins in small RNA-dependent promotion of HCV replication**

Yalena Amador-Canizares, University of Saskatchewan; Joyce Wilson, University of Saskatchewan

**BACKGROUND:** A liver-specific microRNA, miR-122, promotes replication of Hepatitis C Virus (HCV) by a poorly understood mechanism. Argonaute (Ago) proteins are host proteins involved in the activity of miRNAs, and are necessary for miR-122 promotion of the HCV life cycle. Humans express four Ago isoforms. Ago 1 and 2 are more widely and highly expressed among different cell lines and Ago2 is considered the primary Ago involved in HCV replication. TNRC6 (GW182 related) family proteins (A, B and C) interact directly with Ago proteins and are required for miRNA-mediated gene silencing in animal cells but their involvement in HCV replication has not been clarified.

**PURPOSE:** Identify the contribution of Ago1 and 2 and the TNRC6 family proteins in the promotion of HCV replication dependent on small RNAs.

**METHOD:** To investigate the specific role of Ago1 and 2 and the impact of other Ago isoforms in the HCV life cycle, we generated Ago2 and Ago1-2 knockout (KO) cells using the CRISPR/Cas9 technology. To determine the contribution of the TNRC6 family proteins we used lentivirus vectors to express a TNRC6B-derived inhibitory peptide that interacts with Ago proteins and represses miRNA pathways. We transfected in vitro transcribed viral RNA into the Ago-KO and TNRC6-inhibitory peptide expressing cells by electroporation, and compared the viral replication in wild type cells.

**RESULTS:** Sanger sequencing confirmed biallelic indel mutations consistent with abrogation of the expression of Ago2 and Ago1-2 genes, respectively. The absence of expression of both proteins was confirmed by Western blot. Ago2 KO cells supported relatively robust HCV replication with replication levels only 30–50% lower than in wild-type cells. This indicates that at least one of the other Ago isoforms is able to sustain high levels of HCV replication when Ago2 is not present. Interestingly,
in the absence of Ago2’s cleavage activity, perfect match small RNAs directed against miR-122 binding site 1 can promote HCV replication as miR-122 mimics. Data on the ability of the Ago1-2 KO cells to support HCV replication will be presented. Although expression of the TNRC6B-derived peptide abrogated the activity of small RNAs in a plasmid-based reporter assay, preliminary results showed no effect on viral replication.

CONCLUSIONS: Our results suggest that miR-122 specific binding pattern is dispensable for HCV replication, in the absence of the slicer activity of Ago2, and that other small RNAs that bind to the 5’ end of the genome can substitute for miR-122. Additionally, other Ago isoforms can support miR-122-dependent HCV replication. Interestingly, the TNRC6 family proteins seem to be nonessential for the promotion of viral replication. These data add information on the mechanism by which miR-122 promotes the HCV life cycle and also provide insight into the roles of the different Ago isoforms in miRNA activity.

Who are we leaving behind? Comparing rates of opiate agonist treatment initiation according to preferred opioid of abuse among people who inject drugs in Montreal

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BACKGROUND: Opiate agonist therapy (OAT) is considered key in hepatitis C virus (HCV) prevention among people who inject drugs (PWID). Despite concerns surrounding the substantial diversion of prescription opioids (PO) to the illicit market, and the high risk of HCV infection associated with PO injection, little is known about the access to OAT among street-based drug users whose drug of choice is PO, and how it compares to those who prefer heroin.

PURPOSE: The main objective of this study was to assess and compare rates of OAT initiation among PWID according to preferred opioid of abuse (PO vs heroin).

METHOD: Data were drawn from HEPCO, a prospective cohort study of active PWID followed between 2004 and 2011 in Montreal. At six-month intervals, participants were interviewed to collect information on socio-demographics, recent (past month or past six months) drug use behaviours and OAT initiation. For this study, PWID were eligible if they indicated, at baseline, i) their preferred drug of abuse to be heroin or PO and ii) not being on OAT within the past six months, and were followed-up at least once. Participants were censored following first episode of OAT reported during follow-up. First, the baseline characteristics of participants were compared, according to drug of choice. Then, for each group, rates of OAT initiation were calculated using the person-time method, and cumulative incidences, based on Kaplan-Meier estimates, were compared using the log–rank test.

RESULTS: At baseline, 163 PWID (median age: 29.6, 76.1% of male gender) were eligible for this analysis, of whom 63 (38.7%) reported preferring PO and 100 (61.3%) indicated preferring heroin. While no differences were found for age and gender, relative to those preferring heroin, those whose drug of choice was PO were more likely to also report smoking cocaine (68.3% vs 47.0%) and using sedatives (60.3% vs 42.0%), injecting daily (50.8% vs 30.0%) and at a higher frequency [≥3 injections/day (60.3% vs 36.0%)], living in unstable housing conditions (65.1% vs 31.0%) and injecting mostly in public (54.0% vs 36.0%; all p-values < 0.05). Over all, PWID contributed 210.53 person-years (p-y) of follow-up. PWID indicating PO as their drug of choice had a lower rate of OAT initiation relative to those indicating heroin [incidence rates: 34.1 per 100 p-y (95% confidence interval (CI): 24.3–45.0) vs 54.6 per 100 p-y (95% CI: 45.4–63.7); log-rank p-value: 0.03].

CONCLUSION: Compared to those preferring heroin, participants whose drug of choice was PO were more likely to present characteristics potentially placing them at greater risk of HCV infection. Further, our findings suggest that this group were significantly less likely to initiate OAT. Additional
and follow-up; others expressed dislike or uncertainty. Poorer access to mobile technology was reported by treatment naïve, community site, and non-White participants (p values ranging from .02 to .003). Respondents from the community site, as compared to the hospital site, also rated significantly lower levels of comfort in sending/receiving texts (p = .008). A similar trend was found for respondents with incomes below $30,000 as compared to higher income (p = .085). Yet, groups equally liked the idea of using mobile technology in HCV care.

**CONCLUSION:** Mobile technology may be an attractive and feasible alternative model to augment existing HCV care. The majority of participants have access to this technology and expressed favourable attitudes toward using this innovative method in their care. Variability in acceptability and accessibility of this approach was highlighted for specific sub-populations, so it will be critical to tailor care delivery to patient needs in order to effectively engage all individuals with HCV and ultimately increase successful HCV treatment delivery.

**Mobile technology access and patient preferences for HCV care in the new era of DAAs**

Julie Beaulac, The Ottawa Hospital; Curtis Cooper, U Ottawa; Kim Corace, The Royal; Louise Balfour, The Ottawa Hospital; Mark Kaluzienski, The Ottawa Hospital

**BACKGROUND:** In this era of emerging, well tolerated, highly curative but costly HCV DAA treatments, gaps in engaging individuals in HCV care results in harm to infected individuals as well as contributing to ongoing risks of HCV transmission. Alternatives to traditional models of care are needed to reach and engage more individuals. Mobile technology interventions present opportunities for enhancing patient engagement, retention, satisfaction, and outcomes.

**PURPOSE:** To assess the feasibility and patient attitudes toward using mobile technology in HCV care.

**METHOD:** Cross-sectional survey data were collected from HCV patients (N=115) across two sites of The Ottawa Hospital Viral Hepatitis Program, a hospital-based outpatient clinic and a community program. Participants completed measures of demographics, HCV disease status and risk factors, and mobile technology access and preferences. Medical chart review supplemented survey data. Mann-Whitney and chi-square tests assessed for differences in mobile technology access, use, and preferences by treatment experience, ethnicity, site, gender, education level, or income level.

**RESULTS:** 77.6% indicated that they owned a mobile device and of these, the majority also reported having access to the Internet (69.4%) and unlimited text plans on their devices (71.6%). Although most indicated that they had never used mobile technology to communicate with a health care provider, the majority (65.5%) reported comfort in sending/receiving texts. Half of respondents liked the idea of using a cell phone for HCV clinical care and follow-up; others expressed dislike or uncertainty. Poorer access to mobile technology was reported by treatment naïve, community site, and non-White participants (p values ranging from .02 to .003). Respondents from the community site, as compared to the hospital site, also rated significantly lower levels of comfort in sending/receiving texts (p = .008). A similar trend was found for respondents with incomes below $30,000 as compared to higher income (p = .085). Yet, groups equally liked the idea of using mobile technology in HCV care.

**CONCLUSION:** Mobile technology may be an attractive and feasible alternative model to augment existing HCV care. The majority of participants have access to this technology and expressed favourable attitudes toward using this innovative method in their care. Variability in acceptability and accessibility of this approach was highlighted for specific sub-populations, so it will be critical to tailor care delivery to patient needs in order to effectively engage all individuals with HCV and ultimately increase successful HCV treatment delivery.

**Hepatitis C core antigen testing from dried blood spots as a diagnostic alternative for difficult to reach populations**

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**BACKGROUND:** Dried blood spots (DBS) are a simple and effective way to obtain patient samples for diagnosing blood-borne viruses, and are especially useful when sample processing time and cold storage is a challenge. DBS can be used for the detection of anti-hepatitis C antibodies as well as for reflex testing, bypassing the need for a second patient visit to confirm infection. Typically the
confirmatory test has been the detection of viral RNA, however, this method may not be the most cost-effective. An alternative reflex test using HCV core protein is available, but there is relatively little information on core protein stability on DBS. It is also unclear whether variations in temperature affect detectability of core protein.

**PURPOSE:** To determine the stability of HCV core antigen on DBS cards under several environmental temperatures representative of transportation from rural and remote regions of Canada to public health laboratories.

**METHODS:** Blood was collected from five healthy controls and 74 confirmed HCV RNA-positive individuals, and spotted onto five DBS cards and allowed to dry overnight. Cards were subsequently stored under the following conditions for one week: -80°C (gold-standard), 4°C, 21°C, 37°C and alternating between 37°C and 4°C. A matched serum sample stored at -80°C served as a reference. DBS cards were eluted and all samples were tested in duplicate for the presence of anti-HCV antibodies and HCV core antigen.

**RESULTS:** Sensitivity and specificity for anti-HCV antibodies from DBS was 99–100% (depending on the condition) and 100%, respectively. When using a cut-off of 3 fmol/L the sensitivities of HCV core antigen from DBS were: 93% (-80°C), 93% (4°C), 92% (21°C), 90% (37°C), and 91% (37°C/4°C), while all healthy controls tested negative for core antigen. It should be noted that one HCV-positive sample was below a viral load of 500–3500 IU/mL (limit of detection), and therefore our diagnostic sensitivity would slightly improve had we excluded this sample. Interestingly, while we observed excellent concordance between serum and DBS samples for positivity, our data does not support the use of core antigen from DBS for virus quantification. Finally, negligible differences were noted between the storage conditions of DBS cards.

**CONCLUSIONS:** Our data demonstrates HCV core antigen stored on DBS cards is detectable under a range of temperatures. This suggests that the relatively inexpensive core antigen test could be incorporated into an algorithm where HCV antibody testing of DBS samples would be followed by reflex core testing. We propose the use of this method for large-scale, inexpensive screening programs to identify HCV-infected persons in rural or remote locations, as well as to improve testing rates among street-involved persons.

**Eradication of chronic hepatitis C Infection with direct acting antivirals is associated with reduction in fibrosis by transient elastography (Fibroscan)**

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**BACKGROUND:** Eradication of chronic hepatitis C infection (CHC) is associated with reduced mortality and morbidity, particularly in those with advanced fibrosis. Histological regression of liver fibrosis has been reported in interferon (IFN)-based therapies, which may be partly attributed to IFN’s anti-fibrotic effect. There is evolving data for fibrosis regression post-direct acting antiviral (DAA) therapy.

**PURPOSE:** To determine if liver stiffness, an indirect measure of fibrosis, improves with SVR following DAA therapy.

**METHODS:** This was a retrospective study conducted at a University-affiliated, tertiary referral hepatology clinic in Vancouver, Canada.

Patients with CHC treated with IFN-free, DAA regimens between 03/2013 and 10/2016, and SVR at 12 weeks post-therapy were assessed for inclusion in the study. Patients with concomitant non-CHC liver disease, and those missing either pre-therapy or post-therapy transient elastography (TE) were excluded. FibroScan was used for all TE measurements.

**RESULTS:** 105 patients met study criteria and were included. Mean age was 58±8.3 years and 71 (68%) were male. 95 (90%) patients had genotype (GT) 1 (1a – 57, 1b – 33, unknown – 5). 63 (60%) received LDV/SOF based regimens, while 17 (16%) and 16 (15%) received SOF/VEL and PrOD based
Spatial analysis of HCV infection in British Columbia, Canada

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BACKGROUND: ‘Core areas’ of transmission for bacterial sexually transmitted infections have been described previously; however, research on characterizing core areas for chronic viral infections such as hepatitis C virus (HCV) is limited.

PURPOSE: We aimed to identify distinct core areas of HCV infection in British Columbia, Canada during 1990-2013 using geographic mapping and spatial analysis methods.

METHODS: The British Columbia Hepatitis Testers Cohort was used to estimate HCV rates for all BC residents tested for HCV or HIV (~1.5 million) from 1990 to 2013. HCV core areas were identified both spatially and temporally for five time periods (1990-1993, 1994-1998, 1999-2003, 2004-2008 and 2009-2013) by conducting thematic mapping, kernel density estimation, hotspot analysis and cluster analysis (discrete Poisson) at the Census dissemination area level (smallest geographic area for which data were available) in ArcGIS and SatScan (1-5).

RESULTS: All spatial analytic methods showed consistency in identifying HCV core areas. 1) KDE showed core area expansion from the downtown of major cities in Metro Vancouver (MV), Vancouver Island, and Northern BC during 1990 to 1998, to smaller cities in MV and Interior BC from 2000 onward. 2) HSA showed statistically significant hot spots in MV (Vancouver downtown), Northern BC (Prince George) and Vancouver Island from 1990 to 2008 with expansion to other urban areas in MV (Surrey and Abbotsford) from 1990 to 2013. 3) Spatiotemporal cluster analysis (adjusted for injection drug use, HCV testing, age group, sex, material and social deprivation) revealed a persistent most likely cluster in MV (Vancouver downtown) from 1990 to 2008 with secondary clusters in urban areas in Northern and Interior BC. A secondary cluster was observed for Vancouver Island from 1990 to 2003. Recently (2009-13), the most likely cluster was observed in Northern BC (Prince George) with a secondary cluster in MV (Vancouver).

CONCLUSIONS: Persistence of areas with high HCV rates in same geographic areas of Vancouver regimens, respectively. Remaining 9 (9%) received SOF/SIM or SOF/RBV.

After a median follow-up of 34 (range 12–70) weeks post-therapy, there was significant reduction in TE (p=0.016) (see Table 1 below).

Of 53 patients with F3/4 fibrosis, after a median follow-up of 34 (range 12–58) weeks, the TE scores improved from 21.1±14.0 kPa to 15.0±11.0 kPa (p=0.01). Fibrosis stage was downgraded in 25 (47%) patients.

Of 52 patients with F1/2 fibrosis, after a median follow up of 35 (range 12–70) weeks, the TE scores improved from 6.3±1.8 kPa to 5.2±1.6 kPa (p

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and Prince George over past two decades suggest that these are most likely core areas of HCV transmission. Other clusters were identified but were not consistent across all methods and time-frames suggesting they could be outbreak areas or areas with higher transmission activity than other geographic areas. Identification of core areas can assist in targeting interventions to these areas and can help evaluate the impact of programs and interventions over time.

Patterns of practice and barriers to care for hepatitis C in the direct-acting antiviral (DAA) era: a cross-sectional national survey of Canadian physicians

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BACKGROUND: DAA therapy for hepatitis C virus (HCV) infection provides an opportunity to decrease the burden of liver disease in Canada. However, of the 250,000 Canadians with chronic HCV, few have been treated (1). Several health system-related, patient-related, and physician-related barriers to care impede treatment scale up. Physician-related barriers include suboptimal training (2–3), negative attitudes towards treating high risk populations (4), and uneven application of clinical practice guidelines (5).

Infectious diseases (ID) physicians, having experience treating other chronic viral infections such as HIV, represent a physician group important to HCV care delivery in Canada. However, little is known regarding their HCV-related practices. Many may feel unprepared to treat HCV (2). Therefore, improving ID physician engagement in HCV care will be important for treating more HCV-infected patients in Canada.

PURPOSE: To better identify areas in need of physician support or education, and to identify challenges that physicians are facing in the current era, our study aims to investigate the current patterns of practice and perceived barriers to HCV care that Canadian physicians face. We plan to survey general internists, ID physicians, hepatologists, gastroenterologists, and addiction medicine specialists to identify current practice patterns, interest in engaging in care, and factors associated with barriers to care. Herein, we describe our survey of ID physicians.

METHOD: The study population includes ID physicians who are members of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada, the national association representing medical microbiology and infectious diseases physicians. We selected a simple random sample of 30 members within each province. For provinces with fewer than 30 members, we included all members. This resulted in a total sample size of 167 potential respondents. We will deliver a one-time, web-based, response-guided survey. Questions relate to demographics, practice patterns, knowledge, attitudes toward treatment, and barriers to care. To encourage response, we will provide two weekly reminders after the initial invitation, and monetary compensation to each respondent.

RESULTS: Our primary outcome of interest is current level of HCV care provided, ranging to include no care, testing, evaluating, referring, and treating. The secondary outcome is respondent interest in starting to treat HCV in the upcoming year. We will report these findings along with barriers to care identified by respondents, such as suboptimal training or poor access to specialist support.

CONCLUSIONS: HCV therapies have improved dramatically, but treatment rates are low. Our study provides data on the status of HCV care provided by ID physicians, their interest in scaling up treatment, and barriers to doing so. This will help us develop ways to support Canadian ID physicians, and improve the quality of HCV care.

REFERENCES
Characterisation of the role of cyclophilin A in innate immune responses during HCV infection

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BACKGROUND: Cyclophilin A (CypA) is a key player in several viral infections. For example, the capsid of HIV-1 binds CypA to help cloak itself from pattern recognition receptors and evade innate immune responses in macrophages (1). Treatment of HIV-1-infected macrophages with cyclophilin inhibitors (Cypls) elicits interferon (IFN)-β production and suppresses HIV-1 replication. Interestingly, a Cypl (SCY-635) that was evaluated in a phase 1b clinical trial for chronic HCV infection suppressed HCV replication and led to an increase in endogenous IFN levels in patients (2). Cypls have been shown to disrupt formation of the membranous web (3), the virus-induced membrane rearrangements thought to cloak HCV replication intermediates from pattern recognition receptors. Furthermore, CypA was recently shown to regulate the activation of innate antiviral RNA sensing pathways (e.g. RIG-I) (4). These findings suggest a link between CypA and innate immune responses during HCV infection, although the mechanisms are unclear.

PURPOSE: To dissect the role of CypA in innate immune responses during HCV infection.

METHOD: We are employing chemical biology (using a panel of novel Cypls that are either non-immunosuppressive derivatives of cyclosporin A or unrelated synthetic small molecules) in combination with virological, biochemical and biophysical approaches.

RESULTS: We screened the novel Cypls for antiviral activity against HCV. Huh7.5 cells were pretreated with Cypls prior to infection with HCVcc (Luc-J6/JFH1) and then incubated in the presence of Cypls for 72 hours. HCV infection was measured by luciferase reporter activity. Several of the novel Cypls were active at nanomolar or low micromolar concentrations, exhibiting strong antiviral activity against HCV without immunosuppressive effects. Antiviral activity correlated with the binding affinity of the Cypl for CypA (i.e., molecules lacking HCV antiviral activity did not bind to CypA), supporting the specific role of CypA in HCV infection. The active Cypls were more potent against full-length HCVcc than subgenomic replicons, consistent with the involvement of innate immune responses (which target multiple steps of the viral life cycle). Furthermore, the active Cypls were 5- to 10-fold more potent in Huh7 cells (where RIG-I is functional) than in Huh7.5 cells (where RIG-I is defective).

CONCLUSIONS: We have identified novel Cypls with potent anti-HCV activity, which we are currently using in mechanistic studies aimed at elucidating the role of CypA in innate immune sensing of HCV. Our findings may contribute to the development of complementary treatment strategies for HCV. Furthermore, they may open perspectives for novel immunomodulatory antiviral approaches against other medically important viruses that rely on CypA as a host factor and for which curative treatment strategies are lacking (e.g., hepatitis B virus, Dengue virus, Zika virus).

REFERENCES

Paritaprevir/ritonavir/ombitasvir, dasabuvir + ribavirin in people with HCV genotype 1 and recent injecting drug use or receiving OST: The D3FEAT study

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Cunningham, UNSW Sydney; Edward Gane, Auckland Clinical Studies; Catherine Stedman, Christchurch Hospital and University of Otago; Curtis Cooper, U Ottawa; Erika Castro, Centre Hospitalier Universitaire Vaudois; Patrick Schmid, Kantonsspital St Gallen; Kathy Petoumenos, Kirby Institute, UNSW Sydney; Behzad Hajarizadeh, The Kirby Institute; Marks Philippa, The Kirby Institute; Amanda Erratt, The Kirby Institute, UNSW Sydney; Sharmila Siriragavan, The Kirby Institute; Olav Dalgard, Akershus University Hospital; Karine Lacombe, Hôpital Saint-Antoine; Jordan Feld, Toronto Centre for Liver Disease; Julie Bruneau, CRCHUM; Jean-Pierre Daulouede, Csapa Bizia; Jeff Powis, South Riverdale Community Health Centre; Philip Bruggmann, Arud Centres for Addiction Medicine; Gail Matthews, The Kirby Institute, UNSW Sydney; Ian Kronberg, Footscray Hospital; David Shaw, Royal Adelaide Hospital, Adelaide; Adrian Dunlop, Newcastle Pharmacotherapy Service; Tanya Applegate, The Kirby Institute, UNSW Sydney; Sione Crawford, Hepatitis Victoria; Gregory J Dore, The Kirby Institute

BACKGROUND: Direct-acting antiviral therapy is safe and effective in people with HCV receiving opioid substitution therapy (OST), but there are little data among people with recent injecting drug use (IDU).

PURPOSE: The aim of this study was to evaluate the efficacy, and safety of paritaprevir/ritonavir, ombitasvir, dasabuvir with or without ribavirin for chronic HCV genotype (G) 1 among people with recent IDU and/or receiving OST.

METHODS: D3FEAT is an international open-label study that recruited untreated participants with recent IDU (past 6 months) and chronic HCV G1 infection between June 2016 and February 2017 in seven countries. Participants received paritaprevir/ritonavir, ombitasvir, dasabuvir with (G1a) or without ribavirin (G1b) administered twice daily in a one-week electronic blister pack (records timing of each dose) for 12 weeks. The primary endpoint was undetectable HCV RNA 12 weeks post-treatment (SVR12). Modified intent-to-treat analyses was calculated excluding those lost to follow-up and/or not achieving SVR for reasons unrelated to HCV infection or its treatment.

RESULTS: Among 87 participants (mean age 48; 26% female; 8% with cirrhosis, 90% G1a), 21% were not receiving OST and had recent IDU, 43% were receiving OST with no recent IDU and 37% were receiving OST and had recent IDU. Overall, 94% (82/87) completed 12 weeks of therapy and 97% (84/87) had undetectable HCV RNA at the end of treatment (ETR), including 96% (75/78) and 100% (9/9) in those with HCV G1a and G1b, respectively. ETR was similar in those with and without recent IDU prior to screening (96% vs. 97%, P = 0.743). SVR was 91% (79/87). In modified intent-to-treat analyses excluding those lost to follow-up between ETR and SVR (n=3), SVR was 94% (79/84). There were no virological failures and two cases of virologic recurrence (phylogenetic analysis pending to confirm reinfection vs. relapse).

CONCLUSIONS: Paritaprevir/ritonavir/ombitasvir, dasabuvir with or without ribavirin for 12 weeks is effective among people with HCV genotype 1 with recent IDU and/or receiving OST.

Influence of ribavirin on metabolic measures in paritaprevir-ombitasvir-dasabuvir hepatitis C antiviral treatment recipients

Curtis Cooper, U Ottawa; Chrissi Galanakis, Ottawa Hospital Research Institute; Mary-Anne Doyle, The Ottawa Hospital; Angela Crawley, Ottawa Hospital Research Institute

BACKGROUND: Chronic HCV infection perturbs lipid and glucose metabolism. The influence of HCV cure as well as DAA and ribavirin (RBV) exposure on these measures is unclear.

METHODS: HOMA-IR, glucose and lipid metabolic measures were assessed from baseline at week 4, week 12 and 12 weeks post-treatment. Pre- and post-treatment transient elastography were performed. The measures were compared between RBV-free and RBV-containing regimens using t-tests at a significance level of p < 0.05.

RESULTS: 22/24 (92%) patients completed treatment and achieved SVR (PP= 22/23, 96% SVR). Two patients were lost to follow-up at week 12 with one of the latter having detectable virus at the end of treatment. HbA1c decreased during treatment in
BACKGROUND: Fibrosis regresses following direct acting antivirals (DAA) treatment in non-cirrhotic HCV-infected patients. Fibrosis regression has also been noted in cirrhotics, though the extent to which regression occurs in advanced cirrhosis is unclear.

METHODS: We examined fibrosis regression in HCV infected patients with cirrhosis treated with interferon-free DAA. Fibrosis was measured by Fibroscan® Transient Elastography (TE). We compared changes in fibrosis scores pre- and post-treatment in patients with early and advanced cirrhosis. Early cirrhosis was defined as 12.5–19.9 kPa and advanced cirrhosis 20.0 kPa or more. Changes from baseline were measured by chi-square and t-tests at a p < 0.05 significance level. Mid-P exact tests were used for cells with less than five patients.

RESULTS: 43 cirrhotic patients were included. Patients were male (72%) with a mean age of 59 years (SD 8.2). The majority were infected with genotype 1 (74%), treatment naïve (51%) and 25 (58%) were defined as advanced cirrhotics. Patients were mainly treated with Sofosbuvir/Ledipasvir ±Ribo-virin (RBV) (42%) and Simeprevir + Sofosbuvir ± RBV (26%). 38/43 (88%) achieved SVR. Post-treatment Fibroscans were performed a mean of 33 weeks (SD 24.3) after treatment end. Median pre-treatment fibrosis score was 21.8 kPa (IQR 19.2) and the median change from pre- to post-treatment was -6.0 kPa (IQR 10.2). The overall mean fibrosis score decreased (mean change ± SD: -6.7 kPa, SD 10.7, p < 0.0001).15/43 (36%) of patients regressed to a non-cirrhotic range by TE following DAA treatment. Patients with early cirrhosis were more likely to regress to a non-cirrhotic TE range compared to those with advanced cirrhosis (56% early vs. 20% advanced, p=0.02). Patients with early cirrhosis were also more likely to have a lower Metavir score post-treatment compared to patients with advanced cirrhosis among HCV genotype 1 infections (60% early vs. 24% advanced, p=0.04) and among treatment naïve patients (60% early vs. 17% advanced, p=0.05). Despite not regressing to non-cirrhotic range, patients with advanced cirrhosis achieved fibrosis regression as well (mean change -10.9kpa, SD 10.7, p < 0.0001).

CONCLUSIONS: Patients with early and advanced cirrhosis exhibit fibrosis regression with DAA treatment with a more significant decrease in the RBV-containing group (week 4: mean change ± SD RBV-containing -0.89 ± 0.56 vs -0.21 ± 0.25, p=0.01), (week 12: RBV-containing -1.3 ± 0.41 vs -0.08 ± 0.28, p < 0.0001). However, this likely primarily represents a RBV-induced anemia effect and not a true decline in HbA1c. These improvements were not sustained 12 weeks post-treatment where the HbA1c in the RBV-containing group had increased from baseline while RBV-free regimen was associated with a further decrease (mean change ± SD RBV-containing 0.14 ± 2.2 vs -0.18 ± 0.29, p=0.03). No differences were observed in HOMA-IR, glucose and insulin during or 12 weeks post-treatment. LDL-C, non-HDL-C and TC: HDL-C levels increased less during treatment with RBV-containing regimens compared with RBV-free regimens (week 12 mean change ± SD: LDL-C RBV-containing 0.09± 0.59 vs 0.78± 0.93, p=0.04, non-HDL-C 0.09± 0.63 versus 0.89 ±1.0, p=0.03, TC:HDLC -0.04±0.61 vs 1.2±1.4, p=0.01). There was no difference in mean changes in lipid levels 12 weeks post-treatment compared with baseline in either group. Overall fibrosis scores decreased (mean change ± SD: -0.49 ± 5.9) at 12 weeks post-treatment compared to the screening visit. This did not differ among RBV groups (p=0.84) and cirrhosis status (p=0.85). At 12 weeks post treatment, CAP scores increased (29.2 ± 64.6) compared to screening. CAP scores increased in both RBV-free and containing groups (31 ± 71.1 and 25 ± 55.1, p=0.90) and in cirrhotic and non-cirrhotic patients (25 ± 84.5 and 31 ± 57.5, p=0.91), though no significant differences were observed among the groups.

CONCLUSION: Eradication of HCV with RBV-containing regimens resulted in an earlier and more significant decrease in HbA1c yet slower and less pronounced increase in cholesterol levels compared with RBV-free regimens during the treatment phase. Further studies are needed to understand the mechanism by which ribavarin impacts glucose and lipid pathways and the long term significance of these differences.

Cirrhosis regression with DAA treatment in early and advanced cirrhosis

Curtis Cooper, U Ottawa; Chrissi Galanakis, Ottawa Hospital Research Institute
Effects of direct acting antiviral HCV treatment on lactate and glucose patterns
Curtis Cooper, U Ottawa; Chrissi Galanakis, Ottawa Hospital Research Institute; Matt Driedger, University of Ottawa

BACKGROUND: Metabolic function may be influenced by HCV infection, cirrhosis, Direct Acting Antivirals (DAA) and ribavirin (RBV). We explored patterns of lactate and random glucose in DAA+/RBV treated patients with chronic HCV infection.

METHODS: All HCV infected patients treated with interferon-free DAAAs with available lactate and glucose data were included. Lactate and random glucose were evaluated at baseline, week 4, end of treatment and 12–24 weeks post-treatment. Group-based trajectory modeling was used to identify the number of lactate and glucose trajectories. Model selection was based on the Bayes Information Criterion (BIC). The posterior probability of group membership for each trajectory ranged from 0–1. Factors determining the probability of group membership were assessed by multivariate linear regression analysis.

RESULTS: 442 patients received 457 DAA treatments. Patients were male (65%) with a mean age of 56 (SD9.5). Patients were infected with genotype 1 (72%) and 47% were cirrhotic. Treatments consisted of SOF/LDV ± RBV (55%) and 40% contained RBV. 162 patients had available lactate data. Mean baseline lactate was 2.3mmol/L (SD0.67). The 2-group trajectory model best fit the data (BIC -600.74). 93 patients (57%) were assigned to group 1 (declining lactate over the course of treatment and post-treatment), while 69 (43%) patients were in group 2 (increasing lactate on treatment followed by a post-treatment decline in lactate). Cirrhosis predicted 16% greater probability of membership to the group 1 trajectory (B=0.16, 95%CI 0.06–0.27, p 0.05).

CONCLUSION: Distinct lactate and glucose trajectories were identified. Most patients had declining lactate values while those on RBV and with elevated baseline lactate experienced an increase in lactate during treatment. Random glucose is mostly unchanged during DAA treatment and elevated glucose at baseline tends to normalize post-treatment.

Dissecting the role of the poly(C)-binding protein 2 KH domains in the hepatitis C virus life cycle
Sophie Cousineau, McGill University; Selena Sagan, McGill University

BACKGROUND: The hepatitis C virus (HCV) uses a number of cellular elements - including proteins and microRNAs - to promote its own replication and to protect itself from cellular molecular defenses against viruses. One particular cellular RNA-binding protein, the poly(C)-binding protein 2 (PCBP2), is known to mediate the stability and expression of a number of cellular transcripts, and is also known to be co-opted by several positive-strand RNA viruses to promote their replication. Six PCBP2 binding sites have been identified on the HCV genome, including in areas of the 5’ and 3’ untranslated regions which are known to play important roles in HCV translation and RNA replication. However, the exact mechanism by which PCBP2 affects HCV replication still remains to be elucidated.

AIMS: We aim to identify the specific step(s) of viral replication that are affected by PCBP2, and the specific PCBP2 RNA binding domains (called K homologous domains, or KH domains) involved in these interactions.

METHODS: We Are Using The Hcv Cell Culture System (Specifically The Jfh-1T Viral Strain And The Huh-7.5 Cell Line) To Assess How Viral Protein Synthesis, Viral Rna Accumulation, And The Production Of Infectious Viral Particles Is Affected By Sirna-Mediated Knockdown Of Pcbp2 Or The Overexpression Of A Flag-Tagged Pcbp2 Construct. We Have Generated Flag-Tagged Constructs With Mutations In Each Pcbp2 Kh Domain, Which
We Will Use To Identify The Domains Whose Rna-Binding Activity Is Crucial For Pcbp2’S Role In The Viral Life Cycle. We Are Also Using Luciferase Assay Systems To Investigate The Effect Of Pcbp2 On Viral Ires-Mediated Translation Independently Of Hcv Rna Accumulation, And A Chimeric Viral Construct Where Hcv Protein Expression Is Driven By A Pcbp2-Independent Emcv Ires To Assess How Pcbp2 Affects Viral Rna Replication And Accumulation.

RESULTS: We have found that knocking down endogenous PCBP2 inhibits HCV protein expression, RNA accumulation, and infectious particle production—which can all be partially rescued by the expression of wild type PCBP2-FLAG. Our preliminary results show that while the KH3 domain mutant construct is also able to partially rescue HCV replication, the KH1 and KH2 domain mutants are unable to rescue viral RNA accumulation and infectious particle production. Our luciferase assay results suggest that PCBP2 is important - but not limiting - for HCV IRES-mediated translation. We will present preliminary results that examine if PCBP2 has an effect on viral RNA stability and replication.

CONCLUSIONS: We anticipate that investigating PCBP2-HCV interactions will help clarify the role of this host protein in the viral life cycle, and will provide a model for the regulation of viral RNA accumulation, and/or the switch from translation to replication.

Efficacy and adherence to sofosbuvir and velpatasvir among people with chronic hepatitis C virus infection and recent injection drug use: the SIMPLIFY study

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Edward Gane, Auckland Clinical Studies; Chris Fraser, The Cool Aid Community Health Centre; Behzad Hajarizadeh, The Kirby Institute; Marks Philippa, The Kirby Institute; Quiene Sophie, The Kirby Institute; Sharmila Siriragavan, The Kirby Institute; Melanie Lalcalanita, Poliklinik für Infektiologie; Gregory J Dore, The Kirby Institute; Jason Grebely, Kirby Institute, UNSW Sydney

BACKGROUND: Interferon-free direct-acting antiviral therapy (DAA) is safe and effective in people with hepatitis C virus (HCV) receiving stable opioid substitution therapy (OST), but there are little data among recent people who inject drugs (PWID). Improved evidence of DAA outcomes among recent PWID is crucial for elimination efforts, given the potential impact of HCV treatment as prevention.

PURPOSE: The aim of this study was to evaluate the efficacy and adherence to sofosbuvir and velpatasvir therapy for chronic HCV among recent PWID.

METHODS: SIMPLIFY is an international open-label study that recruited participants with recent injecting drug use (previous six months) and chronic HCV genotype (G) 1–6 infection between March and October, 2016 in seven countries (19 sites). Participants received sofosbuvir/velpatasvir daily administered in a one-week electronic blister pack (records the time and date of each dose) for 12 weeks. Adherence was calculated by dividing the number of total doses removed from the blister-pack (to a maximum of one per day) by the total number of expected doses (84 doses). The primary endpoints included sustained virological response at 12 weeks (SVR) after the end of therapy and non-adherence ( daily in the past month. A total of 96% (n=99) of the population completed treatment with four early discontinuations (loss to follow-up, n=3; overdose death, n=1). End of treatment response (ETR) was 96% (99/103). Two participants with an ETR did not have SVR12 (loss to follow-up, n=1; re-infection, n=1). In intent-to-treat analyses among all participants, SVR12 was 94% (97/103). Median adherence to therapy was 94%, although 88% missed at least one dose of therapy and adherence significantly decreased during therapy. Recent injecting of cocaine/amphetamines at treatment initiation and during treatment was associated with non-adherence. Inconsistent dose timing was also associated
with non-adherence to therapy. Non-adherence did not impact sustained virological response.

**CONCLUSION:** This study demonstrated high rates of SVR and high adherence to once-daily sofosbuvir/velpatasvir therapy among a population of people with recent injecting drug use. Despite imperfect adherence to therapy, there was no impact of non-adherence on response to therapy, suggesting that adherence is not a barrier to successful DAA therapy in PWID. These data support the inclusion of people with recent injecting drug use in HCV treatment strategies.

**Real-world effectiveness of sofosbuvir-based regimens for treatment of hepatitis C genotypes 1–3: BC Hepatitis Testers Cohort (BC-HTC)**

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**BACKGROUND:** To assess the effectiveness of ledipasvir/sofosbuvir (LDV/SOF), ledipasvir/sofosbuvir/ribavirin (LDV/SOF/RBV), and sofosbuvir/peg-interferon/ribavirin (SOF/PEG/RBV) for genotype 1 (GT1) and sofosbuvir/ribavirin (SOF/RBV) and SOF/PEG/RBV for genotype 2 (GT2) and 3 (GT3) in routine medical practice using a large population based Canadian cohort.

**METHODS:** The British Columbia Hepatitis Testers Cohort (BC-HTC) includes individuals tested for HCV (~1.7 million) between 1990–2016 linked with data on medical visits, hospitalizations, cancers, prescription drugs and mortality. HCV patients who were prescribed LDV/SOF, LDV/SOF/RBV, and SOF/PEG/RBV for GT1 and SOF/RBV and SOF/PEG/RBV for GT2 and GT3 until December 31, 2016 were included in the study. Outcome was sustained virological response (SVR) assessed at 12 weeks post treatment based on the intention to treat approach. Logistic regression was used to identify factors that were associated with SVR.

**RESULTS:** Among GT1 patients, 1834, 28 and 75 individuals initiated LDV/SOF, LDV/SOF/RBV, and SOF/PEG/RBV, respectively. 170 and 16 GT2 patients and 294 and 53 GT3 patients initiated SOF/RBV and SOF/PEG/RBV, respectively. The overall SVR rate among patients in GT1 treated with LDV/SOF, LDV/SOF/RBV, and SOF/PEG/RBV was 93.7%, 96.47%, and 85.4%, respectively. The overall SVR rate among SOF/RBV and SOF/PEG/RBV treated patients in GT2 was 93.5% and 81.2%, respectively. The overall SVR rate among SOF/RBV and SOF/PEG/RBV treated patients in GT3 was 80.9% and 90.6%, respectively.

In the multivariable model for GT1 and LDV/SOF regimen, male gender (SVR: 92.3% vs 96.5%; OR: 0.43; 95% CI 0.26–0.71), cirrhosis (SVR: 88.8% vs 94.6%; OR: 0.46; 95% CI 0.28–0.77), and treatment duration of less than 8 weeks (SVR: 62.9% vs. 94.5%; OR: 0.09; 95% CI 0.04–0.21); and for SOF/PEG+RBV regimen, treatment duration 24 weeks (SVR: 68.7% vs 89.8%; OR: 0.02; 95% CI 0.00–0.42) were significantly associated with lower SVR rate. In SOF+RBV treated patients with GT2, treatment duration of less than 12 weeks (SVR: 33.3% vs. 94.5% OR: 0.02; 95% CI 0.00–0.43) and previous HCV treatment (SVR: 85.1% vs. 96.7%; OR: 0.22; 95% CI 0.05–0.94) and with GT3, male gender (SVR: 75.7% vs. 88.9% OR: 0.33; 95% CI 0.16–0.69) and HCV-RNA of 243860–989317 (IU/ml) (SVR: 67.1% vs. 86.4% OR: 0.29; 95% CI 0.13–0.65) were significantly associated with lower SVR.

**CONCLUSION:** In this real-world cohort, high SVR rates with LDV/SOF ± RBV among GT1 infected patients and lower SVR with SOF/RBV and SOF/PEG/RBV among GT1, GT2 and GT3 are similar to the data reported from clinical trials and other real-world cohorts. Male gender, presence of cirrhosis, and treatment duration mainly less than 12 weeks were significant negative predictors of SVR. These data confirm the high effectiveness of LDV/SOF regimens among GT1 patients in a real-world
setting, and highlight the sub-optimal SVR of SOF/RBV and SOF/PEG/RBV for GT1, GT2, and GT3.

Real world implications of hepatitis C infection and treatment in Nova Scotia
Siena Davis, Mount Allison University; Lisa Barrett, Dalhousie University

BACKGROUND: Direct-acting antiviral (DAA) medications have been shown to be very effective at curing hepatitis C virus (HCV) in clinical trials. However, these studies typically include highly adherent populations. Many of these trials have also excluded individuals who have comorbidities affecting the efficacy of the DAA medications (eg. HIV co-infection), or who are a member of a vulnerable population (eg. intravenous drug users).

PURPOSE: In order to determine the efficacy of DAA medications within Nova Scotia, the results of HCV treatment from different groups of individuals infected with HCV must be examined. This information may be used to determine sustained viral response (SVR) rates with DAA medications, as well as to view qualitative trends within the population. These findings may be used to inform policy on funding for these medications and update the model of care for HCV in Nova Scotia. The primary outcome of this project was to evaluate the rates of SVR in the population. The secondary outcomes were to investigate trends in demographics of this HCV population.

METHOD: Information was collected from the medical charts of 258 individuals who were seen at the infectious diseases clinic of the Queen Elizabeth II Health Sciences Center (QEII HSC) in Nova Scotia from 2011 until 2017 for HCV care. A database was compiled and analyzed in order to view SVR rates among subpopulations and summarize demographics of the HCV population.

RESULTS: Overall, DAA treatments were more effective than previous interferon-based treatment regimens (SVR 87% vs. 78%), along with less relapsed or failed treatment outcomes. People who inject drugs (PWID) currently or in the past had 83% SVR compared to those who never used intravenous drugs (86%). Those co-infected with HIV had a lower SVR compared to those without (79% vs. 98%). Treatment-experienced individuals had a higher SVR compared to those that were treatment naïve (100% vs. 85%). HCV genotype 1(1a in particular) was most common, followed by genotype 3a. There was a wide range of liver fibrosis scores (F0 to F4). The most common age demographic was between 25 and 34 years, followed by ages 55–64, and the cohort was primarily male (69% vs. 31% female). Most individuals (71%) were previous PWID, with only 9% currently injecting drugs. HIV co-infection was present in 17% of the population.

CONCLUSIONS: The database of HCV patients seen in the infectious disease clinic at the QEII HSC demonstrates that the outcomes of DAA treatment were very successful for all groups of individuals including PWID, those co-infected with HIV and people who had previous HCV treatment. These trends may be used to inform new policy and update the model of care in Nova Scotia to work towards HCV eradication in the future.

Identifying patients subgroups who benefit most from immediate vs. delayed treatment for chronic hepatitis C
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BACKGROUND: Recently introduced direct-acting antivirals (DAA) are highly effective but costly treatments for chronic hepatitis (CHC). Because of their cost, drug plans have restricted access to DAA therapy based on fibrosis level.

PURPOSE: To identify patient subgroups most likely to benefit from immediate treatment vs. delaying treatment by 1 year.
METHOD: A decision-analytic state-transition model with a weekly cycle length was developed to quantify the effects of a 1-year delay in DAA therapy on quality-adjusted life years (QALY) of CHC patient subgroups stratified by age, fibrosis level and viral genotype over their lifetime. The model assumed that patients would receive a Sofosbuvir-based DAA regimen depending on their fibrosis level and genotype as recommended by Canadian guidelines. Stage-specific fibrosis progression rates were estimated for each subgroup using a meta-regression model considering mean age, sex, duration of infection, genotype, alcohol and injection drug use behavior. All other clinical parameters were obtained from published literature. QALY gains associated with immediate vs. delayed treatment for each subgroup was determined and stratified into four levels of benefit. Results are displayed using a look-up table.

RESULTS: On average, 30-year-old patients infected with genotypes 2 or 3 with significant fibrosis (F3) obtained the greatest benefit from immediate vs. delayed DAA therapy (>1.00 QALYs). This was followed by cirrhotic patients younger than 60 years, who also displayed a large benefit (0.50–0.97 QALYs). All other groups had only a small or questionable benefit. More specifically, 40–50 year old genotype-1 patients with significant fibrosis, as well as 60 year-olds with at least significant fibrosis, displayed only a small benefit (0.20–0.45 QALYs) from immediate vs. delayed therapy. Individuals with no or mild fibrosis (F0 or F1) and those 70+ years of age with any level of fibrosis experienced no material gains from immediate treatment (0.05–0.18 QALYs). The relatively greater benefit of immediate treatment for certain groups with significant fibrosis are likely driven by a faster progression from F3 to F4 in younger patients and in those with non-genotype-1 infections, as well as by the higher sustained viral response rates for non-cirrhotic vs. cirrhotic patient.

CONCLUSION: The current study presents estimates of benefit of immediate vs. 1-year delay in DAA therapy for various patient subgroups considering the effects of patient’s age, disease severity and genotype on the natural history of CHC and on DAA treatment choice and outcomes. Results suggest that younger patients with more advanced fibrosis (≥F3) will benefit the most from earlier access to treatment while those with F0-F1 and older patients realize smaller benefit. Results are congruent with current reimbursement criteria focusing on prioritizing more advanced patients.

HBV RNA predictive role for treatment outcomes in HBeAg negative chronic hepatitis B patients treated with PEG-IFN

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BACKGROUND AND AIMS: Hepatitis B RNA (HBV RNA) is a novel serum biomarker that is a direct transcriptional product of cccDNA to form a mature genomic DNA. In recent studies HBVRNA has been associated with HBV DNA and qHBsAg and response in patients during therapy.

We aimed to study the early changes of HBV RNA in PEG-IFN treatment in HBeAg negative patients and to investigate the role of HBV RNA as a response predictor to optimize this treatment.

METHOD: HBV RNA levels were measured in stored serum samples of 133 HBeAg-negative chronic at week 0 (baseline), 12, 24 and 48 (end of treatment) and week 72 (end of follow up) using a RACE-PCR technique (LLQ 800 c/mL). HBV patients were treated in an international randomized controlled multicenter trial (PARC study). Patients received peginterferon a-2a 180 mcg/week +/- ribavirin 1000–1200 mg daily for 48 weeks. All patients were followed until week 72. Response was defined as a combined endpoint HBV DNA level below 2000IU/ml and normalization of ALT at the end of follow up.

RESULTS: The mean age was 42.21 (SD 11) years, 98 (73.7%) were male, and HBV genotype distribution was 17/1/3/80% for genotype A/B/C/D. The mean HBV RNA at baseline was 3.96 (1.4) log10 c/mL and HBV RNA was <LLQ in 28 (23%) patients. No difference in response was found
between patients with or without ribavirin and patients were thus pooled for further analyses.

At 12 and 24 weeks, mean HBV RNA had declined to 2.3 (1.0) and 2.2 (1.1) log c/mL respectively, and HBV RNA was <LLQ in 95 (83%) and 99 (84%) patients at these time points. At the end of follow up, 24 patients (23%) achieved a response. HBV RNA in the responders showed a marked decline compared to the non-responders (AUC at weeks 12 and 24= 0.61 and 0.64 respectively). None of the patients at week 12 and 24 (n=18 and 17 respectively) who exhibited an HBV RNA level above 1500 c/ml (3.18 log10 c/mL) showed a combined response at end of follow up (P= 0.01 and 0.02 respectively).

**RESULTS:** 2406 individuals were identified amongst the 47 clinics who were screened for HCV infection. 527 (21.9%) individuals tested positive for anti-HCV Ab. Those who screened positive for HCV were 32.6% more likely to significantly alter their substance-use behaviors (aOR=1.326; CI95% = 1.08–1.63; p=0.008) and reduce their consumption of non-prescribed opioids according to urine toxicology after the anti-HCV Ab screening when compared to when their HCV-Ab status was not clear. Patients who were diagnosed with HCV infection subsequently had a significantly lower proportion of positive urine drug screens, including non-prescribed opioids (aOR=1.346), benzodiazepines (aOR=1.545), and cocaine (aOR=1.551).

**CONCLUSION:** We have demonstrated that HCV infection screening can have a positive impact on substance-use behaviors among patients engaged in OAT in decreasing their substance use. Expansion and universal screening of OST clients for HCV infection should be encouraged.

**The impact of hepatitis C diagnosis on substance-use behaviors in patients engaged in opioid agonist therapy**

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**BACKGROUND:** Opioid misuse is a public health crisis in many populations. In Canada, the province of Ontario has more than 50,000 opioid-dependent persons who are engaged in opioid agonist therapy (OAT), using mainly methadone and suboxone. Hepatitis C Virus (HCV) infection, with an estimated prevalence of 0.3%-0.9% among all Canadians, is more common in this population. Many experts advocate for testing all OAT patients for chronic HCV infection. To date, the impact of HCV infection diagnosis on the substance use behaviors of OAT patients is unknown. and we aim to explore that here.

**PURPOSE:** To explore the impact of hepatitis C diagnosis on substance use behavior while on opioid agonist therapy

**METHODS:** We conducted a retrospective cohort analysis using the electronic health data, urine toxicology and antibody-based HCV infection screening information from a network of 47 addiction treatment clinics in Ontario from 2007 to 2013. We used a logistic regression analysis determine the impact of HCV infection diagnosis on substance-use behaviors for patients engaged in OAT.

**RESULTS:** 2406 individuals were identified amongst the 47 clinics who were screened for HCV infection. 527 (21.9%) individuals tested positive for anti-HCV Ab. Those who screened positive for HCV were 32.6% more likely to significantly alter their substance-use behaviors (aOR=1.326; CI95% = 1.08–1.63; p=0.008) and reduce their consumption of non-prescribed opioids according to urine toxicology after the anti-HCV Ab screening when compared to when their HCV-Ab status was not clear. Patients who were diagnosed with HCV infection subsequently had a significantly lower proportion of positive urine drug screens, including non-prescribed opioids (aOR=1.346), benzodiazepines (aOR=1.545), and cocaine (aOR=1.551).

**CONCLUSION:** We have demonstrated that HCV infection screening can have a positive impact on substance-use behaviors among patients engaged in OAT in decreasing their substance use. Expansion and universal screening of OST clients for HCV infection should be encouraged.

**Global, regional, and country-level estimates of viraemic hepatitis C virus infection among recent people who inject drugs: A systematic review**

Jason Grebely, Kirby Institute, UNSW Sydney; Sarah Larney, National Drug and Alcohol Research Centre, UNSW Sydney; Amy Peacock, National Drug and Alcohol Research Centre, UNSW Sydney; Sam Colledge, National Drug and Alcohol Research Centre, UNSW Sydney; Janni Leung, School of Public Health, Faculty of Medicine, University of Queensland; Matthew Hickman, University of Bristol; Peter Vickerman,
University of Bristol; Sarah Blach, Center for Disease Analysis; Evan Cunningham, UNSW Sydney; Konstantin Dumchev, Ukrainian Institute for Public Health Policy; Michael Lynskey, National Addiction Centre, King’s College London; Jack Stone, University of Bristol; Adam Trickey, University of Bristol; Homie Razavi, Center for Disease Analysis; Richard Mattick, National Drug and Alcohol Research Centre, UNSW Sydney; Gregory J Dore, The Kirby Institute; Louise Degenhardt, National Drug and Alcohol Research Centre, UNSW Sydney

BACKGROUND: People who inject drugs (PWID) are a priority population in the response to achieving hepatitis C virus (HCV) elimination. However, recent estimates of viremic HCV among PWID at the global, regional, and country-levels are needed.

PURPOSE: We undertook multiple global systematic reviews to estimate the vireamic prevalence and number of recent (within the past 12 months) PWID with HCV infection, and the proportion of all people with HCV infection who are recent PWID. Estimates were produced at global, regional, and country-levels.

METHODS: Data generated from a systematic review of the global HCV prevalence and country-level disease burden models were combined with systematic reviews of global injecting drug use prevalence and HCV prevalence among recent PWID. Vireamic prevalence among recent PWID, the numbers of recent PWID living with HCV infection, and the proportion of total global infections occurring among recent PWID were estimated.

RESULTS: There are an estimated 6.1 million recent PWID aged 15–64 years living with HCV globally [39.2% prevalence among recent PWID, uncertainty intervals (UI) 31.5–47.0]. People who recently inject drugs comprise an estimated 8.7% (UI 5.2–13.7) of all viraemic HCV infections globally. The number of viraemic HCV infections among recent PWID was greatest in East and Southeast Asia (1.5 million, UI 1.0–2.1), Eastern Europe (1.5 million, UI 0.7–2.4), and North America (1.1 million, UI 0.5–1.8). Half of all viraemic HCV infections among recent PWID are from just four countries: the Russian Federation, the United States, China, and Brazil. The proportion of all viraemic HCV infections among recent PWID was greatest in Latin America (21.7%, UI 16.5–29.1), Eastern Europe (19.0%, UI 9.7–33.2), Australasia (17.8%, UI 13.2–24.6), Caribbean (17.0%, UI 9.1–39.4), and Western Europe (16.7%, UI 9.5–36.6). Countries where it is estimated that at least one-third of people with viraemic HCV are recent PWID include Georgia, Austria, Finland, Germany, Malaysia, Puerto Rico, and Canada. In a further eight countries (Estonia, Slovakia, Denmark, Luxembourg, Iran, Brazil, United States, and New Zealand), at least one-quarter of people with viraemic HCV are estimated to be recent PWID.

CONCLUSIONS: There is considerable variation between countries and regions in HCV viraemia prevalence among recent PWID, and in the proportion of total HCV viraemia that is among recent PWID. This study highlights the need to understand the relative importance of recent PWID in local HCV epidemics, and to tailor prevention and treatment responses to meet global HCV elimination targets.

Establishing a multi-centre prospective observational cohort study to document and analyse the hepatitis C cascade of care among people who inject drugs: the Virtual Cascade of Care cohort (VCCC) study

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BACKGROUND: People who inject drugs (PWID) are the principal group at risk of hepatitis C virus (HCV) infection, with injection drug use estimated to contribute over 60% of total HCV disease
burden in Canada. Advances in treatment suggest that HCV could be eliminated as a public health threat by 2030. However, the combination of high prevalence and low treatment uptake in PWID suggests that this will not be achievable without greatly increased engagement in health services. There is a lack of robust longitudinal data describing the entire HCV cascade of care in PWID, and a need for research to guide treatment scale-up in vulnerable populations.

**CONCLUSION:** VCCC provides a middle ground between cohort studies (which may struggle to retain vulnerable participants) and data linkage methodologies (which rely solely on secondary data), and has the potential to become a rich pan-Canadian data source to study HCV infection and care among a relatively hidden population, hard to capture through traditional clinical cohorts or population-based studies.

**Fibrosis reversal in HCV/HIV co-infected people who inject drugs (PWID) after successful HCV treatment**

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**BACKGROUND:** Hepatitis C (HCV) is a virus that, if left untreated, will cause 5–25% of those infected to develop cirrhosis, hepatic failure or hepatocellular carcinoma, over 20 years or more. Individuals co-infected with HIV have been shown to progress more rapidly, with cirrhosis often developing within 10 years. Recent data suggest that an additional benefit of curing HCV infection may be reversal of fibrosis, but this has not been well documented in the setting of HIV co-infection and active intravenous drug use.

**PURPOSE:** To document reversal of fibrosis after successful HCV treatment in HCV/HIV co-infected people who inject drugs (PWID), to provide additional rationale to expand access to HCV treatment in this population.

**METHOD:** VCCC combines in-person data collection at baseline with ‘virtual’ prospective follow-up through health administrative databases (data linkage). Participants will complete one study visit, comprising a ten-minute questionnaire; rapid HCV antibody testing; and collection of a dried blood spot panel for RNA detection and genotyping. During the visit, permission will be sought to access individual records from clinic, hospital, laboratory and pharmacy visits held in federal and provincial databases. Periodic linkages to this data will inform on multiple outcomes (HCV testing and diagnosis, physician visits, hospitalisations, treatment access, liver and non-liver related comorbidities, cause of death) for the next five years. Baseline data will inform on barriers and facilitators to care not available in health administrative databases (questionnaire) and enable preliminary detection of HCV infection outside a clinical setting (biological testing).

The target population includes people who have ever injected drugs; are vulnerable to unmet healthcare needs; and engage with some community services. HCV-negative (including previously treated) individuals are eligible to participate. Recruitment will take place in community-based harm reduction and addiction services with no linkage to HCV care, and may therefore exclude the most marginalised and/or least vulnerable individuals. Pilot sites will be located in Québec and Alberta with the intention of expanding throughout Canada.

**CONCLUSION:** VCCC provides a middle ground between cohort studies (which may struggle to retain vulnerable participants) and data linkage methodologies (which rely solely on secondary data), and has the potential to become a rich pan-Canadian data source to study HCV infection and care among a relatively hidden population, hard to capture through traditional clinical cohorts or population-based studies.
untreated. Direct acting antiviral drugs are available for the treatment of HCV with success rates of over 90%. But these treatments are expensive and cured patients can still be reinfected. To eliminate HCV, a prophylactic vaccine is needed. One of the major challenges in the development of a vaccine is the genetic diversity of the virus. Currently, there are 7 major genotypes and hundreds of subtypes. A global vaccine needs to be effective against all HCV genotypes. Our laboratory is developing an adjuvanted vaccine comprising recombinant E1/E2 viral envelope glycoprotein and non-structural protein components designed to elicit cross-neutralizing antibodies along with broad cross-reactive T cell responses against HCV. Our previous data shows that our E1/E2 glycoprotein component can elicit broad cross-neutralizing antibodies in humans and animals. However, variation is seen in the effectiveness of these antibodies to neutralize different HCV genotypes. Our vaccine-induced antisera showed strong homologous neutralization activity against genotype 1a H77c virus, while exhibiting significant differences in neutralizing activity against two closely related isolates of HCV genotype 2a, the J6 and JFH-1 strains.

METHODS: E1 and E2 glycoprotein domains were swapped between the resistant J6 and sensitive JFH strains to narrow down the location of this differential neutralization sensitivity. Exchanges of variant amino acids in the E2 glycoprotein of these two HCV genotype 2a viruses were then conducted systematically to determine if specific amino acids were important for conferring this differential neutralization sensitivity. In addition, we investigated the role of the N-terminal hypervariable region 1 (HVR1) of the E2 protein in this isolate-specific neutralization by making recombinant virus with the HVR1 deleted or swapped for the JFH-1 version in the J6 virus. We tested these recombinant viruses for neutralization sensitivity against our 1a E1/E2 antisera.

RESULTS: We have shown that 1) the E2 glycoprotein dictates this differential neutralization sensitivity between these two isolates; 2) isolate specific amino acids within E2 do not affect the differential neutralization sensitivity; but 3) differential neutralization is mediated by the HVR1 and; 4) antibodies in our vaccine antisera are not directly targeting the HVR1 of JFH-1 or J6 2a virus.

RESULTS: There are 91 participants: mean age 48 ± 8.8 years, 74% male, 89% Caucasian, 10% Aboriginal, with documentation of HCV and HIV infection 14 ± 6.7 and 15 ± 8.6 years prior to HCV treatment. Post hoc analysis using the Bonferroni correction revealed significant differences between APRI at baseline, (1.54 ± 1.62, n = 91) and 24 (0.56 ± 0.45, n = 73) and 48 (0.54 ± 0.37, n = 64) weeks post-treatment (p = 0.00). There was no difference between the two latter time points. For patients with baseline cirrhosis pre- and post-treatment APRI scores were baseline (3.65 ± 1.72 n = 19), 24 (1.02 ± 0.58, n = 16) and 48 (0.94 ± 0.48, n = 13) weeks post-treatment, while for patients with genotype 3 infection, these were baseline (1.91 ± 2.07, n = 14), 24 (0.73 ± 0.63, n = 11) and 48 (0.52 ± 0.43, n = 11) weeks post-treatment.

CONCLUSION: Among HIV co-infected PWID successfully treated for HCV infection, a very significant reversal of fibrosis is measured. This correlation can also be seen amongst patients with advanced disease at baseline as well as those with genotype 3 infection (where fatty liver disease may be more prevalent), though sample size did not allow for power calculation. This documents another benefit of HCV therapy in a population at higher risk of long-term disease complications.

Investigation of the molecular mechanisms that determine isolate specific differences in neutralization sensitivity of HCV

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BACKGROUND: It is estimated that there are about 1.75 million new Hepatitis C Virus (HCV) infections per year worldwide and around 20% will develop liver cirrhosis or liver cancer if left untreated. Active PWID (drug use < 6 mo prior to HCV treatment), documented cure of HCV infection, and available liver staging data pre-HCV treatment and 24–48 weeks post-treatment were identified. Liver fibrosis was assessed by APRI scoring.
CONCLUSIONS: While HVR1 can be implicated in mediating this isolate-specific neutralization, interestingly, our vaccine antisera does not appear to target the HVR1 of either of the genotype 2a viruses directly implying that HVR1 has an indirect effect. We are currently investigating the potential mechanisms of HVR1’s indirect effect on neutralization sensitivity. Together, our data could help us to design a better vaccine antigen or antigen cocktail capable of expanding and optimizing the breadth of cross-genotype protection.

What is killing people with HCV infection? Analysis of population based cohort in Canada

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BACKGROUND: The causes of death among HCV positive and HCV negative individuals to understand the relative contributions of HCV acquisition risks, viral sequelae, and other mortality causes were compared.

METHODS: The BC Hepatitis Testers Cohort (BC-HTC) includes all individuals tested for HCV or reported to public health as a HCV case from 1990–2016 linked to their corresponding administrative data. ICD-10 codes were used to classify mortality as: 1) liver-related (including decompensated liver disease, liver cancer, HCV, non-alcoholic and alcoholic liver disease, other types of hepatitis); 2) acquisition risk-related (including drug and HIV-related); and 3) all other mortality causes. We compared proportions of mortality causes among HCV positive and negative individuals overall and by birth cohort: born < 1945, 1945–64 and ≥1965.

RESULTS: Of 1,372,391 individuals in the BC-HTC, 72,491 (5.3%) were HCV positive. Overall, 24.6% (17,834/72,491) of HCV positive compared to 9.0% (117,304/1,299,900) of HCV negative individuals died by June 2017. Median age at death was 56 vs. 75 yr., respectively. Deaths from acquisition risks- and liver- related causes, respectively were: negatives 2.6%/6.4%; spontaneous clearers 17.6%/15.3%; HCV RNA positive 17.5%/27.7%; those with SVR 11.5%/27.2%; and No SVR 9.9%/51.8%. Causes of death for birth cohorts < 1945, 1945–64 and ≥1965 among HCV negatives and positives, respectively, were: 1) liver-related: 5.3%/25.8%; 10.2%/26.8% and 5.3%/7.6%; 2) acquisition risk-related: 0.3% / 2.7%, 4.6% /20.9% and 17.8%/46.5%; and 3) all other mortality causes: 94.5%/76.8%, 85.2%/52.3% and 76.8%/45.9%. People in the ≥1965 birth cohort who were HCV RNA positive or spontaneously cleared infection had higher acquisition related mortality while those in the 1945–64 birth cohort who were HCV RNA positive and those who failed treatment had the highest liver related mortality.

CONCLUSIONS: Compared to HCV negative individuals, HCV positive individuals are more likely to die from drug related and liver related causes, and less likely to die from non-liver related causes. The contribution of drug related deaths is substantially higher in younger birth cohorts, while liver related deaths are more common in the 1945–64 birth cohort. These results demonstrate that curative HCV treatments, while likely to reduce deaths from viral sequelae, will not reduce acquisition risk mortality common in younger cohorts. These findings help quantify the need for comprehensive harm reduction programming to reduce overall mortality in persons with ongoing HCV acquisition risks.

The annealing location, not the annealing pattern, is important for the mechanism of small-RNA/miR122 promotion of hepatitis C virus genome replication

Rasika Kunden, University of Saskatchewan; Yalena Amador-Canizares, University of Saskatchewan; Joyce Wilson, University of Saskatchewan

BACKGROUND: Hepatitis C virus infects over 120 million people worldwide and can lead to the development of liver cirrhosis and hepatocellular...
CONCLUSIONS: We have identified nucleotides 13 and 44 as the boundary between which annealing small-RNAs can promote HCV replication, with annealing to nucleotides 19–37 being the most efficient. In future studies, we will identify RNA structures and RNA protein binding modulated by the small-RNAs that promoted HCV replication versus small-RNAs that did not, in order to better understand the mechanism by which miR-122 promotes HCV replication.

A descriptive epidemiology of hepatitis C cases referred for specialized care in Newfoundland and Labrador, 1996–2014
Jennifer Leonard, Memorial University of Newfoundland; Mary Malebranche, University of Calgary; Dawn King, Eastern Health

BACKGROUND: Since its discovery in 1989, chronic infection with the hepatitis C virus (HCV) has become an increasingly recognized public health concern worldwide. Despite this growing awareness, our understanding of the epidemiology and demographic distribution of HCV infection in Canada, specifically in Atlantic Canada, remains limited.

PURPOSE: There is currently little published data on the demographic and clinical profile of HCV positive individuals in Newfoundland and Labrador (NL) outside provincial public health reports, which are unable to capture the full spectrum of relevant demographic and clinical data on individuals infected with HCV in the province. The purpose of this study is to address this knowledge gap.

METHODS: A retrospective cohort study of 714 HCV positive individuals referred for specialized HCV care in St. John’s, NL, between 1996 and 2014, was conducted. Data was obtained through a standardized and comprehensive manual chart review and access to a database comprised of sociodemographic and clinical data on individuals referred for specialized HCV care in St. John’s.

RESULTS: 767 individuals were referred for specialized HCV care during the study period of which
714 were included in our analysis. This represents 57.5% of HCV positive cases identified by the province’s public health department during the same timeframe. HCV infection was more common in men (68.2%) and in urban dwellers (74.8%). The majority of cases were HCV Genotype 1 (52.1%). Intravenous and intranasal drug use were the most common self-reported risk factors for HCV transmission. High loss to follow-up rates were noted in those referred from the province’s correctional system.

CONCLUSION: This study demonstrates that many well-documented epidemiologic characteristics of HCV positive individuals in Canada hold true for individuals referred for specialized HCV care in Newfoundland and Labrador. Most notably it shows that specific attention needs to be paid to HCV positive individuals referred for specialized care from the province’s correctional system as they are at highest risk for loss to follow-up in specialized care. This study provides important insights into the demographic and clinical profile of individuals referred for HCV-related care in Newfoundland and Labrador and fills a gap in our current understanding of HCV positive individuals in this Atlantic province. These findings can help inform future directions for HCV-related health policy, resource allocation and clinical care initiatives in NL and across Canada.

Prevalence and predictors of complementary and alternative medicine modalities in patients with chronic hepatitis B

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BACKGROUND: Use of complementary and alternative medicine (CAM) in patients with chronic hepatitis B (CHB) can interact with antiviral treatment or influence health-seeking behavior.

PURPOSE: We studied the use and determinants of individual CAM modalities in patients with CHB. In particular, we investigated whether migration-related factors, use of antiviral therapy or liver disease severity were associated with CAM use.

METHOD: CHB patients who attended the Toronto Centre for Liver Disease outpatient unit (Toronto, Canada) between June 2015 and October 2016 were asked to participate in this cross-sectional survey study. Using the comprehensive I-CAM questionnaire and health records, data was collected on demographic, socio-economic and clinical variables and on use of different CAM modalities in the last 12 months.

RESULTS: A total of 436 patients completed the questionnaire. The mean (SD) age was 49 (14) years, 60% was male and 46% was on antiviral treatment. Two hundred eight patients were Chinese, 114 South-East Asians, 72 Caucasian and 39 black. Three hundred nine (71%) patients used CAM. Vitamin and mineral preparations (45% of patients) and spiritual practices (29%) were most commonly used. CAM use differed by ethnicity for spiritual practices. Green tea extract (9.2%) and St. John’s wort (0.2%), the only known potentially injurious CAM products, were not associated with liver disease severity. Female sex, a family history of CHB, lower serum HBV DNA, higher level of education, private drug plan coverage and employment status were independently associated with CAM use (p < 0.05). Ethnicity, use of antiviral treatment and severity of liver disease were not associated with CAM use. Liver disease was the main reason to use herbal products in 32% of patients compared to 3% for vitamin/minerals. Physicians had inquired about CAM use in 43% of patients.

CONCLUSIONS: CAM use was common among patients with CHB, especially oral product use. Higher socio-economic status, female sex, a family history of CHB, higher age and lower HBV DNA predicted CAM use; ethnicity, use of antiviral treatment or liver disease severity did not. These findings suggest that regular provider care for CHB should focus on socio-economic rather than ethnic or cultural factors.
Strategies to improve the cascade of hepatitis C (HCV) care at CUPS – an inner city clinic in Calgary.
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BACKGROUND: Calgary Urban Project Society (CUPS) serves those living in poverty in Calgary, Alberta. It integrates health, education, and housing supports together in one building. People with hepatitis C (HCV) are assessed in the primary care clinic and referred to the on-site HCV clinic for counselling, assessment, treatment, and peer support. Our cascade of care was recently defined.

PURPOSE: To develop strategies to improve our cascade of care by suiting patients’ and clinicians’ needs better in terms of screening, testing, and supporting those with HCV.

METHODS: After determining our cascade of care data, electronic medical records were reviewed to assess reasons why people did not progress through from testing to treatment. Ensuing discussions with primary care providers and the multidisciplinary HCV team elicited potential strategies to improve the cascade.

RESULTS: The cascade of care for CUPS showed 13% of antibody tests (119/873) were positive over a 2.5 year period. Only 67% of antibody positive people had a PCR. Of the people with HCV viremia, 39% followed through with the HCV clinic. Loss to follow up is the primary issue why people did not progress through the cascade of care. Additionally, competing issues such as insecure housing, mental health, and addictions are often preventing people from progressing. Breakdown of communication and documentation also accounts for some people failing to progress. 13% (15/119) of antibody positive people had no documentation of being informed of their results. 10 of these people were lost to follow up, making them unable to be informed, but 5 of them had repeat clinic visits. Through discussions with primary care providers and the HCV team, challenges regarding inconsistent charting and variable screening policies were identified. The HCV clinic is open half of the week, limiting options for care, as well as for support to the primary clinic. During the study time-frame, a fibrosis score F2 or greater was required for HCV medication coverage, thus 50% of patients were treatment ineligible.

CONCLUSIONS: With the changing landscape of HCV care, new avenues for engagement are available. Patients no longer require a stage 2 fibrosis score or higher if certain symptoms are present, making more patients eligible for treatment coverage. Point of care (POC) antibody testing was recently implemented by the HCV team to help accelerate the testing process and allow for outreach testing in the future. Standardized documentation is being explored. The HCV clinic is designing a screening tool to assist health care providers in identifying and screening at-risk individuals. These supports should streamline care and provide structure when the HCV team is not available. To help support these changes, education sessions will be held and electronic medical record reminders will be used to help engage staff.

Sex-linked variation in immune composition and inflammatory potential in the human liver
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BACKGROUND: Chronic hepatitis B (CHB) infection is defined by persistent liver inflammation that may lead to cirrhosis, fibrosis, and eventually hepatocellular carcinoma (HCC). The liver microenvironment likely impacts disease incidence and progression. Although the liver is thought to be a tolerogenic organ, TLR ligands—both pathogen-derived and endogenous—are abundant in the liver compared to peripheral blood and could stimulate liver resident cells and trigger inflammation in some predisposed individuals. Men are more likely to develop CHB and are also at
increased risk of progressing to HCC, as are post-menopausal women.

**PURPOSE:** To characterize liver resident immune cells in healthy subjects and identify age and sex-linked differences in liver cell composition that may be responsible for differences in CHB disease susceptibility.

**METHOD:** Peripheral blood and liver perfusate mononuclear cells were isolated from 30 male and female healthy subjects (age range 14–73) using density gradient centrifugation. Cells were subjected to multiparametric flow cytometric analysis to determine cell composition using a panel of antibodies defining 16 leukocyte populations. Monocyte function was assessed by measuring cytokine and chemokine responses following in vitro TLR2, -3, -4, -5 and -8 stimulation.

**RESULTS:** The cell composition of liver intrahepatic mononuclear cells (IHMC) differed significantly from peripheral blood mononuclear cells (PBMC), with increased proportions of innate lymphocytes (NK cells, gamma delta T cells, MAIT cells), increased CD8:CD4 ratio, and elevated CD14+CD16+ monocytes, confirming that IHMC are liver-derived rather than from the circulation. Immune cell frequencies did not vary with age. The frequency of liver CD56hi NK cells was increased in men compared to women. Purified liver CD14+ monocytes stimulated with various TLR ligands responded with robust production of IL1α, IL1β, IL-6, TNFα, MIP1α, MIP1β, IL-10 and IP-10. Strikingly, monocytes from men produced significantly more cytokines (particularly TNFα, IL1β, MIP1α, MIP1β and IL-6) regardless of the TLR stimuli, and cytokine production was increased in older subjects. Importantly, TLR stimulation led to age-related and significantly increased production of IL-6, particularly in monocytes isolated from men, which has been implicated in driving hepatic inflammation and HCC.

**CONCLUSIONS:** Increased production of inflammatory mediators by intrahepatic monocytes in response to TLR ligands may underlie the enhanced susceptibility of men to CHB and/or HCC. Further characterization of the impact of age and biological sex on the intrahepatic immune response is necessary to identify potential host-directed therapies.

**Hepatitis B surface antigen loss among chronic hepatitis B patients receiving oral antiviral therapy: Does it ever occur?**

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**BACKGROUND:** Chronic hepatitis B (CHB) is a significant cause of liver-related morbidity and mortality, affecting more than 250 million people worldwide. High (>1000 IU/mL) hepatitis B surface antigen levels (HBsAg) have been associated with cirrhosis progression and hepatocellular carcinoma in CHB patients, whereas HBsAg loss is associated with improved outcomes. Oral antiviral therapy may lead to small reductions in HBsAg levels, but HBsAg loss has been rarely reported among Asian patients.

**AIMS:** The aim of this study is to estimate the rate of HBsAg loss/seroconversion on oral antiviral treatment and to explore factors associated with this treatment endpoint.

**METHODS:** We retrospectively collected patient and laboratory data for CHB patients attending the Toronto General Hospital Liver from 1/2010 to 8/2017. All patients included were receiving treatment with oral antiviral agents (lamivudine, tenofovir or entecavir) for a minimum of 3 years and were followed every 3–6 months in clinic. Descriptive statistics were used to summarize baseline data and the probability of HBsAg loss will be estimated using the Kaplan Meier method.

**RESULTS:** To date, 45 patients on long-term antiviral treatment who achieved HBsAg loss were included. Mean age was 55±4 years; male to female ratio 27:18; and 42 (93%) patients were of Asian descent. Only 9 (20%) patients were HBeAg-positive pre-treatment, with a mean HBsAg level 3.7 log IU/mL and baseline HBV DNA levels of 5.8 log IU/mL. The majority (>90%) had received treatment with tenofovir 300 mg po daily as
monotherapy. Mean time to HBsAg loss or seroconversion 7.3±2.1 years and at the time of HBsAg loss, all patients were HBeAg-negative, all had HBV DNA < 20 IU/ml, 40 (89%) had normal ALT ( < 40 U/L). Factors associated with HBsAg loss will be explored further.

CONCLUSIONS: HBsAg loss or seroconversion among Asian patients receiving oral antiviral therapy is uncommon, but can occur with long-term continuous treatment. HBV genotype, lower baseline quantitative HBsAg and longer duration of therapy may be factors associated with eventual HBsAg loss among CHB patients receiving treatment.

Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe
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All-oral direct-acting antiviral drugs (DAAs) for hepatitis C virus, which have response rates of 95% or more, represent a major clinical advance. However, the high list price of DAAs has led many governments to restrict their reimbursement. We reviewed the availability of, and national criteria for, interferon-free DAA reimbursement among countries in the European Union and European Economic Area, and Switzerland. Reimbursement documentation was reviewed between Nov 18, 2016, and Aug 1, 2017. Primary outcomes were fibrosis stage, drug or alcohol use, prescriber type, and HIV co-infection restrictions. Among the
Prevalence of occult hepatitis B virus in two African cohorts: making the case for screening
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Identification of a G4-quadruplex structure motif in hepatitis B virus genome: A potential novel drug target
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BACKGROUND: Approximately 240 million people worldwide are chronically infected with hepatitis B virus (HBV), one of the leading causes of liver cirrhosis and hepatocellular carcinoma (HCC). HBV persistence is due to the presence of its compact, stable, covalently closed circular DNA (cccDNA), which resides in the nucleus and acts as the template for all HBV mRNA transcripts. While current antiviral therapies are effective at viral suppression, they do not target HBV cccDNA and cannot eradicate infection, necessitating prolonged, if not lifelong therapy.

The transcription of cccDNA is under the guidance of numerous host factors, which bind to the various promoter regions to aid the replication of HBV. In the pre-core promoter region, specifically, interrupting host-protein interaction via a single nucleotide mutation studies can abrogate the HBV production.

Recently, we have found a unique structural motif in the pre-core promoter region—a G4-quadruplex—a distinct, stacked, four-guanosine folding arrangement of the DNA. Such quadruplexes are being discovered at key transcription and translation sites of numerous organisms and are thought to be important regulators of these processes.

We hypothesize that the host proteins bind at the pre-core promoter site through a G4-quadruplex, and disruption of this inhibits binding, hindering replication.

METHODS: The wild-type and single-nucleotide mutation oligomers of this binding region were solubilized and purified through FPLC. Fractions of the purified products underwent circular dichroism, electrophoretic mobility shift assay, and small angle X-ray scattering analyses. Next, a known quadruplex-binding protein, DHX36 was produced using an E.coli expression system with an added His-tag and purified using a cobalt bead column. Pull-down assays of the DHX36 with the two oligomers was performed. Finally, cccDNA was extracted from an HBV-infected explanted liver via the Hirt extraction method and a similar pull-down assay was performed.

RESULTS: Using various biophysical methods, we demonstrate that the wild-type oligomer forms quadruplex structures, while the mutant oligomer does not. As well, we show a known quadruplex-binding protein, DHX36 to bind only to the wild-type oligomer and provide evidence for an analogous in vitro process with cccDNA.

CONCLUSIONS: This novel finding of a quadruplex in the pre-core region provides a unique opportunity to study a critical host-protein interaction in cccDNA transcription. Through the pursuit of high-resolution structural data, we will be creating the framework for designing a novel inhibitor of the resilient HBV cccDNA, the master template for HBV replication.
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BACKGROUND: Worldwide there are over 240 million people chronically infected with the hepatitis B virus (HBV), one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC). Gross regional differences in prevalence exist, as are screening, vaccination programs and access to care. In sub-Saharan Africa, estimates of prevalence range from 0.5–20%, but one study has shown HBsAg+ prevalence of up to 38% in some cohorts (1,2). Occult HBV, defined as the presence of HBV DNA in the absence of HBsAg, is indicative of prior exposure to HBV and may have clinical implications in immunocompromised patients (3). In regions where HBV testing is not considered standard of care, defining the prevalence of chronic and occult HBV infection has significant implications for the development of monitoring and treatment programs.

Here, we present data from two different patient cohorts in Gondar, Ethiopia—one from a pregnancy clinic (all HIV negative) and the other an HIV clinic.

METHODS: At the University of Gondar Teaching Hospital, a tertiary care site providing medical services to ~5 million people in Northwest Ethiopia, patients were consented and blood samples collected from two outpatient clinics—pregnancy clinic (N=200, all HIV negative) and outpatient HIV antiretroviral (ART) clinic (N=308), from March-July 2016. Sociodemographic and clinical data was collected by patient questionnaire and chart review. Peripheral blood mononuclear cells and plasma samples were isolated from whole blood, and plasma was tested for HBsAg and anti-HBc antibody at the Alberta Provincial Laboratory using a commercial chemiluminescent immunoassay (ARCHITECT;Abbott). HBsAg and anti-HBc antibody positive samples were tested by nested PCR using HBV surface gene specific primers and direct Sanger sequencing to determine the HBV genotype and presence of drug resistance mutations (DRMs).

RESULTS: Median age in the pregnancy cohort was 26 years (15–42). In the HIV+ cohort, the median age was 38 years (range: 18–68), 62.7% were female and the median CD4 count was 405 cells/mm³ (range: 75–734), with 94.2% HAART-experienced. In the pregnancy cohort, 2/200 (1%) of patients were HBsAg positive, and 56/184 (30.4%) were positive for HBV core antibody. In the HIV positive cohort, 17/308 (5.5%) were positive for HBsAg (i.e., HBV/HIV co-infected); while in the remaining, 136/291 (46.7%) patients were positive for HBV core antibody. In the HIV+/HBsAg positive cases the HBV genotype was A, and DRMs were found in 7/13 tested. HBV DNA testing and genotype determination is in progress for all HBsAg negative/anti-HBc+ cases.

CONCLUSIONS: In summary, chronic HBV infection was found in ≤5% of either HIV positive individuals or HIV-negative, pregnant patient cohorts in Gondar, Ethiopia. However, a significant percentage of both patient groups show evidence of prior exposure and natural immunity to hepatitis B virus infection. This data highlight the need for ongoing surveillance, vaccination and treatment programs for hepatitis B in resource poor regions worldwide.

REFERENCE

Hepatitis B virus DNA integrates to human genome immediately after infection

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Hepatitis B virus (HBV) is highly oncogenic virus. Its integration into human genome precedes development of hepatocellular carcinoma (HCC). The sites and kinetic of the spread of HBV integrations across human genome might be relevant to HCC development and progression. The initial sites of HBV-host DNA junctions were unknown. We aimed to identify them by exploring de novo HBV infection of human HepaRG hepatocytes and woodchucks infected with woodchuck hepatitis virus (WHV). HepaRG were investigated in 15 and 30 min, 1, 3, 24 and 72 h, 7 and 10 days, 2, 4 and 7 week post-infection (p.i.) and liver biopsies from woodchucks at 1 h or 3 h and at 6 week p.i. Inverse-PCR followed by amplicon cloning and sequencing was used to detect integrations. HBV DNA junctions became detectable in 1 h p.i. Integrations of HBV X gene with retrotransposon sequences long-interspersed nuclear element-1 (LINE1) and LINE2 became prominent from 3 days. Insertions of HBV X into several other genes were also identified. In woodchucks, integrations of WHV preS and X sequences were evident in 1 and 3 h p.i. The HBV core promoter/enhancer-II region followed by enhancer I region and its WHV equivalent were predisposed to form the earliest junctions with host DNA. Multiple virus-virus DNA joints were apparent. In conclusion, HBV DNA integrates immediately after virus invasion and may utilize retrotransposon elements and translocation genes from the early stages of infection for spread and induction of prooncogenic perturbations throughout the host’s genome. This very early integration was also evident in natural WHV infection in woodchucks, confirming that hepadnavirus under natural conditions integrates to hepatocyte DNA soon after infection. Therefore, our data indicate that HBV must be considered as an unequivocal human carcinogen and that contact with this virus, including miniscule amounts causing asymptomatic, primary occult infection, has to be utterly avoided.

Hepatitis C direct-acting antiviral treatment failures: Clinical characteristics, outcomes and resistance testing from a ‘real-world’ setting

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**BACKGROUND:** A small proportion of patients fail Hepatitis C (HCV) treatment with direct-acting antivirals (DAAs) for various reasons. There is scant real-world data on DAA failures and their relationship to resistance associated substitutions (RAS). This study aims to characterize clinical parameters, RAS patterns and outcomes in patients who failed DAA regimens in a real-world practice.

**METHODS:** Retrospective chart review was conducted at a tertiary hepatology clinic between 01/2015 and 05/2017. Patients were included if SVR-12 was not achieved after DAA therapy. Baseline clinical characteristics, outcomes and RAS testing at SVR-12 were collected. HCV sequence data was obtained from Next Generation Sequencing of an amplified HCV. Mutations >5% of viral population were reported. Resistance phenotype was determined on EC50 fold-shift in mutant vs. wild-type replicons. RAS that confer high level resistance are reported.

**RESULTS:** Forty-two patients were included, with a mean age of 58.5 years (range 43–75) and mostly male (87.8%). Genotypes (GT) were GT1 - 23 (54.8%); GT2 - 3 (7.1%); GT3 – 16 (38.1%). GT1 patients were mostly SOF/LDV failures (n=17; 74.0%), and GT3 were mostly SOF/RBV failures (n=11; 68.6%). Pre-treatment fibrosis by transient elastography (n=26), revealed F0–2 in 10 (38.5%), F3 in 4 (15.4%) and F4 in 12 (46.2%). Eighteen patients were treatment experienced (42.9%). Following DAA failure, 6 patients (14.6%) had decompensating events, including HCC in 4 (de novo 2, recurrence 2) patients.

Post-treatment RAS testing was available for 33 patients, the remainder are pending. In 16 of 17 GT1 patients treated with SOF/LDV, RAS testing was available. 14 of the 16 persons had a NS5A RAS detected. 10 of 14 patients had a 93 position variant. All 16 patients had NS3 RAS, 9 of which were Q80K (64.3%). Two NS5B RAS were present.
that were of uncertain significance (no S282T RAS). Of 2 GT1 patients who failed EBR/GZR, both had a non-Q80K NS3 RAS.

For 15 GT3 patients who failed SOF/RBV (n=11), SOF/RBV/Interferon (n=2) or SOF/LDV (n=2) RAS testing was available in 10. Two SOF/RBV patients had NS5B RAS (321wt/A and 159wt/F), conferring possible SOF resistance. There were no S282T RAS present. One NS5A RAS (30S) was present in a SOF/LDV failure. Two of 3 GT2 patients who failed SOF/RBV were evaluated with no RAS present.

RAS testing from samples stored prior to DAA therapy is pending.

CONCLUSIONS: In GT1 patients who failed an NS5A containing regimen, a high prevalence of NS5A RAS in particular Y93H or Q30 is present. In GT3 patients who failed SOF/RBV, NS5A RAS are generally not conferred, low potency SOF-RAS may be present. The clinical impact of these RAS in a real world-setting is unclear.

Patient-reported quality of life improves after treatment of hepatitis C with direct-acting anti-virals: a real-world experience

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BACKGROUND: Patients with hepatitis C virus (HCV) infection are known to have impaired health-related quality of life (QoL). Data from clinical trials using DAAs to treat HCV suggest that patient-reported measures of QoL improved during treatment, and that these effects are sustained after treatment. Despite this favorable study data, the “real-world” effects of newer DAA-based regimens on QoL are not known.

METHODS: Between Jan 2014 and Dec 2016, consecutive patients aged ≥ 19 years with serologically-confirmed HCV undergoing any oral DAA regimen, seen in consultation by a gastroenterologist at a tertiary outpatient hepatology clinic in Vancouver, BC were considered for inclusion. Participants were excluded if they had incomplete follow-up data or changed treatment to an interferon-containing regimen. Quality of life was measured with the Short-Form 36 Questionnaire (SF36), a well-validated tool of patient reported quality of life in HCV and other conditions.

RESULTS: 54 patients with complete pre- and post-treatment SF36 measures were included. The mean age at treatment was 60 (range 27–75) years. Forty patients (74.1%) were male. 15 patients (27.8%) had one of the following co-morbid conditions: anxiety, depression, chronic fatigue syndrome, sleep disorders or chronic pain syndromes. The most common genotype was 1a in 38 patients (70.4%). Nineteen patients (35.2%) had cirrhosis and 38 (70.4%) were treatment naïve. The most common treatment regimen was sofosbuvir/ledipasvir in 40 patients (74.1%). SVR12 was achieved in 53 patients (98.1%).

QoL testing was performed at baseline and mean 6.10 weeks (range 0–40.4 weeks) after treatment completion. The change in SF36 summary physical component scores after treatment (a composite score of patient-reported physical wellbeing) was 2.05 ± 6.34 (p=0.02). The change in summary mental component scores after treatment (a composite score of patient-reported mental wellbeing) was 0.43 ± 10.34 (p=0.76).

CONCLUSIONS: In this analysis, HCV patients treated with DAAs in a tertiary outpatient clinic report a statistically significant improvement in physical health after treatment. To our knowledge, this finding demonstrates the first “real-world” improvement in patient-reported QoL after DAAs. This data suggests that there is a short-term improvement in self-reported physical, but perhaps not mental, health soon after DAA treatment. Further statistical analysis is underway to elucidate predictive patient or treatment characteristics for positive and negative changes in QoL. Further research is required and underway to determine whether this effect is sustained in the months to years after SVR.
Transplantation of a liver allograft from a hepatitis C Virus (HCV) seropositive donor with previous sustained virologic response to an uninfected recipient suffering steroid refractory acute graft rejection with no evidence of HCV transmission

Robert Mitchell, University of British Columbia; Trana Hussaini, University of British Columbia; Alan Yau, University of British Columbia; Mel Krajen, University of British Columbia; Alissa Wright, University of British Columbia; Charles Scudamore, University of British Columbia; Vladimir Marquez Azalgara, University of British Columbia; Sigfried Erb, University of British Columbia; Eric Yoshida, University of British Columbia

BACKGROUND AND PURPOSE: The goal of treating chronic hepatitis C virus (HCV) infection is sustained virologic response (SVR). There is concern that despite achieving SVR, replication-competent HCV may be sequestered at low levels within the liver and could theoretically reactivate with immunosuppression. We report transplantation of a HCV seropositive liver donor, who achieved SVR, into a seronegative patient without HCV reactivation despite profound immunosuppression.

METHOD: Retrospective chart review.

RESULT: We present a 21-year-old male who was HCV seronegative and received a liver transplant from a donor who had been treated for HCV and achieved SVR. The liver recipient, despite developing severe acute graft rejection and undergoing intense immunosuppression with T-cell depleting antibodies, did not become HCV RNA positive with a follow up period of 8 months. The recipient was HCV seronegative before transplant, but became HCV seropositive immediately post-transplant. The antibodies were undetectable after 97 days, in keeping with a passive antibody transmission or B lymphocyte transmission with the graft.

CONCLUSIONS: To the best of our knowledge, this is the first reported case of an HCV seropositive liver allograft transplanted into a HCV negative recipient. This case, therefore, is an encouraging and novel step in liver transplantation, and demonstrates that SVR may be closer to a true “cure” of HCV in the donor population and that, even in circumstances of very potent immunosuppression in the recipient, this SVR is sustained. To our knowledge, this case also contains the first documented example of an HCV antibody decay phenomenon in the recipient post-liver organ transplant.

Type I interferon-associated impairment of the humoral immune response against HCV

Armstrong Murira, Institut Armand Frappier; Alain Lamarre, Institut Armand Frappier

Type I interferon (IFN-I) has been characterized to enhance cell-mediated immune responses against acute viral infections whilst impair immune activation in chronic viral settings as would be in the case of HCV and HIV. Here, we show that in addition to its effect on T cells, IFN-I drives impairment of effective humoral immune responses through direct interaction with B cells upon chronic viral infection. Using the classic LCMV murine infection model, we co-administered 4-hydroxy-3-nitrophenyl (NP) at the time of infection whereby flow cytometry analysis of B cell proportions and ELISPOT data revealed that compared to a normal humoral immune response in the VSV (acute) infection, LCMV-infected mice developed non-specific hypergammaglobulinemia along with diminished NP-specific responses shortly after infection. Notably, during persistent viral infections, infected hosts also exhibit aberrancies to the humoral response such as polyclonal activation and hypergammaglobulinemia. Accompanying this dysregulation, the emergence of neutralizing antibodies (nAbs) is delayed and bears negligible impact on the progression of the disease by the time they are successfully elicited. Altogether, these perturbations result in a diminished antigen-specific Ab response and an enhanced non-specific polyclonal response. These are hallmarks of disruption in the humoral immune response during a chronic infection. Our results also demonstrated that this impairment was limited to the T-cell dependent B-cell response and function was restored by ablation of IFN signaling through antibody-dependent IFN receptor blockade as well as B-cell specific IFN receptor knockouts. In addition, disrupted lymphoid architecture observed following immunofluorescent microscopy was also restored upon
elimination of B-cell specific IFN signaling. Importantly, restoration of effective B-cell responses in transgenic mice also featured increased neutralizing antibody titers in ELISA assays, which were absent in the wildtype model with functional IFN signaling. Our findings illustrate the role played by IFN in limiting effective antibody responses by action on B-cells. Whereas complete blockade of IFN signaling would be deleterious, targeted B-cell specific restriction could improve humoral responses towards effective therapeutic and prophylactic measures against chronic infections such as HCV.

Post-treatment liver stiffness measurements predict the development of liver-related complications in patients with HCV cirrhosis who achieve SVR post-DAA therapy
Frederic Nguyen, University of Ottawa; Cynthia Tsien, University of Ottawa; Curtis Cooper, U Ottawa; Chrissi Galanakis, Ottawa Hospital Research Institute

BACKGROUND: Chronic hepatitis C virus (HCV) infection may lead to cirrhosis and liver-related complications (LRC) such as hepatocellular carcinoma (HCC), ascites, hepatic encephalopathy (HE) and esophageal varices. Transient elastography (TE) is a reproducible, non-invasive measurement of liver fibrosis in HCV, and may predict LRC. HCV therapy with SVR appears to decrease liver stiffness (LS) however, whether this is also associated with fewer LRC is unclear.

PURPOSE: To evaluate whether a reduction in LS post-HCV treatment with sustained virologic response (SVR) is associated with a lower incidence of LRC in cirrhotic patients within 24 months of therapy.

METHODS: We included all cirrhotic patients (LS >12.5 kPa) treated with direct acting antivirals (DAAs) between May 1, 2013 and June 1, 2016 with SVR and pre- and post-treatment TE. We excluded patients with new/worsening events before post-treatment TE. Those with baseline events (HCC, ascites, etc.) were included, and evaluated for worsening events, as defined by progression of post-treatment grading of ascites/varices/HE compared to baseline. The absence of new or worsening events was recorded as ‘non-event’. ROC curves and Kaplan-Meir analysis were used. Person-time was calculated from the post-treatment TE date to the last clinic visit up to 24 months post-treatment.

RESULTS: Of 57 patients, we excluded 4 patients with new LRC prior to post-treatment TE. TE was performed a median 32 weeks after end of treatment (IQR 28.5 weeks). 40/53 (75.5%) patients had reduction in LS, with a mean decrease of 10.7 kPa (SD 10.4). There were no differences in baseline characteristics of patients with/without decreased LS. Post-treatment, 4 events occurred during follow-up: 1 new varices, 1 new HCC, and 2 progression known varices. The incidence rate for patients with increased LS was 0.47/100 person-weeks, vs. 0.19/100 person-weeks for patients with decreased LS (RR 2.5, p=0.40, 95% CI: 0.26–24.0), with no significant difference in mean time to event (74 weeks vs. 79 weeks, respectively, p=0.55). All events occurred in individuals with LS >20.75 kPa, while no events occurred in individuals with LS score <20.75 kPa (4/20 vs. 0/33, p=0.02). This LS cutoff also had the best AUC (0.786) with a sensitivity of 100% and specificity of 67%. Post-treatment, 20/53 (37.7%) patients still had a LS above 20.75 kPa.

CONCLUSIONS: In our cohort of patients with early cirrhosis (Child-Pugh class A, MELD < 15), successful antiviral therapy led to a reduction in LS in most patients. Prior studies have identified a LS cutoff of 20 kPa as associated with clinically significant portal hypertension, and this was confirmed in our post-treatment cohort. Many (37.7%) patients remained above this cut-off and require LRC monitoring post-SVR. The predictive value of long-term, serial LS measurements requires evaluation.

Analysis of serum hepatitis B virus RNA levels in a multiethnic cohort of pregnant chronic hepatitis B carriers
Nishi Patel, Department of Medicine, University of Calgary; Shivali Joshi, Department of Medicine, University of Calgary; Keith Lau, Department of Medicine, University of Calgary; Eliana Castillo, Department of Medicine, University of Calgary; Carla Coffin, Department of Medicine, University of Calgary
BACKGROUND: Mother to child transmission (MTCT) of HBV is one of the most common routes of transmission worldwide. All infants born to HBV+ mothers should receive complete immunoprophylaxis with HBV immune globulin (HBig) and vaccine. In some mothers with high HBV DNA levels (>2x 10^{5} IU/mL), antiviral therapy is recommended to further reduce MTCT risk. We had previously documented HBV immune (cytokine) and alanine aminotransferase (ALT) flares in pregnancy; as well as, HBV DNA correlation with quantitative (q) HBV surface antigen levels (1,2,3,4). There are no prior studies assessing other HBV replication markers (i.e., HBV RNA and pre-genomic RNA levels) in pregnancy.

AIM: To analyze HBV RNA levels in association with HBV DNA, qHBsAg, genotype and alanine aminotransferase (ALT) levels in pregnant and/or post-partum Chronic Hepatitis B (CHB) carriers.

METHODS: In total, sera and plasma from 38 CHB pregnant and/or post-partum women were tested for HBV DNA, including 34/38 for qHBsAg levels by standard clinical assays (Abbott Architect). Serum HBV RNA levels was assessed by in-house qPCR using HBV X gene specific primers (based on a plasmid dilution standard curve). The HBV genotype was determined in (31/38, 82%) by commercial line probe assay (LiPa) or in-house nested PCR using HBV S gene specific primers and Sanger sequencing, according to previously published protocols. Data was analyzed using paired t-test where p < 0.05 was considered significant.

RESULTS: In 38 pregnant CHB carriers (median age 32 y, 53% Asian, 32% African, 15% other), were 79% (30/38) HBeAg negative, 21% (8/38) on antiviral therapy with Tenofovir Disoproxil Fumarate. In 31/38 patients with HBV genotype results, showed 13% A, 36%B, 19%C, 19%D and 13%E. The median ALT, HBV DNA and qHBsAg levels were 19.5 U/L; 2.85 log_{10} IU/mL and 3.3 log_{10} IU/mL, respectively. Analysis of serum RNA levels showed undetectable HBV RNA in 21% (8/38), detectable but not quantifiable in 32% (12/38), and quantifiable levels in 47% (18/38) tested. In 6 matched pregnant vs. post-partum samples the serum HBV RNA decreased from a median of 3.47 to 3.01 log_{10} IU/mL. There was no significant association between HBV RNA levels and HBV DNA levels, qHBsAg, genotype or ALT levels tested.

CONCLUSION: In this multiethnic cohort of CHB carriers in pregnancy, serum HBV RNA levels are not associated with HBV DNA, qHBsAg, genotype or ALT levels. Further studies involving assessment of other HBV virological and serological markers (i.e., HBV pre-genomic RNA, quantitative HBV core antigen) may help increase understanding of HBV natural history in pregnancy.

REFERENCES

Prevalence of baseline NS5A resistance associated sequences (RAS) in treatment naïve patients with genotype 1 and 3 in two Canadian provinces

Alnoor Ramji, University of British Columbia; Jeanette Feizi, Gastroenterology Research Institute, St. Paul’s Hospital; Anita Howe, British Columbia Centre for Excellence in HIV/AIDS; Alexander Wong, Regina Qu’Appelle Health Region; Sarah Craddock, Regina Qu’Appelle Health Region; Dennaye Fuchs, Regina Qu’Appelle Health Region

BACKGROUND: Treatment of HCV is very effective with SVR in almost all persons treated with DAA based therapy. A small proportion of patients fail HCV treatment with DAAs for various reasons, including the possibility of the presence of baseline RASs. Registry studies and international treatment guidelines (EASL & AASLD) have recommended assessment of baseline NS5A RASs in persons with GT1a and GT3 HCV depending on the choice of DAA regimen and fibrosis stage. In cases where baseline RAS is present, the addition of ribavirin is suggested. The prevalence of baseline RASs for GT1a and GT3 in Canada is unclear.

PURPOSE: To evaluate the prevalence of baseline NS5A RAS in NS5A treatment naïve persons with GT1 and GT3 in a real-world setting.

METHODS: A retrospective chart review from 2 centers, 1 in Regina and 1 in Vancouver, between
Liver enzyme changes after successful HCV DAA treatment: Evidence for a new normal ALT range

Rebekah Rittberg, University of Manitoba; Stephen Wong, University of Manitoba

BACKGROUND: Chronic hepatitis C (HCV) is an infection resulting in hepatic inflammation and elevation of liver enzymes (LE) including alanine aminotransferase (ALT). Hepatocellular LE reference ranges are based on historical norms when HCV was not discovered. Treatment of HCV with new direct-acting antiviral agents (DAAs) improves hepatic inflammation and decreases ALT values which may suggest new normal ALT reference ranges.

OBJECTIVES: 1) To evaluate changes of ALT during and after successful HCV DAA treatment in patients with abnormal or normal ALT values pre-treatment; 2) To determine what percentage of patients with abnormal ALT pre-treatment do not achieve normal ALT after HCV DAA treatment.

METHODS: A retrospective chart review was undertaken of 100 HCV patients who underwent DAA therapy over the last 1–2 years. Patients were excluded if data was incomplete or reference ALT values differed between measurements. Patient data, treatment information, and laboratory results were collected before treatment, end of treatment (EOT), and 3 and 6 months post-treatment.

RESULTS: At this interim analysis, 67 individuals had complete results available and had obtained a sustained virological response (SVR); 43% were male and 57% female. The mean age was 58.9 (±8.0) years, 47% were genotype 1A and 38% were genotype 1B, the remainder were genotype 3 or 4. The normal ALT reference levels were ≤25 IU/L for females and ≤30 IU/L for males. Overall, the mean ALT pre-treatment was 66.3 (±44.9) IU/L. At EOT, mean ALT was 30.3 (±7.1) IU/L, at 3 months post-treatment and 6 months post-treatment ALT was 29.7 (±7.0) IU/L and 29.9 (±7.0) IU/L respectively. The delta ALT from pre-treatment to EOT was 40.5 (±37.6) IU/L, while the delta from pre-treatment to 6 months post-treatment was 48.9 (±46.0) IU/L. At 6 months post-treatment, 85% of patients had ALT within the normal range. Of interest, 15% (10 patients) had ALT within the normal range pre-treatment with a mean ALT of 23.1 (±7.4) IU/L. This cohort’s delta ALT, from pre-treatment to the EOT and 6 months post-treatment, was 6.7 (±8.4) IU/L and 11.0 (±10.2) IU/L respectively.

CONCLUSION: HCV DAA treatment leads to significant improvement in ALT levels. However, 15% of patients’ LE did not normalize after HCV treatment, likely as a result of the presence of another underlying liver disease that had not been
characterized. Additionally, a subset of 15% of HCV patients had normal ALT values pre-treatment that was reduced further with treatment suggesting the presence of liver inflammation that was not recognised by current LE reference ranges. This provides evidence that suggests that the ALT normal reference range may be lower than the current reference ranges.

**Real world impact of direct acting antiviral therapy on patient reported outcomes**

Sahar Saeed, McGill University; Marina Klein, McGill University; Alexander Wong, Regina Qu’Appelle Health Region; Curtis Cooper, U Ottawa; Erica Moodie, McGill University; John Gill, Southern Alberta Clinic; Sharon Walmsley, University Health Network; Mark Hull, BC Center of Excellence; Valerie Martel-Laferriere, Centre de Recherche du Centre hospitalier de l’Université de Montréal; CTN 222 Canadian HIV/HCV Co-Infection Cohort Study, McGill University Research Institute

**BACKGROUND:** Clinical trials evaluating direct-acting antivirals (DAA) show substantial improvements in patient-reported outcomes (PROs) in HIV-HCV co-infected patients. However, trials have limited generalizability and patients are seldom followed post treatment response.

**PURPOSE:** We therefore investigated the impact of all oral-DAA therapy on health-related quality of life (HR-QOL) in a generalizable HIV-HCV co-infected population.

**METHODS:** The Canadian Co-Infection Cohort Study prospectively follows 1785 HIV/HCV co-infected participants from 18 centers. Data on sociodemographic, clinical, PRO and prescriptions are collected biannually through self-administered questionnaires and chart review. A segmented multivariate linear mixed model compared changes in HR-QOL post-DAA compared to pre-treatment trends. HR-QOL was measured using the EQ-5D© questionnaire in English or French. Current health was scored on a visual analog scale (VAS) from 0 to 100 (worst to best health) and participants reported extent of difficulty (no/some/extreme problems) in five health domains: mobility, self-care, usual activities, pain/discomfort, anxiety, or depression. Multivariate models included time-updated CD4 cell count, HIV viral load, injection drug use and fixed covariates at DAA initiation; age, sex, Indigenous ethnicity, liver fibrosis and diagnosis of psychiatric disorder.

**RESULTS:** Between 2014–2016, 318 participants initiated oral DAAs, 200 completed at least 1 visit before and after DAA treatment (total of 1868 visits) with a mean of 3.2 years (SD 2.6) pre- and 0.7 years (SD 0.5) post-DAA follow up time. 70% of DAA regimens consisted of ledipasvir/sofosbuvir. Median age at DAA initiation was 52 (IQR 48, 56), 76% were male, 90% had HIV viral load A meta-analysis of health utilities (preference-based quality of life) in chronic hepatitis C patients

Yasmin Saeed, Leslie Dan Faculty of Pharmacy, University of Toronto; Joanna Bielecki, Toronto Health

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**Table 1.**

<table>
<thead>
<tr>
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<th>HR-QOL (VAS) β (95% CI)</th>
<th>EQ5D β (95% CI)</th>
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<tbody>
<tr>
<td>Mean score at DAA initiation</td>
<td>65 (60, 69)</td>
<td>0.77 (0.73, 0.81)</td>
</tr>
<tr>
<td>Pre-treatment Rate (Secular trend before DAA initiation, per year)</td>
<td>-0.5 (-1.0, 4.9)</td>
<td>-0.004 (-0.009, 0.0004)</td>
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<td>Change in Intercept (Immediate effect)</td>
<td>2.0 (-1.0, 4.9)</td>
<td>-0.004 (-0.03, 0.02)</td>
</tr>
<tr>
<td>Post-DAA Rate (Compared to pre-treatment rate, per year)</td>
<td>1.6 (-1.3, 4.4)</td>
<td>0.005 (-0.021, 0.031)</td>
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**A meta-analysis of health utilities (preference-based quality of life) in chronic hepatitis C patients**

Yasmin Saeed, Leslie Dan Faculty of Pharmacy, University of Toronto; Joanna Bielecki, Toronto Health
Economics and Technology Assessment (THETA) Collaborative; Lusine Abrahamyan, Toronto Health Economics and Technology Assessment (THETA) Collaborative; Petros Pechlivanoglou, Child Health Evaluative Sciences, The Hospital for Sick Children; Murray Krahn, Toronto Health Economics and Technology Assessment Collaborative (THETA), University of Toronto; William WL Wong, School of Pharmacy, University of Waterloo

BACKGROUND: Chronic hepatitis C (CHC) has been shown to negatively impact patients’ quality of life. Health utility is a measure of quality of life that incorporates a patient’s preference for their current health state, and can be used to quantify the burden of a disease in terms of quality-adjusted life years lost. There has been an explosion of new research on health utilities in CHC patients since the advent of new antiviral therapies, yet no meta-analysis has been published in this area since 2008.

PURPOSE: To synthesize the health utilities of patients with CHC in order to understand the burden of CHC; and for use in economic evaluations of CHC treatments and screening programs to guide funding decisions.

METHOD: We searched MEDLINE, EMBASE, and the Cochrane Library for studies measuring health utilities in CHC patients using any instrument. The search was limited to English-language papers published from 1989 onward. Results were pooled by disease severity, treatment status, and utility instrument using meta-analysis. A meta-regression was used to examine patient and study design factors that impact utility scores.

RESULTS: Forty records met inclusion criteria and were included in the analysis. Results for studies using the EQ-5D-3L instrument are presented here. Sixteen clinical studies with a total of 6,012 CHC patients measured utilities using the EQ-5D-3L instrument. The mean age of patients was 45 years, and 64% were male.

Mild/moderate CHC was associated with a mild impairment in health utility (pooled utility score 0.79; 95% CI 0.75,0.82). Compensated cirrhosis (0.73; 0.63,0.83) and hepatocellular carcinoma (HCC) (0.75; 0.68,0.81) utilities were slightly lower, and decompensated cirrhosis utilities were substantially lower (0.65; 0.58,0.71). Being on treatment also lowered utilities (0.74; 0.71,0.78), but sustained virologic response (SVR) (0.82; 0.76,0.87) resulted in higher utilities than mild/moderate CHC.

There was a large degree of heterogeneity between studies in terms of study and patient characteristics. A meta-regression found that randomized controlled trials had higher mean utilities than observational studies (p < 0.05).

Limited utility data exist for certain subpopulations of CHC patients, including: decompensated cirrhosis, HCC, and post-transplant patients; patients with comorbidities such as HIV and haemophilia; and socioeconomically marginalized patients.

CONCLUSIONS: CHC is associated with a significant impairment in quality of life, particularly in advanced disease. Curative therapy can alleviate this burden. The large degree of heterogeneity between studies highlights the need to incorporate synthesized data from a wide range of studies in economic analyses of CHC screening and treatment, as well as the importance of incorporating the associated uncertainty surrounding these estimates. This review included a significant amount of new data compared to a previously published meta-analysis (McLernon 2008). However, further research is still needed in certain subgroups of CHC patients.

Can healthcare-associated HCV outbreaks occur when intravenous medication vials are accessed with clean needles and syringes for use in multiple patients?

Selena Sagan, McGill University; Julie Magnus, McGill University; Sophie Breton, Queen’s University; Rachel Phelan, Queen’s University; Melanie Jaeger, Queen’s University; Janet van Vlymen, Queen’s University; Andrew Day, Kingston General Hospital Research Institute

BACKGROUND: Healthcare-associated hepatitis C virus (HCV) outbreaks continue to occur despite widespread implementation of infection control
guidelines. In Ontario alone, there have been four independent HCV outbreaks documented in outpatient endoscopy clinics in the past 5 years, resulting in 14 new HCV infections. Thorough investigation of each outbreak concluded that contaminated medications, administered by the anesthesiologist, were the likely source of patient-to-patient transmission. Despite these findings, the anesthesiologists denied reusing needles and syringes to access multidose vials. While it is clearly unacceptable to reuse needles or syringes, it is a recognized practice to share multidose medication vials between patients provided new needles and syringes are used with aseptic technique.

PURPOSE: We hypothesized that when caring for HCV-infected patients, anesthesiologists may inadvertently contaminate the vial diaphragm, and that subsequent access with sterile needles and syringes can transfer HCV into the medication where it remains stable in sufficient quantities to infect subsequent patients.

METHODS: We simulated contamination of multidose medication vials in healthcare settings using cell culture-derived HCV (HCVcc) to determine: 1) whether HCV can be transferred, via a sterile needle and syringe, into a medication vial if the rubber access diaphragm is contaminated; 2) whether HCV remains viable in commonly used medications in sufficient quantities over time to initiate an infection; and 3) whether cleaning with 70% isopropyl alcohol is sufficient to eliminate infectivity. In addition, we surveyed 546 anesthesiologists across Canada to assess how common reuse of multidose medication vials is in clinical practice and how contamination risks are mitigated.

RESULTS: Contamination of the rubber diaphragm of medication vials with 33 uL (mean volume of an accidental drop) of HCVcc (800,000 IU/mL) and subsequent access with sterile needles and syringes resulted in contamination of the vial contents in sufficient quantities of HCV to initiate an infection in cell culture. Second, HCV remains viable for ≥72h in several commonly used medications. Third, a single wipe of the vial diaphragm with 70% isopropyl alcohol was not sufficient to eliminate HCV infectivity. Importantly, 83.6% of anesthesiologists reported sometimes or routinely reusing medication vials for multiple patients and only 11.7% reported using the recommended cleaning procedure of scrubbing the vial diaphragm for 10 s and allowing it to dry.

CONCLUSIONS: HCV can be transferred, via sterile needles and syringes, into medication vials if the diaphragm is contaminated with medically relevant quantities of HCV and the virus remains stable in several commonly-used medications over time. Furthermore, a single wipe of the vial diaphragm with 70% isopropyl alcohol is not sufficient to eliminate HCV infectivity. Given these findings, as well as our survey responses, we recommend investment in education and knowledge translation across medical specialties, division (or elimination) of multidose vials, and investment in single-dose vials to minimize nosocomial HCV infections.

Acute flares of chronic HBV in HBeAg negative carriers undergoing loss of HBsAg

Nabeel Samad, University of Manitoba; Gerald Minuk, University of Manitoba; Stephen Wong, University of Manitoba; Carla Osiowy, University of Manitoba; Julia Uhanova, University of Manitoba

BACKGROUND: Acute and potentially life-threatening flares of chronic hepatitis B virus (HBV) infections have been described in HBeAg positive individuals undergoing spontaneous HBeAg seroconversion. Whether similar flares occur in HBeAg negative individuals undergoing spontaneous HBsAg seroconversion has yet to be reported.

PURPOSE: 1) To describe a fatal flare of chronic HBV in an HBeAg negative individual not associated with; basal core promoter (BCP) mutations, superimposed HDV, HEV or other viral infections, or non-viral causes of acute hepatitis. 2) To document the incidence of acute flares in HBeAg negative individuals undergoing spontaneous HBsAg seroconversion.

METHOD: Case Report and review of electronic HBV database from an urban, tertiary, health care facility.
RESULTS: A 49-year-old Vietnamese patient with inactive HBeAg negative (pre-core mutant positive) chronic HBV (genotype C, viral load 758 IU/ml) developed clinical and biochemical evidence of acute liver failure (ALT 2482 U/L, Total bilirubin 420 umol/L) in the absence of BCP mutations, serologic evidence of HDV, HEV or other viral infections and negative testing for non-viral causes of acute hepatitis (drugs, vascular thromboses, tumor, autoimmune hepatitis etc.). HBsAg levels fell from 4565 IU/ml at baseline to 317 IU/ml during his hospital stay. The patient succumbed to complications of acute liver failure. On review of the HBV database, 76 HBsAg positive, HBeAg negative individuals were identified who had undergone spontaneous HBsAg seroconversions during mean 8 years of follow-up. Of these, six (4.5%) had associated ALT flares > 10 x baseline. In only one case (described above) was the flare associated with a fatal outcome.

CONCLUSION: Acute, potentially life-threatening flares of chronic HBV can occur in HBeAg negative individuals who have undergone or appear to be undergoing spontaneous HBsAg seroconversion.

Pilot project to increase HCV linkage to care in Ontario’s First Nations

David Smookler, University Health Network; Leroy Quoquat, Lac Seul First Nation; Jordan Feld, Toronto Centre for Liver Disease; Hemant Shah, University of Toronto, Toronto Centre for Liver Disease; John Kim, Public Health Agency of Canada

BACKGROUND: The government is dedicated to eliminating HCV in Canada by 2030. With SVR rates typically >95%, the challenge for HCV treatment is linkage to care. Multiple studies show First Nations people have especially high exposure to HCV, as well as other blood-borne infections; yet Indigenous Canadians have some of the poorest access to care in the country. How to deliver care to this demographic is essential knowledge for meeting Canada’s target. Comprehensive data on incidence and prevalence of HCV in First Nations communities is lacking, due to limited testing. Complicating efforts to study this is a long history of unethical research performed on Aboriginal people in Canada, which has often left communities feeling used and disempowered.

We are developing a model of HCV testing and treatment for remote First Nations in Northwestern Ontario that addresses these challenges. By partnering with community leaders and local healthcare providers, introducing novel techniques for gathering HCV blood samples, and training local community members to obtain samples, we hypothesize that we can dramatically increase regional HCV testing and improving access to care. Here we recount the results of our pilot endeavor to introduce testing in a First Nation community in Northwestern Ontario.

METHOD: A pilot community was selected based on the invitation of the local chief, after the proposal was presented to a Chiefs’ Committee on Health in Northwestern Ontario. The community’s health director assembled a testing team composed of health staff and members of that community. The team developed a locally relevant approach to informing and incentivizing community members to participate in HCV testing. Team members were trained in Dry Blood Spot (DBS) sample gathering by the Public Health Agency of Canada. Pilot testing drive initiated in January 2017.

RESULTS: 226 people in a community with an adult population of 655 were tested for HCV. 85% of those were also tested for HIV, and >90% for HBV. Testing was conducted over 3.5 days. Costs for the reagents and sample analysis were covered by the federal government; and local government was willing to pay for staff time and rewards for attendance, resulting in minimal financial outlay for the initiative. Qualitative evaluation of satisfaction of team members suggested excellent response to the initiative, with strong encouragement from the local Health Director to continue the initiative in other communities.

CONCLUSION: This pilot gathered blood samples using DBS, which is presently unusual in Canada for HCV testing with linkage to care. This tactic of HCV testing, using DBS; with a community-guided, participatory approach; utilizing local community members is a successful method to obtain widespread HCV testing, one which could form the basis for an expanded model to test for
infectious disease in First Nations communities throughout Canada.

A descriptive analysis of the effectiveness of direct acting antiviral therapies at achieving SVR-12 in chronic HCV patients with various co-morbidities and characteristics in New Brunswick

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BACKGROUND: Chronic Hepatitis C Virus (HCV) affects approximately 0.7% of Canadians and is associated with significant burden for both patients and the healthcare system. New Direct Acting Antiviral (DAA) treatments have been demonstrated to be up to 99% effective across a variety of genotypes.

PURPOSE: There is limited research demonstrating the effectiveness of DAs in New Brunswick (NB) patients with differing underlying comorbidities. Using data contained within the Hepatitis C Positive and at Risk (HEAR) database, the study aims to describe cure rates amongst patients in NB who presented with various comorbidities at baseline in order to inform physicians, patients and policy makers.

METHOD: Data was collected from the HEAR database, an anonymous registry that contains data on roughly 800 New Brunswick patients who are either infected with HCV or at-risk of infection. Patients who received treatment between April 2014 and April 2016 and whom had SVR-12 results available prior to April 30, 2016 were included in the current analysis. Univariate comparisons of those who did and did not achieve SVR-12 on the basis of a number of potential confounders were conducted using Fisher’s exact tests, chi-squared tests, p-values and 95% confidence intervals, as appropriate.

RESULTS: Of the 139 patients in the registry who received DAA containing therapy for their HCV infection, 92.8% (95% CI, 88.5–92.2) achieved SVR-12. No medical or psychiatric comorbidities reported at baseline were found to be a statistically significant predictor for treatment success or failure.

CONCLUSIONS: The findings of the current study demonstrate that patients in NB can be successfully treated with a variety of DAA regimens, regardless of their baseline comorbidities. This study adds valuable local data to the treatment knowledge base with the potential to assist in informing policy makers involved in expanding access and care across the province.

A retrospective analysis of pegylated-interferon (PEG-IFN) treatment outcomes in chronic hepatitis B (CHB)

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BACKGROUND: PEG-IFN is first-line therapy for CHB offering the advantage of a finite treatment, but is rarely used due to concerns about tolerability and efficacy. Nucleot(s)ide analogues (NUC) therapy are well tolerated but require prolonged therapy, with significant cost, and potential for adverse effects long-term.

AIM: We aim to assess tolerability and outcomes in treatment-naive patients who received PEG-IFN for CHB. The primary outcome assessed was durability of off-treatment response (i.e., HBV DNA).

METHODS: In this retrospective cohort study, CHB patients who received antiviral therapy from January 1st, 2007, to July 1st, 2017, were identified via the Calgary Liver Unit Hepatitis B database. Data collected included age, sex, ethnicity, FibroScan® results, labs (HBV DNA, genotype, qHBsAg, ALT), treatment duration, on treatment virological response (HBV DNA and qHBsAg,
if available) and reported side effects. Patients treated for hepatitis D coinfection with Peg-IFN (n=4) were excluded.

**RESULTS:** In total, 893 patients were started on antiviral therapy, of which 50 (5.6%) patients received PEG-IFN therapy, (including 3 currently on treatment). In the PEG-IFN treated patients, median age was 43±9.3 years, 72.3% male, 81% East Asian, 6.38% A, 29.7% B or C, 6.4% D, 57% unknown genotype. 70.2% (33/47) completed the 48 weeks of PEG-IFN therapy. 29.2% (14/47) discontinued IFN early (64.2% due to treatment failure & 21.4% due to side effects). To date, 18/47 (38%) who received PEG-IFN did not receive NUC treatment during median follow-up of 33.9 months (+27.5, range 0.9–82.1), with median ALT 24 U/L and median log HBV DNA levels 2.8 log IU/mL on most recent follow-up. 3/47 (6%) are lost to follow-up or being monitored to determine need for subsequent therapy. 55% (26/47) of patients treated had virological and biochemical rebound requiring initiation of a NUC within a median of 18.7 months (±15.6, range 3.2–55.4) post PEG-IFN treatment. In those with sustained response to Peg-IFN, 13/18 had available end-of-treatment qHBsAg of which 8/13 (61.5%) had levels

**CONCLUSION:** In this cohort study, 38% of patients treated with Peg-IFN did not require subsequent antiviral therapy, including many with low qHBsAg levels (< 1 000 IU/mL), indicating robust immune control of HBV. Careful patient selection and adherence to treatment discontinuation rules based on qHBsAg levels will optimize usage of PEG-IFN for CHB.

**CONCLUSION:** Improved bone and renal safety at 1 year after switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF): Results from 2 phase 3 studies in HBeAg-positive and HBeAg-negative patients with chronic hepatitis B (CHB)

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**BACKGROUND:** TAF has shown less bone and renal effects with similar efficacy rates compared to TDF in two large multinational Phase 3 studies after 96 weeks of double-blind (DB) treatment. We evaluated patients who completed 96 weeks of DB treatment with TAF or TDF and switched to open label (OL) treatment with TAF, including those with 1 year of data (through Week 144) to determine changes in bone mineral density (BMD), creatinine clearance (CrCL), and the maintenance of viral suppression.

**METHODS:** In two identically-designed studies, 1298 CHB patients who were HBeAg-negative (Study 108; N=425) or HBeAg-positive (Study 110; N=873) were randomized and treated with TAF 25 mg QD or TDF 300 mg QD. At Week 96, 541 (42%; TAF 361; TDF 180) patients enrolled in these ongoing 8 year studies had completed DB treatment with TAF or TDF and switched to OL TAF 25 mg QD. DXA scans were evaluated every 24 weeks as were serial assessments of CrCL and viral suppression. Analyses included subjects with values at Week 96 and at Week 144 for creatinine clearance (n=401), spine BMD (n=288) or hip BMD (n=287), HBV DNA (n=394) and ALT normalization by AASLD criteria (n=398).

**RESULTS:** CrCL improved significantly in patients who switched from DB TDF to OL TAF at Week 144 compared to Week 96 (n=122, median (Q1, Q3) change = +3.6 (-4.2, +8.4) ml/min, p < 0.001); and remained stable in those previously receiving TAF. BMD also showed improvements at Week 144 from Week 96 among patients switched from DB TDF to OL TAF (hip: n=88, mean (SD) % change = +0.94% (1.825), p < 0.001; spine: n=88, mean (SD) % change = +1.54% (2.680), p < 0.001). BMD changes in hip and spine for DB TAF patients entering the OL TAF period were relatively stable. Compared to results at Week 96, high rates of virologic control (HBV DNA < 2 9 IU/mL) were maintained across patients in both treatment groups at Week 144 (TDF
findings will explore a gendered Indigenous perspective to inform the development of a peer-led support model to improve engagement in HCV and HIV health care.

METHODS: Peers4Wellness is an Indigenous Peer-led Community Based Research project. It applies a “Two-eyed-Seeing” framework which emphasizes sharing circle data collection, and weaves Indigenous and Western methods together. Sharing circle methodology imbued with Indigenous philosophies and protocols will be used as the main data collection method for participants and peer navigators. Individual interviews will be used for consultation with community organizations. Study findings will be synthesized through community-led participatory data coding and analysis.

RESULTS: We have been successfully engaging the community to build the relationships and trust necessary for sharing circle recruitment. In developing our sharing circle model, we carefully considered the special vulnerabilities and needs of our research participants. This ensured protection of the cultural and personal safety of women participants, and respected Indigenous practice. The study includes a total of five sharing circles, five interviews and a total of 40 research participants. We expect the majority of participants to have HCV lived experience. We expect to conclude our study in the Spring of 2018.

CONCLUSION: This study engages Indigenous communities to address some of the research and practice gaps in relation to HCV health care engagement and peer support among IPC. It introduces an innovative Indigenous model of peer support for IPC with lived HCV and/or HIV experience. Peers4Wellness embodies a reconciliation-based research approach which emphasizes both Indigenous and Western paradigms.

Peers4Wellness: Creating Indigenous ways of HCV care and support utilizing the peer navigation concept

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BACKGROUND: In Canada, the rates of Hepatitis C virus (HCV) are at least five times higher among Indigenous Peoples in Canada (IPC), particularly Indigenous women. Yet, IPC are underrepresented in HCV health care programs, likely due to the lack of Indigenous ways of care and support. Utilizing the concept of conventional peer navigation (PN), we will provide an Indigenous approach to address the under engagement of IPC with HCV health care. In Indigenous culture, it is critical to build relationships and trust before developing any care model. PN provides a promising concept to be re-contextualized to meet the specific needs of Indigenous people with lived HCV and/or HIV experiences and will provide evidence for improving health care engagement.

PURPOSE: This study begins with building relationships and trust with Indigenous communities. In doing so, we will address some of the gaps in PN literature and practice, with a focus on Indigenous women (cis- and trans-gender) with lived HCV and/or HIV experience in Vancouver and the surrounding region. It involves a three-pronged sharing circle consultation with the following community stakeholders: 1) Indigenous women with lived HCV and/or HIV experience, 2) peer navigators, and 3) community organizations. Study

Z-PROFILE: Real-world utilization and effectiveness of elbasvir/grazoprevir in adult patients with chronic hepatitis C in Canada

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BACKGROUND: Elbasvir/grazoprevir (EBR/GZR) is approved in Canada for the treatment of chronic HCV infection with genotypes (GT) 1 and 4, with/without ribavirin, and for GT3 with sofosbuvir (SOF). Broad government and private reimbursement is now available.

PURPOSE: The aim of this study is to describe the effectiveness of EBR/GZR and the profile of patients selected for treatment in a Canadian real-world setting.

METHOD: A multicenter retrospective chart review of HCV-infected patients treated with EBR/GZR among selected Canadian health care providers was undertaken. In this interim analysis, patients initiating EBR/GZR treatment between 01/2016 and 05/2017 were included.

RESULTS: A total of 185 patients from 10 sites were included in this interim analysis. The mean age was 53.2 years, 56.8% were male, 80.5% Caucasian and 7.6% Aboriginal. Genotype distribution included patients infected by GT1a (n=116, 62.7%), GT1b (n=30, 16.2%), GT1 subtype unavailable (n=8, 4.3%), GT3 (n=19, 10.3%), GT4 (n=8, 4.3%), GT6 (n=1, 0.5%) or mixed infections (n=3, 1.6%). Pre-treatment fibrosis was evaluated by FibroScan in 86% of cases. Fibrosis score ranged from F0–1 (n=101, 54.6%), F2 (n=34, 18.4%), F3 (n=17, 9.2%), F4 (n=32, 17.3%) and 1 unknown. In this cohort, 7.6% had CKD stages 3–5 and 21.1% had documented injection of illicit drugs within 12 months of EBR/GZR treatment initiation. Baseline NS5A resistance-associated substitutions (RAS) were only detected in 1/17 evaluated patients (H58wt/Y) infected by GT1a or GT1 subtype unavailable. Prescribed regimens included: EBR/GZR x 12 weeks (n=168, 90.8%); or EBR/GZR+RBV x 16 weeks (n=17, 9.2%). Patients receiving longer courses of treatment were most often infected by GT1a (n=12) and/or treatment experienced (n=14, including 3 who previously failed all-oral DAAs). SOF was prescribed with EBR/GZR for all 19 patients with GT3. Per protocol evaluation demonstrated an SVR12 of 99.0% (97/98) and an SVR24 of 98.2% (56/57). The single relapsed patient was F1, GT1A and PegIFN+RBV treatment-experienced who received 16 weeks of EBR/GZR+RBV. One patient also had a confirmed reinfection by genetic testing.

CONCLUSION: Following approval of EBR/GZR in Canada, it has been used quite broadly across its entire range of indications. The achievement of SVR in all but one patient to date in the per protocol analysis of this Real-World cohort supports the utility of EBR/GZR as a therapeutic modality for the treatment of chronic HCV infection. This study is collecting Real-World Evidence on 400 patients from 25 sites across Canada.
Reduced risk of HCV seroconversion among individuals undergoing psychotherapy: A population-based retrospective cohort of multi-testers 1992–2013

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BACKGROUND: Most new hepatitis C Virus (HCV) infections in developed countries occur among people who inject drugs (PWID); many of whom have concurrent mental illnesses. Although intervention strategies are recommended including psychotherapy, there is limited data on the effectiveness of psychotherapy.

PURPOSE: To examine the effectiveness of psychotherapy counseling for reducing the risk of HCV seroconversion, and to compare this association across various at-risk subgroups.


STUDY DESIGN: Population-based retrospective cohort, with time to event analysis.

METHOD: Incidence rates of HCV seroconversion was calculated using an intercept only Poisson regression model and reported per 1,000 person-years. Univariable and multivariable Cox proportional hazards model was used to examine the associations between psychotherapy counseling and HCV seroconversion, and this analysis was repeated on stratified subgroups.

RESULTS: A total of 364,774 individuals were included in the study cohort, of which 7,669 (2.1%) experienced a HCV seroconversion event, and 14,560 (4.0%) underwent at least one psychotherapy session. Incidence of HCV seroconversion were highest among persons who inject drugs (14.9 [95%CI: 14.4, 15.4]), individuals living with...
METHODS: Twenty-two patients recruited from 2014–2016 from community with prior experience to HCV therapy

EXCLUSION: Liver transplant, HCC, HBV, Hemoglobinopathies (Sickle cell), HIV RNA undetectable, CHF, Renal insufficiency, prior allergy to DAA’s, cirrhosis of liver with MELD > 12, sepsis, cardiomyopathy, active IVDU, active cocaine, no family support, non-compliant to drug rehab program, Major depression, decompensated affective disease, treatment failure prior because non-compliance, high dose PPI

PRIOR DAA FAILURE:
• n=7 were on Harvoni
• n=8 were on Olysio
• n= 5 Viekera Pak
• n=2: Sofosbuvir plus Ribavirin

All HIV co-infected individuals were on Atripla; while few were also on Raltegravir.

FURTHER SUBDIVIDED INTO TWO GROUPS:
• Group A (n=10): Elbasvir 100 mg + Grazoprevir 50 mg + Sofosbuvir 400 mg for 12 weeks
• Group B (n=12): Elbasvir 100 mg + Grazoprevir 50 mg + Sofosbuvir 400 mg for 12 weeks with RBV 600 mg a day

PATIENT CHARACTERISTICS:

Group A: (n = 10) Mean age 59, Genotype 1a (n = 5), 1b (n = 5), Mean HCV viral load 4.7 million, Mean CD4 count 560, Mean HIV viral load 3699. Out of the total 10, past response unknown in 4/10, 3/10 were partial responders and 3/10 were relapsers.

Group B: (n = 12) Mean age 58, Genotype 1a (n =6), 1b (n = 6), Mean HCV viral load 3 million, Mean CD4 count 436, Mean HIV viral load 387. Out of the total 12, past response rate was unknown in 4/12, 4/12 were relapsers, 3/12 were partial responders and 1/12 was non responder.

RESULTS:
In group A HCV RNA load became undetectable in 8/10 by week 4 and 10/10 by week 8, retention was 100% and ITT was 100%. Mean hemoglobin and ALT remained stable throughout 24 weeks.

CONCLUSION: Psychotherapy is effective at reducing the risk of HCV seroconversion among individuals with substance use issues, and the number of counseling visits was shown to be influential. Psychotherapy could be part of a package of services targeted to prevent HCV incidence to achieve World Health Organization elimination goals.

Elbasvir, grazoprevir; with or without ribavirin and its effectiveness with sofosbuvir resulting SVR in chronic hepatitis C genotype 1 prior experienced co-infected individuals. A randomized open label clinical prospective trial: EGRESS- C

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OBJECTIVES: Oral directly acting anti-viral therapy has virtually cured Chronic Hepatitis C. However, for a few sub-groups (genotype 1,3 and 4 with co-infection with HIV ) in HCV remain challenging. Also baseline resistance associated variance in genotype 1a and 3 need longer duration of therapy.

AIM: Study evaluates the safety and SVR of Elbasvir, Grazoprevir; with or without Ribavirin and its effectiveness with Sofosbuvir
In group B HCV RNA load became undetectable in 10/12 by week 4 and 11/12 (91.67%) by week 8. One patient withdrew due to shortness of breath and chest pain. Retention was 91.67% and ITT was 100%. Mean hemoglobin and ALT remained stable throughout 24 weeks.

Side Events:
- Fatigue, Nausea, Vomiting, Headache, Anemia (group B 9/29), Insomnia, Diarrhea
- Constipation, UTIAbdominal pain, Hematuria, Renal Stone
- Gouty attack, Hypoglycemia, Hyperglycemia, URI, Dysgeusia
- Pruritus, Pneumonia (Group B, stopped meds and got hospitalised)

CONCLUSION: Clinical trial reveals promising SVR in a very selective Cohort of Chronic Hepatitis C Co-Infection in Prior experienced population with severe fibrosis and significant morbidities. A larger trial needs to validate.

Socio-demographic characterization of Calgary’s cohort of the surveillance of persons who inject drugs (PWID) for hepatitis C virus (HCV) seroconversion in inner city clinics study

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BACKGROUND: Approximately 60% of incident HCV infections are due to intravenous drug use. The ability to engage PWID in prevention, testing and treatment for HCV remains challenging.

PURPOSE: Understanding the sociodemographic characteristics of PWID could inform the need for additional resources, target screening initiatives and treatment programs.

METHODS: Our institution was part of a larger prospective cohort study to enroll HCV negative PWID in order to assess candidates for the HCV vaccine. All participants provided written informed consent at the time of study enrolment and completed an interviewer-administered questionnaire. Data were gathered to document drug use, sexual health, viral hepatitis/ HIV testing history, and community services utilization.

RESULTS: In total, data were collected from 239 PWID (median age 40, 82% M, 65% Caucasian, 19% Aboriginal, 0.8% (2/239) HIV+). 28% (67/239) were anti-HCV positive (median age 41, 73% M, 72% Caucasian, 1.5% (1/67) co-infected with HIV). 55% (37/67) were referred for further follow-up and testing, but 45% were lost to follow-up. The drug most commonly injected was crystal methamphetamine (39%), anti-HCV+ participants reported using more opiates than HCV - people; morphine (23% vs. 11% p < 0.05), the anti-HCV+ group reported using less crystal methamphetamine and cocaine (usually by non-injection routes). 29% of the anti-HCV+ group had been enrolled in a methadone program compared to 9% of the HCV – group (P< 0.005). There was no significant difference in history of previous incarceration (78% vs. 79%), and only 10% of both groups reported IDU during their incarceration. The majority of the migration to Calgary was interprovincial (usually Edmonton), followed by British Columbia and Ontario. Both groups also reported similar number of sexual partners in the last six months (usually 1 partner or 2–5 partners), however a high proportion did not use condoms (24% HCV- group vs. 40% of the antiHCV+ group P < 0.05). Although, 66% of the group reported previous HCV testing, ~ 32 % of the antiHCV+ group reported testing over 4 years ago, compared to 14% of the HCV negative (P<0.05). 79% of the total cohort and 73% of the antiHCV+ group reported previous HIV testing.

CONCLUSION: In this cohort study of 239 PWID in Calgary, we note significant differences in injection drug use in HCV+ vs. anti-HCV persons, as well as a longer interval since last HCV testing. More HCV+ people had engaged with opiate substitution services, making these sites vital in HCV programs. Additional identification of sociodemographic risk factors in PWID and long term follow up is important to understand trends on high-risk behaviour, improve access to healthcare and community services and to ultimately reduce HCV risk, increase testing and HCV treatment.
Biomarkers of disease activity during and after pregnancy in patients with autoimmune hepatitis

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BACKGROUND: Autoimmune hepatitis (AIH) is a disease with a strong female preponderance, with a female to male ratio of 3:1 in type 1 AIH and reaching 9:1 in type 2 AIH. In recent years, due in large part to the success of immunosuppressive treatments, an increasing number of young women with AIH are becoming pregnant, which poses a serious challenge for clinicians. Pregnancy in autoimmune hepatitis patients has been linked to both spontaneous remission and post-partum flares of disease activity or new onset of AIH. The influence of pregnancy on AIH is poorly defined; the processes involved are unknown and there are no validated biomarkers to monitor/predict disease activity in these patients.

PURPOSE: The aim of this study was to identify biomarkers that could predict the impact of pregnancy on the course of AIH and identify factors responsible for the spontaneous remission and flares of AIH observed during and after pregnancy.

METHOD: We used our newly created AIH Research Biobank, composed of biological samples and clinical data from patients with AIH at the Centre Hospitalier de l’Université de Montréal (CHUM) to measure cytokine levels in the plasma of AIH patients during pregnancy. Expression of cytokines by peripheral blood mononuclear cells (PBMC) from these patients was also assessed using qPCR.

RESULTS: ALT levels during pregnancy were significantly lower than levels before pregnancy or after delivery (p< 0.0001). Plasma levels of IL-2 were significantly higher during pregnancy (30.1±3.2 pg/mL, n=4) compared to non-pregnant AIH patients (4.2±0.41 pg/mL, n=18, p< 0.0001), AIH/PBC overlap syndrome patients (4.6±0.41 pg/mL, n=12, p< 0.0001) or type 2 AIH patients (6.9±1.1 pg/mL, n=2, p< 0.0001). Plasma levels of IL-16 during pregnancy were similar to those of AIH patients (p=0.4680). Expression of IL-2 by PBMCs was significantly higher during pregnancy compared to AIH patients (p=0.0012). Expression of IL-16 by PBMCs rapidly increased after delivery (from 80.5±21.5 to 5579±3383). Expression of IL-16 during and after pregnancy correlated significantly with ALT levels (r=0.9791, p=0.0209).

CONCLUSION: Lower ALT levels during pregnancy in AIH patients are associated with higher plasma level of IL-2 and an increased secretion of IL-2 by PBMCs. Despite being a pro-inflammatory cytokine and growth factor for effector T cells, low levels of IL-2 as those observed during pregnancy, could favor the expansion of CD4+ regulatory T cells and lead to an anti-inflammatory response. IL-16 expression could be involved in the flares of liver disease following delivery. Further research is needed to understand the role of IL-2 and IL-16 on disease activity during and after pregnancy in patients with AIH.

Integrative Meta-analysis of Genomics in NASH

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BACKGROUND: Non-alcoholic steatohepatitis (NASH), a disease involving inflammation and fat accumulation in the liver, has become increasingly prevalent as an indication for liver transplantation. The primary objective of this meta-analysis is to determine whether specific single nucleotide polymorphisms (SNPS) are associated with NASH pathogenesis.

METHODS: MEDLINE was searched for relevant studies up to May 2017, with screening moderated by a third-party arbiter. Exclusion criteria were any studies based on cell lines, animal models,
or studies on the progression of NASH. Studies were curated, with data on demographic and clinical features. Measures of association between the most common SNPs and NASH were analyzed via regression analysis. Ingenuity Pathway Analysis software was used to identify the key SNPs and associated pathways central to NASH pathogenesis, taking into account protein-protein interactions.

RESULTS: There were 293 studies based on MeSH (Medical Subheadings) terms for NASH and SNPs. Of these, 123 studies were included. Extracted clinical information and demographics included gender, age, body mass index, liver enzymes and diabetes status. Preliminary results show SNPs in the PNPLA3 gene (associated with adipocytes and cell metabolism), specifically rs738409, to be significantly associated with NASH incidence. Additionally, other SNPs in PNPLA3 and TM6SF2 were the most predictive of fibrogenesis associated with NASH.

CONCLUSIONS: This integrative meta-analysis of gene wide association studies in NASH suggests that SNPs in PNPLA3 are central to NASH pathogenesis and development of fibrosis. These results indicate a genetic risk for NASH that is independent of demographic factors, and suggest that screening for genetic risk in patients with NAFLD is a future strategy to prevent development of cirrhosis and its complications.

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Wilsonian fulminant hepatic failure in children and adolescents: A systematic review of 274 cases
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BACKGROUND: Wilsonian Fulminant Hepatic Failure (WFHF) is a serious condition, typically requiring liver transplantation (LT). As a result of its relative rarity, WFHF has been difficult to study in depth. Data in pediatric populations.

RESULTS: A total of 56 (case reports [30], case-series [23] and cohort studies [3]) manuscripts involving 274 participants met the study inclusion criteria. The majority of studies were conducted in Asia (21) followed by 19 in North America, 15 in Europe, and 1 in Australia. Studies ranged in size from 1–61 subjects with a median age of 12.9 years at presentation (range 4.0–17.6 years). Females represented 74% (202/274) of all patients. Kayser–Fleischer rings were seen in 80% (191/274), specifically rs738409, to be significantly associated with NASH incidence. Additionally, other SNPs in PNPLA3 and TM6SF2 were the most predictive of fibrogenesis associated with NASH.

CONCLUSIONS: This integrative meta-analysis of gene wide association studies in NASH suggests that SNPs in PNPLA3 are central to NASH pathogenesis and development of fibrosis. These results indicate a genetic risk for NASH that is independent of demographic factors, and suggest that screening for genetic risk in patients with NAFLD is a future strategy to prevent development of cirrhosis and its complications.

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Association of distance from a tertiary care centre with access to waitlist placement, receipt of liver transplantation, and survival in Alberta.

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BACKGROUND: Centralization of specialized health care services such as liver transplantation (LT) is advocated to improve outcomes. Studies from the USA have shown poorer outcomes with increased travel distances to transplant centres. In the Canadian province of Alberta, prospective LT patients are evaluated at two major centres (Calgary and Edmonton) with waitlisting and LT occurring in Edmonton.

AIMS: To evaluate the association between distance from the Southern Alberta Liver Transplant Clinic (SALTC) in Calgary and: 1) waitlisting for LT; 2) receiving LT; and 3) mortality.

METHODS: We conducted a retrospective cohort study of all patients with chronic liver failure seen at SALTC between July 1, 2004 and December 31, 2014 using the LT databases in Calgary and Edmonton. Distance from SALTC was classified as 1) rural (>150km); 2) Calgary area (36–150km); and 3) city of Calgary (< 35km). Crude and adjusted logistic regression models and competing risk Cox regression models were performed to identify time from first pre-transplant assessment at SALTC to 1) wait-listing; 2) transplant; and 3) death (or delisting for reasons other than recovery), stratified by distance from SALTC. Models were adjusted for age, sex, etiology, and MELD, MELD-Na and 5vMELD scores.

RESULTS: A total of 558 patients were seen at SALTC during the study period (64.0% male). The most common diagnoses were hepatitis C virus (n=144; 25.9%), hepatocellular carcinoma (HCC) (n=123; 22.1%), and alcohol-induced cirrhosis (n=109; 19.6%). Median MELD at transplant was 22 (IQR 18–28), and 23% were listed with MELD exception points. A total of 262 (46.9%) were wait-listed of whom 146 (55.7%) received a transplant. 102 (38.9%) waitlisted patients from SALTC died or were delisted while waiting for LT (29.4% had HCC). There was no significant association between distance to SALTC and the odds of being waitlisted or the odds of mortality even after adjustment for confounders. The crude odds ratio of receiving a transplant for those living in a rural area was significantly lower than those living within Calgary (OR 0.49; 95% CI 0.26–0.91). There was no significant difference in time to waitlisting or mortality based on distance to SALTC even after confounder adjustment. The crude hazard ratio for transplant was lower for those living in rural areas compared to Calgary (HR 0.56; 95% CI 0.36–0.88).

CONCLUSIONS: Distance from the SALTC does not influence time to wait-listing or death, but does significantly influence time to transplant. The hazard and odds ratio of receiving LT are lower for those in rural areas followed by the SALTC. With a nearly 40% waitlist mortality for SALTC patients and evidence that distance to our centre influences LT rates, future studies should examine this relationship at a provincial level, and work to identify barriers and enablers to improve equitable access to LT in Alberta.

Systematic integrative analysis of gene expression identifies HNF4A as the central gene in pathogenesis of non-alcoholic steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the Western world, and encompasses a spectrum from simple steatosis to steatohepatitis (NASH). There is currently no approved pharmacologic therapy against NASH, partly due to an incomplete understanding of its molecular basis. The goal of this study was to determine the key differentially expressed genes (DEGs), as well as those genes and pathways central to its pathogenesis. We performed an integrative computational analysis of publicly available gene expression data in NASH from GEO (GSE17470, GSE24807, GSE37031, GSE89632). The DEGs were identified using GEOquery, and only the genes present in at least three of the studies, to a total of 190 DEGs, were considered for further analyses. The pathways, networks, molecular interactions, functional analyses were generated through the use of Ingenuity Pathway Analysis (IPA). For selected networks, we computed the centrality using igraph package in R. Among the statistically significant predicted networks (p-val < 0.05), three were of most biological interest: the first is involved in antimicrobial response, inflammatory response and immunological disease, the second in cancer, organismal injury and development and the third in metabolic diseases. We discovered that HNF4A is the central gene in the network of NASH connected to metabolic diseases and that it regulates HNF1A, an additional transcription regulator also involved in lipid metabolism. Therefore, we show, for the first time to our knowledge, that HNF4A is central to the pathogenesis of NASH. This adds to previous literature demonstrating that HNF4A regulates the transcription of genes involved in the progression of NAFLD, and that HNF4A genetic variants play a potential role in NASH progression. The patient tissue validation is work in progress.
Rate of change of platelet count is associated with risk of variceal bleeding in children with biliary atresia

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BACKGROUND: No accurate test has been identified for detecting the subset of children with biliary atresia (BA) who suffer variceal bleeding.

METHODS: We reviewed medical charts of children with BA who underwent Kasai portoenterostomy between 1990 and 2013 and were subsequently followed at our institution. Platelet counts measured during follow-up were collected from the hospital laboratory database. Generalized estimating equation was used to model longitudinal Poisson data, with a focus on ages 1–5 years. Patients were censored at time of first bleed or transplant.

RESULTS: Among 98 children (60% female), 15 developed variceal or major GI bleeding (“bleeders”), 45 underwent liver transplant but did not bleed (LTNB), and 38 did not bleed and were not transplanted (NTNB) during up to 17 years’ follow-up. Initial mean platelet counts were high (400–450x10^9/l), did not differ significantly between groups, and fell rapidly during the first year. Between 1 and 5 years of age, although the range of platelet counts overlapped between groups, platelet count continued to fall in bleeders (-0.05% per day, or -26x10^9/litre per year, p=0.002 compared to bleeders) but remained stable in LTNB (+0.01% per day, +8x10^9/l per year, p=0.035 compared to bleeders).

CONCLUSION: Our single-centre study suggests rate of change of platelet count between 1 and 5 years of age may be associated with variceal bleeding in children with BA. We recommend further study in larger populations of children with BA to more accurately determine the predictive ability of this approach.

Metabolic reprogramming of hepatocellular carcinoma cells is mediated by a rearrangement in glucose transporters

Shamir Cassim, Centre de Recherche du CHUM; Valérie-Ann Raymond, Centre de recherche du CHUM; Marc Bilodeau, CHUM

Otto Warburg described for the first time a phenomenon where cancer cells increase their glucose (glc) consumption through aerobic glycolysis to meet their energy requirements. Although the metabolic reprogramming displayed by cancer cells differs according to the tumor microenvironment, glc uptake constitutes a key factor of this adaptation process. Therefore, the study of glc uptake within cancer cells remains of high interest.
especially in hepatocellular carcinoma (HCC) since it arises from hepatocytes that are central for glc metabolism. We hypothesized that the degree of aggressiveness of HCC cells not only depends on their capacity to use glc as a source of energy but also to modulate the expression of GLUT-1/2 surface receptors to allow the entry of glc.

Hepatocytes were isolated from adult male C57BL/6 mice using the two-step collagenase perfusion method. A well characterized mouse HCC cell line, Dt81-Hepa1–6 (Dt), and primary hepatocytes (PH) were cultured in standard conditions for a period of 24–48h. mRNA was measured by qPCR. Metabolite quantification was assessed by HPLC. Functional analysis of glycolysis was evaluated using Seahorse. Glc uptake was assessed using the fluorescent glc analog 2-NBDG through flow cytometry. GLUT-1 and 2 protein levels were determined by western bloting and then quantified using ImageJ.

First, we evaluated the production of lactate through the measure of extracellular acidification rate which is a measure of glycolysis by Seahorse: results show higher glycolytic activity in Dt before and after glc exposure. Moreover, when mitochondrial ATP synthase was inhibited with oligomycin, the glycolytic activity of Dt further increased while it only marginally did so in PH. In accordance with the previous results, Dt displayed significantly higher gene expression levels for several glycolytic-related enzymes (Hk II, Pfkl, Pdh, Pdk1, Pgc-1α) as well as Hif-1α, a transcription factor that activates Hk II. In the same vein, Dt cells showed higher levels of GDP/GTP (P < 0.001) and ADP/ATP (P < 0.001), demonstrating the functionality of the glycolytic cascade. We next investigated the level of glc uptake between the 2 cell types. Dt showed an increased ability to uptake glc compared to PH (P < 0.0001). Finally, protein level analysis demonstrated higher expression of Glut-1 (P < 0.001) as well as Glut-2 (P < 0.05) in Dt cells in comparison to PH.

Our findings demonstrate that the Warburg effect occurs in HCC cells. In vitro, the metabolic plasticity displayed by Dt, with a higher rate of aerobic glycolysis but also a greater energetic metabolite content, is explained by higher expression of glc transporter proteins GLUT-1 and GLUT-2 that increase the entry and utilization of glc. These observations add new pieces of evidence about the metabolic reprogramming that can take place in neoplastic hepatocytes.

**Establishment of Hepatocellular Carcinoma In Vivo is associated with major metabolic reprogramming**

Shamir Cassim, Centre de Recherche du CHUM; Valérie-Ann Raymond, Centre de recherche du CHUM; Lacoste Benoit, Centre de Recherche du CHUM; Marc Bilodeau, CHUM

Cancer cells show unique metabolic responses and increased capacity to adapt to specific microenvironments: yet, the molecular and biochemical events responsible for these observations are unknown. The manner by which cancer cells use glucose (glc) to adapt to the microenvironment is thought to bear a significant impact on tumor progression/invasion. We generated a mouse hepatoma cell line Dt81-Hepa1–6 (Dt) that displays features of cancer stem cells and has greater tumorigenicity in vitro and in vivo. We studied the use of glc by Dt in vivo and compared it to what is observed in vitro with the hypothesis that cancer tissues adapted their metabolism to the liver microenvironment.

For in vitro analyzes, Dt were compared to primary hepatocytes (PH) to assess the differences in glc metabolism between non-malignant and malignant cells. PH were isolated from male C57BL/6 mice by using the two-step collagenase perfusion method. Both cell types were cultured in 25 mM glc during 48h and then harvested for qPCR and metabolite quantification (HPLC). For in vivo analyzes, intrahepatic tumors were obtained following intrasplenic injection of Dt cells (1M) in mice that were sacrificed 21 days later. Dt-derived tumors (T), nontumoral (NT) and control normal livers (CT) were dissected for qPCR, HPLC, protein assessment and triglyceride (TG) measurements. GLUT-1 and GLUT-2 protein levels were determined by western bloting and then quantified using ImageJ.

Following establishment of intrahepatic tumors, T showed higher expression of 7 glycolytic-related genes in comparison to CT and NT: Hk II (P < 0.001), Pfkl (P < 0.001), Pdh (P < 0.001), Pdk1 (P < 0.001), Pgc-1α (P < 0.001), HIF-1α (P < 0.001) and Cyclin D1 (P < 0.001). HPLC also demonstrated greater levels of energetic metabolites such as ATP, ATP/ADP and Energy charge in T. Furthermore, NADH/NAD and lactate/Pyruvate ratios indicated efficient aerobic glycolysis only in T. 

qPCR and protein analysis demonstrated higher...
expression levels of GLUT-1 and lower expression of GLUT-2 in T, when compared to CT and NT. We then investigated the fatty acid (FA) metabolic pathway. In vitro, Dt displayed a significantly higher capacity to synthesize and accumulate FA in comparison to PH: Fasn (P < 0.05), Acly (P < 0.05), Acc (P < 0.001), DHAP (P < 0.01), Malonyl-CoA (P < 0.01) and TG content (P < 0.001). On the other hand, when Dt formed tumors in vivo, they showed significantly less capacity to synthesize and accumulate FA in comparison to CT and NT: Fasn (P < 0.05), Acly (P < 0.05), Acc (P < 0.001), DHAP (P < 0.001), Malonyl-CoA (P < 0.01) and TG content (P < 0.001).

These results strongly suggest that metabolic reprogramming occurs within the tumors during HCC initiation and invasion. In vivo, in an unrestricted normal glucose environment, Dt-derived tumors display a metabolic strategy for the preferential and efficient use of glucose through aerobic glycolysis (known as the Warburg effect) probably explaining the lack of use of FA metabolism for their energy requirements.

Adherence to enhanced post-treatment surveillance is associated with increased detection of early stage recurrence after radiofrequency ablation but not surgical management of hepatocellular carcinoma

Yin Chan, University of Calgary; Kelly Burak, University of Calgary; Samuel MacDennan, University of Calgary; Lisa Douglas, University of Calgary; Stephen Congly, University of Calgary; Elijah Dixon, University of Calgary; Jason Wong, University of Calgary; Carla Coffin, Department of Medicine, University of Calgary

BACKGROUND: Little is known about the optimal surveillance schedule after curative intent treatment of hepatocellular carcinoma (HCC). Current guidelines advocate cross-sectional imaging at 3–6 months intervals for the first 2 years, but are not backed by strong evidence of benefit. In Calgary, we perform MRI one month after radiofrequency ablation (RFA) and 3–6 months after surgery. Thereafter we alternate contrast enhanced ultrasound and MRI every 3 months for two years and then every six months for another 3 years.

AIMS: We conducted a retrospective study to investigate the impact of surveillance intensity on clinical outcomes following curative HCC treatment.

METHODS: From a combined surgery and interventional radiology database in Calgary (2012–2015), 124 unique HCC patients receiving post-treatment surveillance after successful resection (n=46) or RFA (n=78) were identified after excluding patients who received transarterial chemoembolization (TACE) (n=43), failed to achieve radiological remission (n=38) or died within three months (n=10). Baseline characteristics, imaging frequency, and clinical outcomes were collected. A surveillance rate defined as sum of actual number of images performed divided by the sum of the expected number of images in the defined surveillance period for each subject was calculated.

RESULTS: Baseline characteristics including age, gender and liver disease were similar in both groups. The surgery group had a higher percent of Barcelona Clinic Liver Cancer (BCLC) staging 0 (p=0.00052), non-cirrhotic (p=0.0045), and first HCC (p=0.00027) then the RFA group. The two-year disease-free survival and five-year mortality rate on Kaplan-Meier analysis, as well as mean surveillance rate (89±15% vs 84±21%) were comparable. Interestingly, BCLC B/C recurrence (n=8) was significantly associated with a lower surveillance rate as compared to BCLC 0/A recurrence in RFA patients (76±22% vs 92±14%, p=0.015), but this was not observed in the surgical cohort. Comparison of mean imaging interval (120±47 days vs 82±29 days, p =0.038) and time to recurrence (591±245 days vs 399±222 days, p=0.048) between BCLC B/C and 0/A recurrence also differed in the RFA cohort. Univariate analysis did not identify other predictors of more significant recurrence.

CONCLUSIONS: In conclusion, high intensity post-treatment surveillance of HCC patients after locoregional therapy, but not surgical resection, appears to be associated with detection of recurrence.
at an earlier stage. Ongoing follow-up will determine if this is associated with a survival benefit.

De novo and recurrent nonalcoholic steatohepatitis after liver transplantation: a prospective study employing cytokeratin 18 and transient elastography with controlled attenuation parameter

Sila Cocciolillo, McGill University; Giada Sebastiani, McGill University; Marc Deschenes, McGill University; Peter Ghali, McGill University; Philip Wong, McGill University; Tianyan Chen, McGill University; Peter Metrakos, McGill University; Maria Osikowicz, McGill University

BACKGROUND: Liver transplantation (LT) is a life-saving procedure that resolves complications of cirrhosis. However, the metabolic risk factors for nonalcoholic steatohepatitis (NASH) persist and potentially worsen in the post-transplant setting thereby increasing the risk for de novo or recurrent NASH. Due to the invasiveness of liver biopsy, prospective longitudinal data about NASH following LT are scarce. We investigated incidence and cofactors of NASH diagnosed by transient elastography (TE) with controlled attenuation parameter (CAP) and the biomarker of hepatocyte apoptosis cytokeratin 18 (CK-18) in LT recipients.

METHODS: Consecutive LT recipients from a single centre were prospectively followed every 3 months for 1 year with serial TE with CAP and CK-18. Patients transplanted for HCV genotype 3 infection were excluded. Fatty liver, significant liver fibrosis (stage 2 out of 4) and NASH were diagnosed as CAP>248 dB/m; TE measurement>8 kPa; CK-18>246 U/L, respectively. Cofactors of de novo or recurrent NASH were determined using logistic regression analysis.

RESULTS: 40 LT recipients (mean age 57+9 years, 72% men, BMI 25.6+4.6; 91% on immunosuppressive therapy with tacrolimus plus steroids and/or mycophenolate) were enrolled. The main indications to LT were NASH (26.5%), alcohol abuse (32.3%) and HCV (20.6%). At baseline (month 1 post-LT), there were high prevalences of NASH, fatty liver and significant liver fibrosis likely due to residual inflammation affecting the results of the non-invasive tests adopted. From month 3 until 1 year, there was a progressive increase in non-invasive diagnostic tests for liver disease, resulting in high proportions of patients having NASH, fatty liver and significant liver fibrosis at the end of the follow-up period (see Table 1). This translated into overall incidence rates of 3.1, 4.6 and 7.0 per 100 person-years, respectively. Liver biopsy was available in 24% of patients and confirmed the non-invasive diagnosis of NASH, liver fibrosis stage and fatty liver in 87% of cases. By multivariable analysis, after adjusting for age and gender, independent predictors of de novo and recurrent NASH were higher BMI (odds ratio=1.30, 95% CI 1.02–1.67) and diabetes (odds ratio=5.15, 95% CI 1.08–24.5).

CONCLUSIONS: De novo and recurrent NASH is a very frequent occurrence during the first year following LT. Early implementation of interventions targeting metabolic risk factors should be pursued. Our data suggest also that non-invasive diagnostic tools such as TE with CAP and CK-18 may be used in the post-transplant setting to monitor occurrence of NASH.

Table 1. Proportions of LT recipients with NASH, fatty liver and significant liver fibrosis during the follow-up period. p-value refers to chi-test between Month3 and Month 12

<table>
<thead>
<tr>
<th></th>
<th>Month1</th>
<th>Month3</th>
<th>Month6</th>
<th>Month9</th>
<th>Month12</th>
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<tr>
<td>NASH (%)</td>
<td>53</td>
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<td>15</td>
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<td>Fatty liver (%)</td>
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<td>19</td>
<td>27</td>
<td>45</td>
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<td>Liver fibrosis (%)</td>
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<td>10</td>
<td>27</td>
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Organ damage and vascular occlusion during bacterial infection causing sepsis is ameliorated through attenuation of NETs

Rachelle Davis, University of Calgary; Craig Jenne, University of Calgary; Braedon McDonald, University of Calgary

Sepsis is a life-threatening complication during infection in which the immune response becomes hyperactive, resulting in organ damage. Further complications such as Disseminated Intravascular Coagulation (DIC) can lead to thrombocytopenia and microvascular occlusion, and can be difficult to treat due to the intricate balance needed between restoring homeostatic function while preventing further systemic spread of infection. Neutrophils are the sentinel immune cell recruited to a site of infection, and can sequester bacteria through the release of neutrophil extracellular traps (NETs). These structures are composed of webs of extracellular DNA coated with anti-microbial proteins, allowing for pathogen capture and killing. Although NETs have been shown to aid in pathogen defense, they have also been implicated in host tissue damage. To investigate this, mice were infected with E.coli and livers (primary site of pathogen sequestration and clearance) were analyzed using intravital microscopy (IVM), allowing for direct visualization of cell populations within live tissue. IVM allows for detection and quantification of NETs and neutrophils, as well as co-localization of NETs and markers of coagulation (thrombin, fibrin). Additionally, since it’s known that neutrophils are dependent on platelets to release NETs, and that platelets are also required for coagulation, platelets were labelled in vivo to measure extent of aggregation. Further in vitro blood analysis 24h post-infection was performed to assess for markers of coagulation (TAT, PAI-1) as well as markers of organ damage (ALT). Results indicate that both coagulation and organ damage are attenuated by disruption of NETs (DNAse treatment, anti-histone antibody treatment) as measured by reduced levels of intravascular thrombin, reduced ALT levels and increased tissue perfusion. This work provides a possible therapeutic avenue in which NETs could be targeted as a treatment for sepsis to disrupt vascular occlusion and prevent a degree of organ damage associated with septic conditions.

Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis

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BACKGROUND: Two major body composition compartments, skeletal muscle and adipose tissue, confer divergent characteristics and functions. While there is consensus that sarcopenia is an independent predictor of mortality in patients with cirrhosis, prognostic significance of adipose tissue mass (adiposity) in cirrhotic patients is not clear. Considering variability in adiposity within each BMI category, BMI cannot be applied as an appropriate indicator of adiposity.

PURPOSE: We aimed to explore the prognostic significance of the main body composition compartments, skeletal muscle, visceral and subcutaneous adipose tissue, in cirrhotic patients (n=677) assessed for LT, according to the sex.

METHODS: Clinical and demographic characteristics of the patients were collected from the medical charts. CT images taken at the 3rd. lumbar vertebra were quantified for three body composition areas, each normalized to height² (cm²/m²): visceral adipose tissue index (VATI), subcutaneous adipose tissue index (SATI), and skeletal muscle index (SMI). Cox proportional and Fine-Gray subdistribution hazard models were conducted to assess associations between mortality and body composition features. Cut-offs for SATI to predict mortality was established using a receiver-operating characteristic (ROC) analysis.

RESULTS: Majority of patients were male (67%) with a mean age of 57±8 years, MELD score of 14±8 and mean BMI of 27±6 kg/m². The primary reason for cirrhosis was hepatitis C (40%), alcohol (23%), autoimmune liver disease (8%), hepatitis B (6%) and NASH-cryptogenic (23%). Despite similar BMI between the sexes, men had greater SMI (53±12 vs. 45±9) and VATI (39±30 vs. 31±22), whereas SATI (67±52 vs. 48±37) was higher in females [P < 0.001 for each]. In sex- stratified multivariate analyses
Obeticholic acid (OCA), is a selective and potent farnesoid X receptor agonist approved for the treatment of primary biliary cholangitis (PBC). OCA is a semi-synthetic bile acid with similar pharmacokinetic (PK) properties as endogenous bile acids. It has been reported that patients with cirrhosis have 18x higher systemic exposure of endogenous bile acids, but only a 2x increase in hepatic exposure compared to normal liver function. In previous clinical studies, OCA-treated patients with severe hepatic impairment had plasma OCA exposures that were 17x higher and 4x higher for patients with moderate hepatic impairment compared to healthy volunteers with normal hepatic function. Liver and intestinal exposure are most relevant to the pharmacology of OCA and are estimated to only change modestly in patients with moderate and severe hepatic impairment; however, higher systemic exposure must be balanced while remaining efficacious.

A titration dosing regimen for OCA was developed for hepatically-impaired patients with PBC that establishes tolerability and efficacy at lower doses and titration to higher doses to achieve adequate response. The dosing regimen of OCA for patients with PBC without hepatic impairment is 5mg QD, which can then be titrated to 10mg QD after 3months based on tolerability and clinical response. A previously developed physiologic PK model was used to simulate the systemic and liver exposure of OCA in patients with hepatic impairment based on Child-Pugh score using alternative dosing regimens. The resultant dosing scheme and projected plasma and liver OCA levels for patients with and without hepatic impairment are shown in Table 1.

**CONCLUSIONS:** A lower subcutaneous adipose tissue index associates with higher mortality in female patients with cirrhosis. Skeletal muscle, on the other hand, predicts mortality in male patients. This emphasizes the necessity for further studies to investigate potential interactions between muscle and subcutaneous adipose tissue indices on mortality.

**Development of a dose regimen for obeticholic acid in patients with primary biliary cholangitis and hepatic impairment**

Jeffrey Edwards, Intercept Pharmaceuticals, Inc.; Carl LaCerte, Intercept Pharmaceuticals, Inc.; Thomas Peyret, Pharsight; Nathalie Gosselin, Pharsight; JF Marier, Pharsight

<table>
<thead>
<tr>
<th>Physiologic Compartment</th>
<th>Hepatic Impairment Status</th>
<th>OCA 5mg QD</th>
<th>OCA 10mg QD</th>
<th>Step 1 OCA 5mg QW</th>
<th>Step 2 OCA 5mg BIW</th>
<th>Step 3 OCA 10mg BIW</th>
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<tr>
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<tr>
<td></td>
<td>Severe</td>
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<td>-</td>
<td>404</td>
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*Data are Total OCA Cave,ss (ng/mL)*

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The recommended dosing regimen in patients with moderate and severe hepatic impairment begins at 5mg QW for 3 months, titrated to 5mg BIW, and then to 10mg BIW. The dosing regimen is designed to establish tolerability and efficacy at lower doses prior to titrating to higher doses to achieve better efficacy. A Phase 4 clinical study is forthcoming to evaluate this dosing regimen.

Serum immunoglobulin A levels in adult patients with alcoholic and non-alcoholic fatty liver disease

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BACKGROUND: The immune response to gut-derived endotoxins is thought to contribute to the pathogenesis of alcoholic (ALD) and non-alcoholic fatty liver disease (NAFLD). Immunoglobulin A (IgA) synthesis is an important component of that immune response.

OBJECTIVES: To document the prevalence of elevated serum IgA (E-IgA) levels in adult ALD and NAFLD patients and determine whether serum IgA levels correlate with the severity and course of the liver disease.

METHODS: Adult patients attending an urban tertiary care centre were identified from a computerized clinical database. Severity and course of disease were assessed by standard liver biochemistry, MELD and Fib-4 scores at initial presentation and last follow-up visit.

RESULTS: 175 ALD and 941 NAFLD patients were identified. The mean age ± SD of ALD patients was 61±11 years and NAFLD patients 57±13 years. 65% of ALD patients and 49% of NAFLD patients were male. The prevalence of E-IgA was 67% and 27% respectively. The mean ages and gender distributions of E-IgA ALD and NAFLD patients were similar to those with normal IgA levels (N-IgA) in their respective cohorts. E-IgA ALD and NAFLD patients had significantly more impaired hepatic function (hyperbilirubinemia, prolonged INR and hypoalbuminemia) and higher MELD scores than N-IgA patients. The percent of E-IgA ALD and NAFLD patients with Fib-4 scores suggestive of cirrhosis at baseline was higher in the E-IgA than N-IgA cohorts (ALD: 53% vs 34%, p < 0.01 and NAFLD: 25% vs 6.5%, p < 0.0001). After median follow-up of 53±23 (ALD) and 43±37 (NAFLD) months, biochemical evidence of hepatic dysfunction remained more impaired and MELD scores significantly higher in E-IgA than N-IgA ALD and NAFLD patients. The percent of pre-cirrhotic patients at baseline who developed cirrhosis (by Fib-4 testing) during follow-up was similar in E-IgA and N-IgA ALD patients (21% vs 17%, p=0.62) but significantly higher in E-IgA than N-IgA NAFLD patients (12% vs 3.1%, p < 0.0001).

CONCLUSIONS: Elevated serum IgA levels are common findings in ALD and to a lesser extent in NAFLD patients. In both conditions, elevated IgA levels correlate with biochemical evidence of disease severity. However, only in NAFLD are elevated levels at baseline associated with subsequent progression to cirrhosis. These findings suggest that IgA may contribute to the pathogenesis of NAFLD but are less like to be of pathophysiologic importance in ALD.

Reductions in liver stiffness by magnetic resonance elastography (MRE) predict fibrosis improvement in a multicenter clinical trial of subjects with nonalcoholic steatohepatitis (NASH)

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CONCLUSION: In this multi-center trial of SEL in patients with F2–3 fibrosis, any reduction in MRE-stiffness was predictive of fibrosis improvement. These data support the use of MRE as a noninvasive endpoint in clinical trials of patients with NASH.

Evaluation of liver histology and transient elastography in pediatric Fontan patients

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BACKGROUND: The Fontan operation is widely used in the management of children with complex congenital heart abnormalities. Such patients are well known to be at risk for liver disease, but non-invasive tools for the assessment of their liver status are poorly defined. Transient elastography (TE) and the aspartate aminotransferase to platelet ratio index (APRI) are validated tools for assessment of liver fibrosis in patients with other chronic liver diseases.

PURPOSE: To evaluate histological changes in the livers of Fontan patients, and to assess the utility of TE in this patient group.

METHODS: Sixty children with Fontan physiology were prospectively enrolled from the Children’s Heart Centre at BC Children’s Hospital from 2015–2017. All patients had yearly measurement of liver biochemistry (liver enzymes, albumin, bilirubin) as well as CBC, INR and abdominal ultrasound. The AST to platelet ratio index (APRI) was calculated. Patients underwent TE measurements yearly, as well as at the time of liver biopsy. Thirteen patients underwent transjugular liver biopsy at the time of scheduled cardiac catheterization, with histology assessed by a single pathologist blinded to clinical data.

RESULTS: A total of 86 TE measurements were performed on 60 children (55% male, median age 11.3 years, IQR 7.7–14.7). There was a moderate
Predictors of endoscopic high risk esophageal varices in compensated cirrhosis: Can we avoid Fibroscan?

Julian Hercun, l’Universite de Montreal; Marc Bilodeau, CHUM; Julien Bissonnette, CHUM; Genevieve Huard, CHUM; Jeanne-Marie Giard, CHUM

BACKGROUND: Patients with cirrhosis are at risk of developing esophageal varices (EV). Recently, criteria based on elastography and platelet count (Baveno VI criteria) have been adopted and included in practice guidelines to circumvent screening endoscopy (EGD). However, elastography measurement is not widely available.

PURPOSE: The aim of the study was to determine predictive factors excluding liver stiffness in order to predict high-risk EV in patients with compensated cirrhosis.

METHOD: Retrospective chart review of all compensated cirrhotic adult patients who underwent screening EGD at Saint-Luc Hospital between 01/2014 and 12/2016. Patients with decompensated cirrhosis (ascites, hepatic encephalopathy, jaundice), past history of EV/TIPS or liver transplantation, acute upper gastrointestinal bleeding, acute alcoholic hepatitis were excluded. High-risk EV were defined as medium or large EV and/or presence of red wale signs. Splenomegaly was defined as a spleen ≥ 13 cm on imaging. Thrombocytopenia was defined as a platelet count < 150 x 10^9/L. The score was not predictive of high-risk EV (OR 1.7; p=0.337). Among the 172 patients having normal spleen size and platelet count ≥ 150 x 10^9/L, only 2 (1.2%) patients had high-risk EV at screening EGD. The presence of splenomegaly and/or thrombocytopenia had a sensitivity of 95.6% and a negative predictive value of 98.8% for the presence of high-risk EV at screening endoscopy.

CONCLUSIONS: In compensated cirrhosis, the combination of normal spleen size and normal platelet count translates into a 98.8% chance of absence of high-risk EV at screening EGD. Using these criteria, 172 (37.1%) screening EGD could have been avoided in our population. Therefore, the use of elastography is not mandatory in the decision of recommending screening EGD in patients with compensated cirrhosis.

Efficacy of obeticholic acid treatment through 24 months of open-label extension in patients with primary biliary cholangitis and cirrhosis: Data from POISE

Gideon Hirschfield, Centre for Liver Research, NIHR BRU, University of Birmingham; Dave Jones, Institute of Cellular Medicine, Newcastle University Medical School; John Vierling, Baylor College of Medicine, St. Luke’s Episcopal Hospital; Roberto Groszmann, Yale University School of Medicine; Kris Kowdley, Swedish Medical Center; Richard Pencek, Intercept Pharmaceuticals, Inc.; Elizabeth Smoot Malecha, Intercept Pharmaceuticals, Inc.; Leigh MacConell, Intercept Pharmaceuticals, Inc.
**BACKGROUND:** Obeticholic acid (OCA) is a potent and selective farnesoid X receptor agonist indicated for treatment of primary biliary cholangitis (PBC) in patients with inadequate response or intolerance to ursodeoxycholic acid (UDCA). POISE was a double-blind (DB), placebo-controlled, randomized Phase 3 study examining the efficacy of OCA in PBC. After 12 months (mo) DB, patients could enroll in an ongoing open-label extension (OLE), and OCA treatment was initiated in all OLE patients. The objective of this post-hoc analysis is to assess the durable response of OCA through 24 mo OLE in the subset of patients with cirrhosis who were at higher risk of progression to liver-related outcomes or death.

**METHODS:** A total of 216 patients with PBC on stable dose or no UDCA with alkaline phosphatase (ALP) ≥1.67×ULN and/or total bilirubin (BILI) >ULN to <2×ULN were randomized to placebo (PBO) (n=73), OCA 5-10mg (n=70), or OCA 10mg (n=73). Patients were considered cirrhotic if they had biopsy-proven cirrhosis, transient elastography ≥16.9 kPa, or a history of cirrhosis.

**RESULTS:** Cirrhosis was present in ~17% of patients: PBO, n=13; OCA 5-10mg, n=13; OCA 10mg, n=10. Of these, 6 (PBO), 10 (OCA 5-10mg) and 6 (OCA 10mg) patients completed 24mo OLE with lab measurements. Reduction in ALP was significant in both OCA groups at 12mo DB, and this response was maintained through 24mo OLE (see Table 1). PBO patients had a durable reduction in ALP after initiating OCA in the OLE. BILI increased in the PBO group and significantly decreased in both OCA groups after 12mo DB. Mean BILI in the 10mg group remained below baseline through 24mo OLE. Pruritus was the most common adverse event (AE), but patients on OCA in the DB phase showed a decrease in incidence of pruritus during the OLE (DB: 69–80%; OLE: 22-54%). In comparison, 23% of PBO patients had new or worsening pruritus in the DB phase.

**CONCLUSION:** In PBC patients with compensated cirrhosis treated with OCA during POISE DB and OLE, ALP improvements were significant during DB and maintained during OLE; BILI reductions were significant in DB and remained stabilized during OLE. The observed biochemical changes suggest OCA may contribute to slowing disease progression in these patients.

*As patients can up- and down-titrate during OLE, AEs are grouped by last dose received prior to AE start date. Therefore, patients can be counted toward and have events in multiple OLE dose-groups.

**Effect of mixed lipid, ω-3 fish oil and ω-6 soybean oil parenteral lipid emulsions on hepatic fatty acid and phytosterol composition and bile acid transport in neonatal piglets**

Daniela Migliarese Isaac, Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, University of Alberta; Celeste Lavallee, Department of Pediatric Gastroenterology and Nutrition, University of Alberta; Abeer S Alzaben, Department of Agricultural Food and Nutritional Science, University of Alberta; Vera C Mazurak, University of Alberta; Jason Yap, Department of Pediatric Gastroenterology and Nutrition, University of Alberta; Pamela R Wizzard, Department of Pediatric Gastroenterology and Nutrition, University of Alberta; Patrick N Nation, Department of Pediatrics, University of Alberta

Table 1.

<table>
<thead>
<tr>
<th>Original treatment group</th>
<th>PBO</th>
<th>OCA 5–10mg</th>
<th>OCA 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP (U/L) - DB Baseline</td>
<td>322.5 (138.9)</td>
<td>352.0 (173.6)</td>
<td>305.7 (91.6)</td>
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<tr>
<td>ALP (U/L) - ∆OLE 24mo†</td>
<td>106.8 (119.7)</td>
<td>110.6 (109.5)*</td>
<td>71.8 (131.5)</td>
</tr>
<tr>
<td>BILI (µmol/L) – DB Baseline</td>
<td>13.0 (7.8)</td>
<td>14.2 (7.7)</td>
<td>16.5 (7.7)</td>
</tr>
<tr>
<td>BILI (µmol/L) - ∆OLE 24mo‡</td>
<td>0.7 (1.1)</td>
<td>2.1 (5.5)</td>
<td>2.1 (5.5)</td>
</tr>
</tbody>
</table>

*p < 0.05. Values are mean (SD). †P-value for the within treatment comparisons vs. DB Baseline are obtained using the Student’s t-test.
of Laboratory Medicine and Pathology, University of Alberta; Yuan-Yuan Zhao, Department of Agricultural Food and Nutritional Science, University of Alberta; Jonathan M Curtis, Department of Agricultural Food and Nutritional Science, University of Alberta; Diana R. Mager, Department of Agricultural Food and Nutritional Science, University of Alberta; Paul W. Wales, Division of General Surgery, Hospital for Sick Children, University of Toronto; Justine Turner, Department of Pediatric Gastroenterology and Nutrition, University of Alberta

BACKGROUND: Determining the optimal parenteral nutrition (PN) lipid emulsion for pediatric intestinal failure patients remains an important clinical question given the risk of PN associated liver disease (PNALD) and associated cholestasis. The mechanism of PNALD is poorly understood, but clinical experience with soybean oil (SO) versus fish oil (FO) containing emulsions suggests that fatty acid (FA) composition (higher ω-3 and lower ω-6 FA) and phytosterol (PS) composition may be important.

PURPOSE: Using a neonatal piglet model, this study aimed to identify mechanisms for PNALD by comparing the effect of mixed lipid (ML; ω-6:ω-3 FA 2.5:1, PS 207 μg/mL), ω-3 predominant FO (ω-6:ω-3 FA 1:8, no PS), and ω-6 predominant SO (ω-6:ω-3 FA 7:1, PS 439.07 μg/mL) emulsions on: i) bile flow (BF) and ii) hepatic FA and PS composition. The relationship to gene expression of canalicular transporters was further explored to elucidate mechanisms of PNALD.

METHODS: Neonatal piglets received either SO (n=5), FO (n=5), or ML (n=5) throughout 14 days of PN. Cholestasis was assessed by measuring BF, γ-glutamyl transpeptidase (GGT), bile acids (BA) and total bilirubin (TB). Liver tissue was assessed for hepatic PS and FA composition in the triglyceride fraction. Relative expressions of genes involved in BA synthesis and transport were determined through quantitative polymerase chain reaction. One-way ANOVA was used to compare continuous variables, and multivariate stepwise regression analysis to determine predictors of BF and gene expression.

RESULTS: Comparing SO to FO and ML, BF was lower (p < 0.001), TB (p=0.02) and serum BA (p=0.04) higher, and GGT not different (p=0.19). As a proportion of total hepatic FA, FO had the highest ω-3 FA (35.7 ± 14.3%), followed by ML (18.9 ± 4.2%), and SO (6.1 ± 1.1%; p < 0.001). FO and ML had lower ω-6 FA (p < 0.001) and campesterol (p < 0.0001) levels than SO. Stigmasterol and β-sitosterol were not detected in FO, but were significantly higher in SO than ML (p < 0.0001). β-sitostanol was only detected in the SO group. Univariate predictors of BF were: campesterol (r= -0.769, p=0.001), β-sitosterol (r= -0.743, p=0.002), stigmasterol (r= -0.742, p=0.002), ω-6 FA (r=-0.722, p=0.002), ω-3 FA (r=0.592, p=0.02), and expression of the hepatic basolateral bile acid transporter organic solute transporter alpha (OSTA) (r=0.673, p=0.006). Only campesterol independently predicted BF (β= -0.769 [-1.23 to -0.412], p=0.001). Campesterol was correlated to OSTA (r=0.73, p=0.002).

CONCLUSIONS: ML and FO lipid emulsions were associated with reduced cholestasis, improved BF, and lower hepatic FA and PS content. Campesterol decreased BF and correlated with increased OSTA expression, a transporter that mediates the efflux of BA from hepatocytes into blood. Phytosterols may play a key role in BA metabolism and the development of PNALD. Both the FA and PS composition of FO containing lipids may explain their hepatoprotective effects, and PS toxicity may be a key factor requiring further investigation.

Reductions in hepatic proton density fat fraction (PDFF) predict histologic improvement in a multi-center clinical trial of subjects with nonalcoholic steatohepatitis (NASH)

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CONCLUSION: In this multi-center trial of selonsertib, ≥25% relative reduction in MRI-estimated PDFF was predictive of histologic response. These data support the use of MRI-PDFF as a noninvasive endpoint in clinical trials of interventions for NASH.

Acute liver failure from tumor necrosis factor-α antagonists: report of four cases and literature review

Beverley Kok, University of Alberta Hospital; William Lee, UTSouthwertern; Dean Karvellas, University of Alberta Hospital; Erica Lester, University of Alberta Hospital

BACKGROUND: Tumor necrosis factor-α antagonists (anti-TNF-α) have been increasingly used in the treatment of inflammatory conditions and over 1.5 million patients have been exposed to the medication. With the widespread use of the drug, incidence of drug-induced liver injury (DILI) has been increasingly reported. The specific mechanism leading to anti-TNF-α-induced DILI remains incompletely understood though the commonest form of DILI reported is a hepatocellular injury with both serological (in up to 92%) and histological features of autoimmune hepatitis. Cases of anti-TNF-α-associated acute liver failure, however, have only been rarely reported.

PURPOSE: To identify cases of anti-TNF-α-associated acute liver failure and evaluate patterns of liver injury and common characteristics to the cases.

METHODS: The United States Acute Liver Failure Study Group (ALFSG) database was searched from 1998–2014. Four subjects with acute liver failure from anti-TNF-α were identified and case histories were thoroughly reviewed. Case adjudication was determined in each case by two independent reviewers using the Roussel Uclaf Causality Assessment Method (RUCAM). A literature search was conducted in PubMed in March 2017 to identify published articles that reported anti-TNF-α-associated acute liver failure. This identified five additional cases, bringing the total of this case series to n = 9 patients.
**RESULTS:** The majority of individuals affected were female (8 of 9 cases). Age of individual ranged from 20 to 53 years. RUCAM scores were ascertained in the four ALFSG cases and all were deemed to have at least probable causality from the anti-TNF agent (RUCAM scores 6–7). The anti-TNF-α agent most commonly incriminated was infliximab (n = 8), which was associated with all cases that resulted in liver transplant (n = 6). In all cases, liver function tests had been normal prior to commencement of anti-TNF-α. In 3 cases, anti-nuclear antibodies became serologically positive during the episode of the liver failure whereas negative before; in 5 cases autoimmune serologic markers remained negative throughout. The latency between initial drug exposure and acute liver failure ranged from three days to over a year, likely indicating an idiosyncratic drug reaction. Of the nine cases, six required emergency liver transplantation. Liver biopsy was obtained in 7 cases with a preponderance towards a cholestatic-hepatitic pattern of injury, and none showed clear histological autoimmune features (even in those with new autoimmune serology). In the 3 cases where acute liver failure resolved and liver transplantation was avoided, steroid therapy had been administered in 1 case, N-acetylcysteine in 1 case, and both steroids and N acetylcysteine in 1 case.

**CONCLUSION:** Anti-TNF-α-associated acute liver failure displays somewhat different characteristics compared with anti-TNF-α-induced DILI and may represent a distinct severe idiosyncratic drug reaction related to anti-TNF-α, potentially culminating in liver transplant. Infliximab was implicated in the majority of cases. A cholestatic-hepatitic pattern of injury was frequently found on pre-transplant and explant histology.

**IL-16 as a biomarker in autoimmune liver diseases**

Pascal Lapierre, Centre de Recherche du CHUM; Marc Bilodeau, CHUM; Valérie-Ann Raymond, Centre de recherche du CHUM; Catherine Vincent, CHUM; Anupam Adhikari, Centre de recherche du CHUM; Fernando Alvarez, CHU Sainte-Justine, l’Université de Montréal

**BACKGROUND:** A key element in the pathogenesis of inflammation in autoimmune liver diseases is the recruitment of immune cells to the liver. CD4+ T cells are an important lymphocyte subset present in the liver inflammatory infiltrates of patients with autoimmune hepatitis (AIH) and overlap syndrome (AIH/PBC). CD4+ T cells can provide T-cell help to B cells for the secretion of IgG and autoantibodies and activate cytotoxic CD8+ T cells. These cells are therefore central for the development of the B and T cell autoimmune responses. IL-16 is a proinflammatory cytokine functioning as a chemoattractant of CD4+ T cells. The cell signaling receptor of IL-16 is the CD4 molecule present on T cells. IL-16 is also anti-apoptotic for IL-2-stimulated T cells. Therefore, IL-16 could be central in the aetiology of autoimmune liver diseases.

**PURPOSE:** The aim of this study was to assess the involvement of IL-16 in patients with AIH and overlap syndrome (AIH and PBC).

**METHOD:** We used our newly created AIH Research Biobank, composed of biological samples and clinical data from patient with AIH features at the Centre Hospitalier de l’Université de Montréal (CHUM) to measure IL-16 and IL-2 levels in the plasma of patients with AIH and AIH/PBC. Expression of IL-16 by peripheral blood mononuclear cells (PBMC) from these patients was also assessed using qPCR.

**RESULTS:** Patients with an overlap syndrome showed significantly higher plasma levels of IL-16 compared to AIH patients (300.2±64.5 versus 167.9±15.98 pg/mL, p=0.018, n=41). Levels of IL-16 were not significantly different between type 1 and type 2 AIH patients (p=0.3653) or between untreated and treated AIH patients (p=0.2913). Levels of IL-16 did not correlate with plasma IL-2 levels (p=0.4619), age (p=0.4378) or ALT levels (p=0.8527). Levels of IL-16 were significantly higher in patients with F1 to F2 fibrosis levels (348±75 pg/mL) compared to patient with higher levels of fibrosis (136±18.6 pg/mL, p= 0.0029). PBMCs from patients with overlap syndrome expressed more IL-16 than AIH patients and both significantly more than healthy controls (2695±823 versus 2233±586 compared to 22.40±2.943, p=0.0105 and p=0.0284 respectively). Expression of IL-2 by PBMC was not significantly different between AIH and AIH/PBC patients (29±4.3 compared to 38±21.69, p=0.6873).

**CONCLUSION:** Anti-TNF-α-associated acute liver failure displays somewhat different characteristics compared with anti-TNF-α-induced DILI and may represent a distinct severe idiosyncratic drug reaction related to anti-TNF-α, potentially culminating in liver transplant. Infliximab was implicated in the majority of cases. A cholestatic-hepatitic pattern of injury was frequently found on pre-transplant and explant histology.

**REFERENCES:**


CONCLUSION: IL-16 is specifically increased in patients with overlapping features of AIH and PBC. Levels of IL-16 in patients were independent of age, serum ALT or plasma IL-2 levels. AIH/PBC patients with mild to moderate fibrosis had the highest levels of IL-16. These results suggest that plasma IL-16 levels could be a useful biomarker of overlap syndrome. Further research is needed to understand the contribution of IL-16 in the pathogenic process at play in patients with AIH and AIH/PBC overlap syndrome.

Is recurrent primary biliary cholangitis following liver transplantation an infectious disease process? A multicenter study from the Global PBC Study Group

Andrew Mason, University of Alberta; Aldo J. Montano-Loza, University of Alberta; Bettina Hansen, Institute of Health Policy, Management and Evaluation; Douglas Thorburn, The Royal Free Hospital; Palak Trivedi, University of Birmingham; Gideon Hirschfield, Centre for Liver Research, NIHR BRU, University of Birmingham; Christophe Corpechot, Hôpital Saint-Antoine; Raoul Poupon, Hôpital Saint-Antoine; Davide Roccarina, UCL Institute for Liver and Digestive Health, Royal Free Hospital; Jerome Dumortier, Liver Transplant Unit, Edouard Herriot Hospital, Hospices Civils de Lyon; Alexie Bosch, Liver Transplant Unit, Edouard Herriot Hospital, Hospices Civils de Lyon; Emiliano Giostra, Liver Transplant Unit, Edouard Herriot Hospital, Hospices Civils de Lyon; Albert Pares, University of Barcelona; Irene Franceschet, Department of Surgery, Oncology and Gastroenterology, University of Padova; Annarosa Floreani, University of Padua; Jorn Goet, Erasmus University Medical Center; Maren Harms, Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam; Henk van Burren, Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam; Frederik Nevens, University Hospitals Leuven, KU Leuven; Xavier Verhelst, Ghent University Hospital; Federica Malinverno, Transplant Hepatology Unit, Gastroenterology and Hepatology, Maggiore Hospital Policlinico; Ellina Lytvyak, University of Alberta

BACKGROUND: Recurrent primary biliary cholangitis (rPBC) frequently occurs following liver transplantation (LT). More potent immunosuppressive regimens incorporating tacrolimus are associated with more severe and earlier recurrence, whereas cyclosporine is protective against the development of rPBC. Notably, cyclosporine has broad spectrum antiviral activity and has been shown to inhibit betaretroviruses linked with PBC. Further, patients with progressive rPBC unresponsive to UDCA have been treated with open label combination antiretroviral therapy to provide biochemical responses and marked improvement in both grade and stage of histological disease.

AIMS: As recurrent disease triggered by infectious agents usually produce abnormal liver tests soon after LT, we tested that hypothesis that rPBC is associated with cholestasis within the first 12 months following LT.

METHODS: 785 patients from 15 different LT centers were evaluated for liver biochemistries within the first 12 months following LT for histologically established rPBC. Severe cholestasis was defined as bilirubin ≥100 umol or ALP >3x ULN and mild cholestasis as ALP >2 and < 3 or the combination of abnormal ALP and bilirubin.

RESULTS: 89% of patients were female with a mean age of 54±9 years at LT. rPBC was diagnosed in 240 patients and probability of recurrence was 22%, 36%, 50%, and 55% at 5-, 10-, 15-, and 20-years, respectively. Age at diagnosis < 50 (HR 1.64, P=0.003), use of tacrolimus (HR 2.31, P<0.001), severe cholestasis at 6-month (HR 1.79, P=0.008), mild cholestasis 12 months (HR 1.63, P=0.01) and severe cholestasis 12 months (HR 1.49, P=0.04) were associated with higher risk of rPBC, whereas the use of cyclosporine was protective (HR 0.62, P=0.001). Overall median survival was 16±1 years in patients with rPBC versus 21±1 years in patients with no recurrence (P=0.001).

CONCLUSIONS: The link of rPBC with development of cholestasis within the first 12 months is consistent with an infectious disease process rather than autoimmune mediated pathology because the immunosuppression levels are usually highest during this period. The decreased survival found in patients with rPBC warrants further investigation of therapeutic interventions to prevent graft loss, such as adjunctive therapy or prophylactic UDCA at the time of LT or the first development of cholestasis following LT.
Universal screening of newborns for biliary atresia: A cost-effectiveness comparison of alternative strategies

Lisa Masucci, St Michael’s Hospital; Richard A Schreiber, University of British Columbia; Janusz Kaczorowski, l’Université de Montréal; Jean Paul Collet, University of British Columbia; Stirling Bryan, Center for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute

BACKGROUND: Biliary Atresia (BA), a rare newborn liver disease, is the most common cause of liver related death in children and the main indication for pediatric liver transplantation. Early disease detection and timely surgical intervention with a Kasai Portenterostomy offers the best chance for long-term patient survival. Recently, novel BA screening strategies such as a home-based stool color card program or newborn conjugated bilirubin testing have been introduced.

PURPOSE: The objective of this study was to conduct a cost-effectiveness analysis comparing no universal screening to screening for BA using either a home-based stool color card with passive card distribution strategy or screening using conjugated bilirubin testing.

METHODS: A Markov model was developed to simulate a cohort of newborns over a 10-year time horizon. The model structure, costs and probabilities were informed by the literature and clinical expert opinion. Health benefits were expressed as life-years gained. This analysis was conducted from the perspective of the Canadian publicly funded health care system. Both deterministic and probabilistic analyses were conducted.

RESULTS: The mean cost for conjugated bilirubin testing was $3.19. The printing and administrative cost for an infant stool card was $0.65. The conjugated bilirubin testing resulted in 4 less liver transplants than no universal screening. The home based ISCC strategy resulted in 3 less liver transplants. Screening using a home-based stool color card with passive card distribution was found to be a cost-effective option. For a population of 392,902 annual births in Canada, this strategy cost approximately $172,000 more but led to 10 life-years gained (incremental cost-effectiveness ratio (ICER) = $17,288 per life-year gained). Screening using conjugated bilirubin testing was found to not be cost-effective (ICER= $197,000). A one-way sensitivity analysis found that the results were sensitive to the ISCC specificity. If the specificity is reduced to 0.98, the universal home based ISCC screening strategy is no longer cost-effective. If the specificity of the conjugated bilirubin testing were increased to 100%, this screening strategy would still not be a cost effective option.

CONCLUSIONS: In conclusion, a home-based BA screening program using infant stool color cards with a passive distribution strategy could be highly cost-effective when administered at a low unit cost and with a reasonable screening performance.

Non-Wilson’s disease associated hypoceruloplasminemia

Gerald Minuk, University of Manitoba; Annie Gong, University of Manitoba; Samantha Leitold, University of Manitoba; Julia Uhanova, University of Manitoba

BACKGROUND AND AIMS: Low serum ceruloplasmin levels have been reported in patients with non-Wilson’s Disease (WD) liver disorders. When present, extensive, costly and potentially harmful additional investigations for WD may be
undertaken. The purpose of this study was to document the prevalence of low serum ceruloplasmin levels in adult non-WD patients and describe the features commonly associated with this finding.

**METHODS:** Serum ceruloplasmin levels were measured by an enzymatic assay in 3,040 adult patients attending an urban, liver diseases outpatient clinic.

**RESULTS:** 122 (4.0%) patients had serum ceruloplasmin levels below the lower limit of normal documented at their initial visit. Their mean age was 44±14 years and 80 (66%) were male. The Model of End stage Liver Disease (MELD) score was 9.0±4.0. Approximately one half (65/122, 53%) had underlying viral hepatitis (52% hepatitis B and 48% hepatitis C). When compared to 64 MELD-matched control patients with normal or elevated serum ceruloplasmin levels, there were no significant differences in liver enzyme/function tests, ferritin, creatinine values or survival. However, the low serum ceruloplasmin cohort were younger (43±14 versus 52±13 years, p=0.0002), less often male (66% vs. 88%, p=0.001) and viral hepatitis was significantly more common (53% versus 27%, p=0.0005).

**CONCLUSIONS:** Low serum ceruloplasmin levels were documented in 4.0% of adult non-WD patients attending this urban liver diseases outpatient clinic. These patients tend to be younger, less often male and more often have viral hepatitis as the underlying cause of their liver disease.

Suboptimal adherence to screening guidelines for primary sclerosing cholangitis in a Canadian centre

Robert Mitchell, University of British Columbia; Nazlee Tabarsi, University of British Columbia; Amy Wong, Gastroenterology Research Institute (GIRI), St. Paul’s Hospital; Alnoor Ramji, University of British Columbia; Hin Hin Ko, University of British Columbia

**BACKGROUND:** Patients with primary sclerosing cholangitis (PSC) are known to be at increased risk for complications including cholangiocarcinoma, colorectal cancer, gallbladder cancer, and metabolic bone disease. AASLD guidelines provided recommendations for screening of these conditions, but little is known about the adherence to these guidelines and prevalence of complications.

**METHODS:** A retrospective chart review was conducted of patients with confirmed PSC under the care of gastroenterologists at an academic tertiary care center in Vancouver between January 2010 and April 2017.

**RESULTS:** Eighty-five patients with PSC were identified. The mean age at diagnosis was 37.8 ± 18.4 years. 62.5% of patients were asymptomatic at presentation. Diagnosis of PSC was confirmed by ERCP in 41.2% of patients, MRCP in 38.8%, and biopsy in 17.6%.

63 (74.1%) had a concomitant diagnosis of inflammatory bowel disease. Among patients with PSC and IBD without colectomy, 60.4% had colonoscopy for colorectal cancer surveillance every one to two years. 78.8% had colonoscopies at least every five years. Among patients with IBD, 44.4% were on a 5-ASA agent, 17.5% infliximab, 6.3% vedolizumab, 14.3% azathioprine and 28.6% were on no IBD therapy. Among patients with concomitant IBD, 14 (22.2%) had undergone bowel resection—in 11 patients (17.5%) this was for refractory IBD, and in three patients the reason for resection was unclear (4.8%). 68.2% of PSC patients without IBD underwent a screening colonoscopy. Only one patient (1.2%) had colorectal cancer diagnosed following PSC diagnosis.

Only 11.8% of PSC patients had bone mineral density testing performed. 45.9% had CA 19-9 measured at least once while only 13.4% had CA19-9 measured annually. Amongst those with CA19-9 measured at least once, 15.4% had values exceeding 130 U/mL. Four PSC patients (4.7%) developed cholangiocarcinoma and three were identified to have died from complications of cholangiocarcinoma (3.6%). Amongst patients with PSC and IBD without colectomy, 60.4% had colonoscopy for colorectal cancer surveillance every one to two years. 78.8% had colonoscopies at least every five years. Among patients with IBD, 44.4% were on a 5-ASA agent, 17.5% infliximab, 6.3% vedolizumab, 14.3% azathioprine and 28.6% were on no IBD therapy. Among patients with concomitant IBD, 14 (22.2%) had undergone bowel resection—in 11 patients (17.5%) this was for refractory IBD, and in three patients the reason for resection was unclear (4.8%). 68.2% of PSC patients without IBD underwent a screening colonoscopy. Only one patient (1.2%) had colorectal cancer diagnosed following PSC diagnosis.

18.6% of patients had adherence to annual ultrasound for gallbladder cancer surveillance and 5.9% had cholecystectomy performed for suspected gallbladder cancer. Only 24.7% had surveillance every 1–2 years by MRCP/ERCP.

**CONCLUSIONS:** Despite guidelines advocating close surveillance of PSC patients for complications
of their disease, our results show that even in an academic tertiary care center there is considerable room for improvement in practice. Strategies to enhance guideline adherence are clearly needed. Further statistical analysis of this data is underway to determine whether adherence to guideline screening recommendations predicts favorable outcomes in this cohort.

Validation of Baveno VI criteria for triaging patients for screening endoscopy in primary biliary cholangitis and primary sclerosing cholangitis
Carlos Moctezuma-Velazquez, University of Alberta; Andrew Mason, University of Alberta; Aldo Montano-Loza, University of Alberta; Juan Abraldes, University of Alberta; Jan Nilsson, University of Alberta

BACKGROUND: Baveno-VI guidelines recommend that patients with compensated cirrhosis with liver stiffness by transient elastography (LSM) 150,000/mm³ do not need upper endoscopy (UE) to screen for varices, since the risk of having varices needing treatment (VNT: large varices or small varices with high risk stigmata) is 10kPa. We evaluated the Baveno-VI criteria, a continuous model based on LSM/platelets using a risk threshold of 5% (Hepatology, 2016), extended criteria (Liver Int, 2017) and previously recommended criteria for PBC (Clin Gastroenterol Hepatol, 2007) in predicting the absence of VNT.

PURPOSE: Assess the performance of Baveno-VI criteria and other prediction rules in patients with compensated advanced chronic liver disease (cACLD) due to Primary Biliary Cholangitis (PBC) and Primary Sclerosing Cholangitis (PSC)

METHODS: Retrospective cross-sectional study of patients with PBC/PSC assessed with UE and paired LSM within one year. Criteria to perform UE was the presence of cACLD diagnosed by biopsy, clinical, or imaging criteria, or LSM>10kPa. We evaluated the Baveno-VI criteria, a continuous model based on LSM/platelets using a risk threshold of 5% (Hepatology, 2016), extended criteria (Liver Int, 2017) and previously recommended criteria for PBC (Clin Gastroenterol Hepatol, 2007) in predicting the absence of VNT.

RESULTS: Our study included 58 patients with PBC and 43 with PSC. Prevalence of varices and VNT was of 40% and 15%, respectively. Table 1 shows the performance of the different criteria. Baveno-VI would have spared 28% of UEs, with a 0% false negative rate (FNR). The continuous LSM-platelet model would have saved 33% UEs, with a FNR of 0%. The calibration of this model (developed in a sample with predominantly viral etiology) was excellent suggesting the relation between LSM-platelet and VNT is not relevantly different in this population. Expansion of these criteria would increase the FNR, but would have saved around 50% UEs. In PBC, previously described criteria resulted in a FNR>5%.

CONCLUSIONS: Applying Baveno-VI criteria is safe in PBC/PSC, and could save ~30% UEs. Expansion of these criteria would increase the spared UEs but also the FNR. Unfortunately, criteria not using LSM resulted in an unacceptable FNR.

Table 1. Performance of the different criteria to rule out VNT

<table>
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<th>Baveno VI</th>
<th>Abraldes et al., 2016</th>
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<th>Jangouk et al., 2017</th>
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Younger age is associated with lower transplant-free survival relative to a general population in patients with primary biliary cholangitis

Carla Fiorella Murillo Perez, Toronto General Hospital - UHN; Henk van Buuren, Erasmus University Medical Center; Willem Lammers, Erasmus Medical Centre; Aliya Gulamhusein, Toronto General Hospital - UHN; Angelia Cheung, Mayo Clinic; Cyriel Ponsioen, Academic Medical Center; Andrew Mason, University of Alberta; Christophe Corpechot, Hôpital Saint-Antoine; Marlyn Mayo, UT Southwestern Medical Center; Pietro Invernizzi, University of Milan-Bicocca; Pier Maria Battezzatti, University of Milan; Annarosa Floreani, University of Padua; Albert Pares, University of Barcelona; Frederik Nevens, University Hospitals Leuven, KU Leuven; Kris Kowdley, Swedish Medical Center; Tony Bruns, University of Jena; George Dalekos, University of Thessaly; Kalliopi Zachou, University of Thessaly; Douglas Thorburn, The Royal Free Hospital; Nicholas Larusso, Mayo Clinic; Palak Trivedi, University of Birmingham; Raoul Poupon, Hôpital Saint-Antoine; Xavier Verhelst, Ghent University Hospital; Harry Janssen, Toronto Centre for Liver Disease; Gideon Hirschfield, Centre for Liver Research, NIHR BRU, University of Birmingham; Keith Lindor, Arizona State University; Bettina Hansen, Institute of Health Policy, Management and Evaluation; Marco Carbone, University of Milan-Bicocca

BACKGROUND: The effect of age on survival of Primary Biliary Cholangitis (PBC) patients is difficult to evaluate due to the small proportion of young patients diagnosed. Although asymptomatic patients over 55 years of age have been shown to have the same mortality rate as an age- and gender-matched general population, the effect of age on survival in a representative cohort of PBC patients remains unclear.

PURPOSE: The aim of this study was to identify whether age is associated with distinct transplant-free survival relative to the general population.

METHOD: Patient data was retrieved from the Global PBC Study group database, which comprises data from 17 centers across Europe and North America. A total of 4,355 ursodeoxycholic-treated patients diagnosed between 1961 and 2014 were included in the analyses. The patients were grouped according to age at the start of ursodeoxycholic acid treatment and transplant-free survival was compared. Furthermore, life table survival and Cox regression analyses within each age group compared transplant-free survival of PBC patients to an age-, gender-, and birth year-matched general Dutch population.

RESULTS: Patients were grouped according to age at the start of treatment: 65 (n=890). On Kaplan-Meier analysis, the 10-year transplant-free survival rate decreased with age in the corresponding age groups from youngest to oldest: 89.4%, 87.0%, 82.4%, 77.7%, and 64.1% (p 65 [HR 1.39, 95% CI 1.23–1.57] years of age had the lowest).

CONCLUSION: Younger age in PBC is associated with lower transplant-free survival relative to a matched general population. This emphasizes the need for increased monitoring and additional therapies in younger patients.

Bilirubin is predictive of transplant-free survival even within the normal range in patients with primary biliary cholangitis

Carla Fiorella Murillo Perez, Toronto General Hospital - UHN; Henk van Buuren, Erasmus University Medical Center; Willem Lammers, Erasmus Medical Centre; Aliya Gulamhusein, Toronto General Hospital - UHN; Angela Cheung, Mayo Clinic; Cyriel Ponsioen, Academic Medical Center; Andrew Mason, University of Alberta; Christophe Corpechot, Hôpital Saint-Antoine; Marlyn Mayo, UT Southwestern Medical Center; Pietro Invernizzi, University of Milan-Bicocca; Pier Maria Battezzatti, University of Milan; Annarosa Floreani, University of Padua; Albert Pares, University of Barcelona; Frederik Nevens, University Hospitals Leuven, KU Leuven; Kris Kowdley, Swedish Medical Center; Tony Bruns, University of Jena; George Dalekos, University of Thessaly; Kalliopi Zachou, University of Thessaly; Douglas Thorburn, The Royal Free Hospital; Nicholas Larusso, Mayo Clinic; Palak Trivedi, University of Birmingham; Raoul Poupon, Hôpital Saint-Antoine; Xavier Verhelst, Ghent University Hospital; Harry Janssen, Toronto Centre for Liver Disease; Gideon Hirschfield, Centre for Liver Research, NIHR BRU, University of Birmingham; Keith Lindor, Arizona State University; Bettina Hansen, Institute of Health Policy, Management and Evaluation; Marco Carbone, University of Milan-Bicocca

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University Hospital; Harry Janssen, Toronto Centre for Liver Disease; Bettina Hansen, Institute of Health Policy, Management and Evaluation

**BACKGROUND:** Due to the slowly progressing nature of Primary Biliary Cholangitis (PBC), surrogate parameters have been evaluated for their prognostic value on clinical outcomes. It is widely established that bilirubin is strongly associated with transplant-free survival and the threshold with the highest performance for predicting poor outcomes is at the upper limit of normal (ULN). However, its predictive value below this threshold has not been assessed.

**PURPOSE:** This study aims to evaluate whether bilirubin levels within the normal range are associated with transplant-free survival.

**METHOD:** Patient data was retrieved from the Global PBC Study group database, which comprises data from 17 centers across Europe and North America. UDCA-treated and untreated patients with normal bilirubin levels (≤1xULN) at either baseline, 1, 3, or 5 years were included. The influence of bilirubin was assessed as a scale and categorical variable in a Cox proportional hazards model while adjusting for sex, age at start of follow-up, year of diagnosis, ursodeoxycholic acid treatment, alkaline phosphatase (xULN), and albumin (xLLN).

**RESULTS:** Four cohorts of patients with available follow-up were selected with normal bilirubin at baseline (n=2795), 1 year (n=2967), 3 years (n=1596), and 5 years (n=1274). Each cohort was stratified into bilirubin quartiles (Q1–Q4). The 5-year transplant-free survival for baseline Q1–Q4 was 97%, 95%, 96%, and 91%, respectively (p < 0.001). Lower quartiles from the remaining time points also had an improved transplant-free survival. In multivariable Cox regression analyses, bilirubin quartiles remained a significant predictor for transplant-free survival. In addition, higher bilirubin (per 0.1xULN increase) was associated with an increased chance for death or transplantation (baseline: HR 1.14, 1 year: HR 1.21, 3 years: HR 1.19, 5 years: HR 1.17, p < 0.05).

**CONCLUSION:** Bilirubin levels within the normal range at baseline and follow-up are predictive of transplant-free survival. This may imply that we have to aim for the lowest possible bilirubin levels in future intervention studies of PBC.

**Driving under the influence of hepatic encephalopathy: An assessment of Canadian provincial regulations and legal ramifications.**

Henry Nguyen, University of Calgary; Stephen Congly, University of Calgary

**BACKGROUND & AIMS:** Hepatic Encephalopathy (HE) is a manifestation of liver cirrhosis. Symptoms range from subclinical aberrations in neurological and psychological domains to overt findings coinciding with Grade 2–4 HE on the West Haven Criteria scale. Up to 55% of cirrhotic patients have underlying covert hepatic encephalopathy (CHE) with impairments in the domains of attention, psychomotor speed, visuospatial perception and response time; all of which are detrimental to a patient’s ability to safely operate a motor vehicle. Moreover, increased motor vehicle accidents and traffic violations have been noted in patients with HE; underlining the need for physicians to adequately diagnose and counsel patients with HE. However, a recent survey found that unfamiliarity with local traffic regulations may prevent physicians from implementing this in practice. Our aim was to assess motor vehicle codes in each of the Canadian provinces/territory and review the Canadian legal database for cases of automobile accidents involving patients with HE.

**METHODS:** The transportation agencies of each Canadian province/territory were contacted via telephone and/or email. Requirements of physicians to report medical conditions (including any liver disease and HE) affecting a patient’s fitness to drive was assessed. A search of Canadian legal databases for cases on hepatic encephalopathy-related lawsuits made against patients or physicians caring for patients with HE was also carried out.

**RESULTS:** Mandatory reporting of medical conditions impairing a patient’s ability to safely drive is required of a physician in all provinces other than Alberta, Nova Scotia, and Quebec (requirement in 9/13 provinces/territories). Data on Nunavut was not obtained given a lack of response to our phone...
calls and emails. In all the provinces/territories, reporting physicians would receive legal immunity. Where reporting was mandatory, terms including HE, liver cirrhosis, or advanced liver disease was not specifically identified as a reportable medical condition. Our search of Canadian legal databases did not identify any cases made against physicians for failing to identify or counsel patients with liver disease and/or hepatic encephalopathy involved in motor vehicle accidents. Similarly, no legal cases made against patients with HE involved in motor vehicle accidents were identified.

CONCLUSION: Identification of cirrhotic patients with HE (covert or overt) who are unfit to drive is an important patient and public safety issue. The majority of provinces in Canada require physicians to report drivers with medical impairments. Terms including liver cirrhosis, advanced liver disease and/or hepatic encephalopathy should be included as reportable medical conditions. To date, no legal cases against physicians failing to diagnose or counsel patients with hepatic encephalopathy involved in motor vehicle accidents was identified in our Canadian legal database search.

Health-related quality of life and psychosocial functioning in pediatric liver transplant recipients after attending disease specific camp: A pilot study

Arpita Parmar, The Hospital for Sick Children; Vicky L Ng, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Transplant and Regenerative Medicine Centre, The Hospital for Sick Children, University of Toronto; Christina Kosar, The Hospital for Sick Children; Emily Ghent, The Hospital for Sick Children; Stacey Pollock Bar-Ziv, The Hospital for Sick Children; Shannon M. Vandriel, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Transplant and Regenerative Medicine Centre, The Hospital for Sick Children, University of Toronto; Mar Miserachs, The Hospital for Sick Children; Yaron Avitzur, The Hospital for Sick Children; Maria DeAngelis, The Hospital for Sick Children; Nicola Jones, The Hospital for Sick Children

BACKGROUND: With improved long-term survival rates after pediatric liver transplantation (LT), focus has shifted beyond quantity of years restored, to improving health-related quality of life (HRQOL) in this patient population. HRQOL is a multi-dimensional construct that provides a more comprehensive evaluation of the impact of an illness and its treatment, compared to disease parameters alone. HRQOL in pediatric LT recipients is impaired, highlighting the need for intervention strategies targeting improvement of this important outcome metric. Additionally, HRQOL is also associated with poor psychosocial functioning in pediatric LT recipients, also warranting intervention. Camps for children with chronic health conditions have been reported to improve HRQOL and psychosocial functioning in pediatric patients with chronic disease. However, the effects of summer camp on HRQOL outcomes in the pediatric LT population have not been reported.

PURPOSE: This pilot study assessed the impact of attending a pediatric transplant-specific camp on the HRQOL and psychosocial functioning in pediatric LT recipients.

METHODS: Children between 8 to 18 years of age who received an isolated LT, and were attending the transplant-specific summer camp, were invited to participate. Consented participants completed two questionnaires before and after attending a one week transplant summer camp, the Pediatric Liver Transplant Quality of Life (PeLTQL) tool, a disease-specific HRQOL measure and the Strengths and Difficulties Questionnaire (SDQ), a tool that measures psychosocial functioning.

RESULTS: Amongst 21 eligible pediatric LT camp attendees, 16 (76.1%) consented to participate. Mean age of the participants was 14.0 ± 2.96 years, mean BMI Z score was 0.47 ± 0.36 and mean time since LT was 6.4 ± 3.5 years. Five of the consented patients were lost to follow up. Median time from end of camp until completion of post-camp tools was 31 (range 7–67) days. Follow up questions on the SDQ revealed that patients found camp to be helpful and that “difficulties”/problems were improved or remained unchanged after attending camp. Pre-camp and post-camp PeLTQL and SDQ total scores were not significantly different.

CONCLUSIONS: Disease-specific camp is beneficial for LT recipients. Future studies should consider camper assessments to be done whilst still at camp...
towards timely and enhanced assessment of effects and impact of summer camp on HRQOL of this patient population.

**Obesity exacerbates the neurological impairments associated to hepatic encephalopathy in chronic liver disease**

Rafael Ochoa-Sanchez, l’Université de Montréal (CR-CHUM); Mélanie Tremblay, Hepato-neuro lab, Centre de Recherche du Centre Hospitalier de l’Université de Montréal; Christopher Rose, Hepato-neuro lab, Centre de Recherche du Centre Hospitalier de l’Université de Montréal

**BACKGROUND:** Hepatic encephalopathy (HE) is a neuropsychiatric syndrome, a major complication of chronic liver disease (CLD/cirrhosis). With an increasing prevalence of obesity-induced cirrhosis and evidence linking blood-derived lipids to neurological impairment, we hypothesize that obesity increases the risk, severity and progression of HE.

**PURPOSE:** Development of an animal model of cirrhosis and obesity to investigate the synergistic effect of obesity and CLD on the development of neurological impairment and HE.

**METHODS:** Animal model of CLD and HE: 6-week bile-duct ligation (BDL) rats, as well as Sham-operated controls, were used. Inducing obesity: High-fat diet (HFD) was given for 3 weeks before BDL or Sham surgery. Groups: 1. Obese-BDL rats received HFD for 3 weeks pre-BDL and regular diet (RD) for 6 weeks post-BDL; 2. Lean-BDL rats received RD pre- and post-BDL; 3. Lean-Sham rats received RD pre- and post-Sham surgery. Behaviour: Recognition memory, motor coordination and muscular strength were assessed before surgery, as well as 3 and 6 weeks post-surgery using the novel object recognition, rotarod and grip-strength tests, respectively. Body-composition (echoMRI): Fat vs. lean mass and free water (ascites) were also monitored.

**RESULTS:** Before the surgery, body weight (BW) and fat mass of rats on HFD (Obese-BDL) were increased in comparison to rats on RD (Lean-BDL and Lean-Sham). Three weeks after surgery, BW, fat mass, lean mass and free water were increased in Obese-BDL rats vs. Lean-BDL rats. Long-term memory was reduced in Obese-BDL, but not in Lean-BDL, vs. Lean-Sham rats. Six weeks after surgery, similar to Lean-BDL rats, Obese-BDL rats lost BW, fat and Lean mass, while free water increased vs. Lean-Sham rats. Motor coordination, forelimb strength and long-term memory were impaired in Obese-BDL rats in comparison to Lean-BDL or Lean-Sham rats, whereas hind-limb strength and short-term memory were impaired in both Obese- and Lean-BDL rats, compared to Lean-Sham rats.

**CONCLUSION:** HFD induces obesity features in healthy non-cirrhotic rats. Such effects are maintained in cirrhotic-BDL rats. Obesity also accelerates the accumulation of free water in cirrhotic-BDL rats. Interestingly, some neurological impairments are detected in Obese-BDL but not in Lean-BDL rats (long-term memory), while others are exacerbated (motor coordination, forelimb strength). This new animal model of CLD and obesity suggests a synergistic effect, which accelerates and worsens the disease-associated abnormalities observed in CLD and HE. Thus, obesity-induced cirrhosis in patients may result in more complex neurological manifestations, suggesting more susceptibility to poor neurological performance.

HIV-infected individuals with cirrhosis receive less screening for esophageal varices than other liver diseases: A prospective application of the Baveno VI criteria

Chiara Saroli Palumbo, McGill University; Amine Benmassaoud, McGill University; Thomas Pembroke, McGill University; Achuthan Aruljothy, McGill University; Bertrand Lebouché, McGill University; Philip Wong, McGill University; Marc Deschenes, McGill University; Marina Klein, McGill University; Peter Ghali, McGill University; Giada Sebastiani, McGill University

**BACKGROUND:** HIV positive (HIV+) people are at increased risk of developing cirrhosis and its complications, including variceal hemorrhage. The Baveno VI consensus provides guidance as to which patients with cirrhosis should be screened for esophageal varices, and which can safely forego
Holistic treatment for persons with liver disease caused by alcohol use disorder
Debra Selkirk, Selkirk Liver Society

BACKGROUND: From December 2007 to November 2010, I experienced the perils of liver disease as my husband’s health declined and he ultimately died. His liver disease was caused by alcohol use disorder; his death was the direct result of a policy that denied him timely treatment.

Since 2012, I have advocated for change, and legally challenged the 6-month wait for transplant for ALD patients. My court documents included an expert witness affidavit from Dr. John Fung, renowned surgeon who was the right hand of liver transplant pioneer surgeon Dr. Thomas Starzl, and who trained liver transplant surgeons from around the world. My husband’s case attracted significant media attention.

As a direct result of my work, in 2018, Ontario will become the first jurisdiction in North America to adopt an innovative pilot program that assesses ALD patients without an alcohol-free period, combining addiction treatment with liver transplantation.

PURPOSE: I would like to speak at the 2017 Canadian Liver Meeting. My insight into patient care comes from the perspective of the wife of a patient whose life could have easily been saved. Reflecting back on that three-year period, I came to realize that holistic treatment of his liver disease, which was caused by alcohol use disorder, may have saved my husband’s life and lessened the likelihood of progression to transplantation.

METHOD: In referring my husband to a hepatologist, his family doctor was attempting to stall the decline in his liver health. His hepatologist did an outstanding job in treating his liver disease, which initially returned him to improved health. However, his liver cirrhosis was a symptom of a larger picture that included alcohol use disorder and poor nutrition. He did not understand how liver cirrhosis progresses; he had no idea the food he preferred was toxic to his liver; he was never referred to an addiction specialist or prescribed medication to control his cravings. The window of opportunity to save his life was wasted.

Liver cirrhosis clinics with a holistic treatment program would offer a new approach to treating esophagogastroduodenoscopy (EGD), based on transient elastography (TE) and platelet values. We aimed to determine whether Baveno VI consensus guidelines are appropriately applied in HIV+ as compared to HIV negative (HIV-) individuals with liver disease.

METHODS: A prospective cohort study was conducted since 2015, which included HIV+ and HIV- persons who underwent TE as part of a routine screening program for liver disease. Liver cirrhosis was defined as TE measurement >13kPa. Baveno VI guidelines (TE measurement 150,000) were applied to identify those at very low risk of having varices, and who could avoid screening with EGD. Multivariable logistic regression analysis was used to investigate independent cofactors associated with deviation from the Baveno VI guidelines. Diagnostic accuracy of screening according to Baveno VI guidelines as compared to universal EGD was computed.

RESULTS: 725 HIV+ (mean age 49 years, 75% men, 35% with fatty liver, 21% HIV/HCV co-infected) and 785 HIV- patients (mean age 51 years, 59% men, 36% with fatty liver, 38% infected with HCV) were included. Prevalence of cirrhosis in the whole cohort was 19%. Overall, 7% HIV+ and 74% HIV- patients met the Baveno VI criteria for not requiring screening EGD. In the remaining cases who required screening, EGD was performed in only 23% of HIV+ as compared to 87% of HIV- patients (p < 0.001). Incidence of variceal bleeding was higher in HIV+ than HIV- patients (5.8% vs 1.9%, p < 0.05). In HIV+ patients, the Baveno VI guidelines had a sensitivity 0.82, specificity 0.62, positive predictive value 0.26, negative predictive value 0.95 for the diagnosis of esophageal varices as compared to universal EGD, which were similar to HIV- patients. In multivariable analysis, after adjustment for age, gender, BMI and anti-HCV positivity, being HIV+ was the strongest factor associated with failure to screen when indicated by Baveno VI guidelines (aOR=10.0, 95% CI 7.5–13.5; p < 0.0001).

CONCLUSIONS: Despite the Baveno VI guidelines performing well in HIV+ patients, they are significantly less likely to receive standard of care screening for esophageal varices than HIV- patients, placing them at higher risk of fatal complications from hemorrhage.

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characteristics were used to identify predictors of 90-days readmission.

**RESULTS:** Of the 81,179 patients admitted with cirrhosis related complications in 2014, 19,889 (25%) were readmitted within 90 days due cirrhosis related complications. Readmission rates at 30 and 60 days post discharge were 15% and 21% respectively. The average total charge per cirrhosis-related index admission was $60,197 with a weighted cumulative national estimate ~ $10 billion, while the average total charge for readmission was $61,865 and weighted cumulative national estimate ~ $2.6 billion. The main causes of readmission were ascites (54%), hepatic encephalopathy (44%) and esophageal varices (42%). Readmitted patients at 90-days were younger (median age 58 vs. 60; P < 0.001), male gender (62% vs. 61%, P < 0.01), less likely to be privately insured (20% vs. 24%, P < 0.001), and having ≥2 comorbid conditions (87% vs. 84%, P < 0.001). Independent predictors of 90-days readmissions were male gender (adjusted OR: 1.05, 95%CI, 1.02–1.09), age≥ 60 (aOR: 0.80, 0.78–0.83), private insurance (aOR: 0.78, 0.75–0.81), having ≥2 comorbid conditions (aOR: 1.53, 1.40–1.67), and being discharged against medical advice (aOR: 1.40, 1.26–1.55). Hospital teaching status and location were not predictors of readmission.

**CONCLUSIONS:** A quarter of patients admitted with cirrhosis-related complications were readmitted within 90 days, representing a significant economic burden related to readmission of this population. Patient characteristics and comorbidities are the main predictors of readmission. Interventions and resource allocations to reduce readmission rates among cirrhotic patients is critical.

**Nationwide estimates and risk factors of readmission in patients with cirrhosis in the United States**

Abdel Aziz Shaheen, University of Calgary; Gilaad Kaplan, University of Calgary; Mark Swain, Dept of Medicine, University of Calgary; Stephen Congly, University of Calgary

**BACKGROUND:** The burden of cirrhosis on the health care system is substantial, and growing. Hospitalized patients due to cirrhosis complications are likely to be readmitted. Our objectives were to estimate the readmission rates, and hospitalization cost, as well as to identify the risk factors for 90-day readmission in patients with cirrhosis.

**METHODS:** We conducted a weighted analysis of the 2014 Nationwide Readmission Database (NRD) to identify adult patients with cirrhosis-related complications in the United States. An admission was considered cirrhosis-related if the primary diagnosis was cirrhosis or a liver-related complication (based on ICD-9 codes). We assessed readmission rates at 30, 60 and 90 days post-index hospitalization. Weighted regression models adjusting for patient (e.g. demographics, insurance, and Elixhauser comorbidities) and hospital characteristics were used to identify predictors of 90-days readmission.

**RESULTS:** Of the 81,179 patients admitted with cirrhosis related complications in 2014, 19,889 (25%) were readmitted within 90 days due cirrhosis related complications. Readmission rates at 30 and 60 days post discharge were 15% and 21% respectively. The average total charge per cirrhosis-related index admission was $60,197 with a weighted cumulative national estimate ~ $10 billion, while the average total charge for readmission was $61,865 and weighted cumulative national estimate ~ $2.6 billion. The main causes of readmission were ascites (54%), hepatic encephalopathy (44%) and esophageal varices (42%). Readmitted patients at 90-days were younger (median age 58 vs. 60; P < 0.001), male gender (62% vs. 61%, P < 0.01), less likely to be privately insured (20% vs. 24%, P < 0.001), and having ≥2 comorbid conditions (87% vs. 84%, P < 0.001). Independent predictors of 90-days readmissions were male gender (adjusted OR: 1.05, 95%CI, 1.02–1.09), age≥ 60 (aOR: 0.80, 0.78–0.83), private insurance (aOR: 0.78, 0.75–0.81), having ≥2 comorbid conditions (aOR: 1.53, 1.40–1.67), and being discharged against medical advice (aOR: 1.40, 1.26–1.55). Hospital teaching status and location were not predictors of readmission.

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**The impact of nursing volume on inhospital mortality among patients with cirrhosis: A population-based study**

Abdel Aziz Shaheen, University of Calgary; Jacob Charette, University of Calgary; Gilaad Kaplan, University of Calgary; Mark Swain, Dept of Medicine, University of Calgary; Robert Myers, Gilead Sciences, Inc.

**BACKGROUND:** Although the intensity of nursing care has been associated with improved outcomes in many conditions, the impact of nursing staff
volume in patients with cirrhosis is unknown. Our objective was to delineate the association between nurse staffing and in-hospital mortality in patients with cirrhosis.

METHODS: We used the 2011 Nationwide Inpatient Sample (NIS) database to identify cirrhosis-related hospitalizations in the United States. An admission was considered cirrhosis-related if the primary diagnosis was cirrhosis or a liver-related complication (based on ICD-9 codes). Hospital-level nursing staff volume, which includes the volume of registered nurses, licensed practical nurses and nurse aids, was categorized into tertiles (low [6.4 nurse full-time equivalents (FTEs) per 1,000 adjusted inpatient days]). Weighted regression models assessed the impact of nursing volume on in-hospital mortality. We adjusted for patient (e.g. demographics, insurance, and Elixhauser co-morbidities) and hospital characteristics, including hospital volume for cirrhosis-related admissions.

RESULTS: There were 41,916 cirrhosis-related hospitalizations in 2011 corresponding to an estimated 203,588 admissions in the United States. Compared with patients admitted to hospitals with low nursing volume, those hospitalized in high nursing volume centers were younger (median age: 57 vs. 58; P < 0.001), more likely to be privately insured (27.6% vs. 22.5%; P < 0.001), and more frequently admitted to high-volume (for cirrhosis) hospitals (68.1% vs. 14.8%; P < 0.001). The prevalence of ≥2 comorbid conditions was higher among low nursing volume centers (83.7% vs. 81.8%; P < 0.001). Although in-hospital mortality was similar across nursing volume groups (high vs. low: 6.0% vs. 6.3%; P=0.19), patients admitted to high nursing volume hospitals had increased hospitalization charges ($34,768 vs. $24,622) compared to low nursing volume centers (P < 0.001). After adjusting for patient and hospitalization characteristics, neither nursing nor hospital volumes were independent predictors of in-hospital mortality (high vs. low nursing volume: adjusted odds ratio 0.97, 95% CI 0.86–1.09; high vs. low hospital volume: aOR 1.01, 0.90–1.13). Subgroup analysis for each decompensated feature of cirrhosis yielded similar results.

CONCLUSIONS: Nursing staff volume was associated with increased cost but not with in-hospital mortality in patients with cirrhosis. Our study necessitates further assessment of the relationship between nursing staff volume and cirrhosis outcomes. This will potentially have a significant impact on health care resources utilization and costs.

Characteristics and outcomes of cystic fibrosis pediatric patients admitted with cirrhosis in the United States

Abdel Aziz Shaheen, University of Calgary; Ranjani Somayaji, University of Calgary; Michael Parkins, University of Calgary; Mark Swain, Dept of Medicine, University of Calgary

BACKGROUND: Cystic fibrosis (CF) is the most fatal genetic disease of Caucasians in North America and Europe. There are approximately 33,000 individuals with CF in the United States and 70,000 globally. CF liver disease (CFLD) is the third leading cause of death in CF patients accounting for 2.5% of overall mortality. CFLD is a unique form of liver disease and can progress to multi-lobular cirrhosis but the characteristics and outcomes of pediatric patients with CF and cirrhosis are not well studied. We aimed to describe the characteristics of CF pediatric patients admitted with cirrhosis related diagnosis and to estimate predictors of in-hospital mortality, length of stay (LOS) and hospitalization charges among this cohort.

METHODS: We used the 2012 Kid’s Inpatient Database (KID) database to identify cirrhosis-related hospitalizations among CF pediatric patients (age 0–20) in the US. An admission was considered cirrhosis if a diagnosis of cirrhosis or cirrhosis related complication was identified (based on ICD-9 codes). We compared demographic, socio-economic (insurance status) and clinical characteristics (Elixhauser co-morbidities) of CF patients (e.g. demographics, insurance, and Elixhauser comorbidities) with and without a cirrhosis-related diagnosis. Adjusted logistic regression models were used to identify predictors of in-hospital mortality, LOS and hospitalization charges among CF patients with cirrhosis.

RESULTS: Of the 10,256 pediatric CF hospitalizations identified in 2012, 555 (5.4%) had a diagnosis of cirrhosis. Compared with CF patients without cirrhosis, those with cirrhosis were older (median
AIM: This study aimed to systematically review existing literature of centre-specific screening protocols for recurrent HCC after liver transplantation.

METHODS: MEDLINE, Medline in Process, Epub Ahead of Print and EMBASE + EMBASE Classic, OvidSP were searched for studies up to February 2017 describing (a) HCC recurrence in adults who underwent liver transplantation, and (b) screening protocol and treatment options for these patients. Outcomes sought included post-transplantation overall survival, recurrence free survival and post-recurrence survival.

RESULTS: 151 studies were included in this review. Preliminary results from studies published 2013–2017 (n=72) are reported here. All studies were observational, and none compared multiple screening protocols. Mean HCC recurrence rate was 20% (range 5.4–59%). There was great heterogeneity in screening protocols. The most commonly used modalities were alpha-fetoprotein (n=59), CT (n=56) and ultrasound (n=36), with most studies using multiple modalities (n=65). 53 studies involved screening at least every 3 months, although many screened less frequently after 1–3 years (n=38). 24 studies reported treatment strategies for HCC recurrence, among which locoregional therapy was the most commonly used approach (n=22). Preliminary analyses of the past two years show a slightly worse outcomes in studies that use < 6 months screening frequency, however the full review is underway to ascertain this finding.

CONCLUSIONS: Review of literature revealed only observational studies with great heterogeneity. Preliminary results suggest a trend towards worse outcomes with < 6 months screening frequency, however the full review is underway to ascertain this finding.

Systematic review of literature on the detection and management of recurrent hepatocellular carcinoma after liver transplantation.
Alexandra Shingina, IHPME, University of Toronto; Catherine Hu, McMaster University; Gonzalo Sapiochin, Multi Organ Transplant Program, University Health Network; Mamatha Bhat, Multi Organ Transplant Program, University Health Network

BACKGROUND: Liver transplantation remains the only curative treatment for hepatocellular carcinoma (HCC). Despite careful patient selection, the post-transplantation recurrence rate is estimated around 20%.

IgG4-related autoimmune hepatitis: A case report
Myriam St-Pierre-Lussier, Université de Sherbrooke; Dusanka Grbic, Université de Sherbrooke; Martin Borduas, Université de Sherbrooke

INTRODUCTION: Immunoglobulin G4 (IgG4)-related autoimmune hepatitis (AIH) is a newly described disease characterised by elevated levels of
serum IgG4 and hepatic infiltration by IgG4 positive plasma cells. This disease entity is very rare and its prognosis remains unknown. Here we report the case of a patient with IgG4-related AIH and synchronous generalized lymphadenopathy.

**CASE REPORT:** A 73-year-old woman presented with fatigue, nausea, weight loss, liver dysfunction and generalized lymphadenopathy. She had no relevant past medical history. Her liver function tests (LFTs) showed: aspartate aminotransferase (AST) 52 IU/L, alkaline phosphatase (ALP) 212 IU/L, total bilirubin (26 umol/L) and prothrombin time-international normalized ratio (PT-INR 2.80).

Serum total IgG concentration was 4400 mg/dL (normal range: 870–1700 mg/dL). Autoantibodies titers (ANA, smooth muscle antibody and anti-mitochondrial antibody) were all negatives. Liver ultrasound showed no signs of hepatopathy or portal hypertension.

Positron emission tomography/computed tomography (PET) showed lymphadenopathy on both sides of the diaphragm with maximal uptake around the hepatic hilum. Multiple biopsies (hepatic lymph node fine-needle aspirations, axillary lymph node excisional biopsy and bone marrow biopsy) showed only reactional lymphadenitis.

Three months after initial consultation, the patient presented with acute calculus cholecystitis and a laparoscopic cholecystectomy was performed. Surprisingly, the surgeon discovered signs of portal hypertension and hepatopathy. At that moment, her LFTs showed: AST 62 IU/L, ALP 235 IU/L and PT-INR 1.46.

Liver biopsy showed chronic hepatitis with classical features of HAI, including plasma cells-rich portal inflammation, interface hepatitis and hepatic rosette. With the presence of elevated total IgG, the patient was diagnosed with a probable AIH according to the International Autoimmune Hepatitis Group (IAIHG) scoring system.

Serum IgG4 concentration was also elevated (936 mg/dL, normal range 3–201 mg/dL). Immunostaining for IgG4 was conducted on the liver specimen and showed many IgG4+ plasma cells in the hepatic infiltrate. More than 10 IgG4+ plasma cells were counted per high power field (HPF), and more than 40% of plasma cells were IgG4-positive. Neither imaging nor histological findings showed cholangiopathy or pancreatitis.

The patient was treated with prednisone 40 mg daily, tapered over the course of 2 months, followed by azathioprine 150 mg daily. Serum IgG4 concentration and liver enzymes normalized, and the adenopathy completely disappeared on the follow up PET scan.

**CONCLUSION:** The clinical course of this patient shows that IgG4-related AIH can present with concomitant generalized lymphadenopathy and may respond well to immunosuppressive therapy.

**Significant lung injury and its prognostic significance in acute liver failure**

Ken Sun, University of Alberta; Dean Karvellas, University of Alberta Hospital; Victor Dong, University of Alberta; Michelle Gottfried, Medical University of South Carolina; Filipe Cardoso, Central Lisbon Hospital Center; Mark McPhail, Imperial College London; Richard Stravitz, Virginia Commonwealth University; William Lee, UTSouthwestern

**BACKGROUND:** Respiratory failure is a concerning complication of acute liver failure (ALF), and high oxygen requirements often preclude ALF patients from undergoing liver transplantation (LT).

**PURPOSE:** The aim of this study was to evaluate the association between significant lung injury (SLI) and important clinical outcomes (21-day survival, liver transplantation) in ALF patients.

**METHODS:** A prospectively collected, retrospective cohort study which included 947 (out of 3,025) patients enrolled by the US Acute Liver Failure Study Group from January 1998 through December 2016 who were mechanically ventilated and for whom data regarding chest radiography and oxygenation (PaO2/FIO2) were available. ALF patients were stratified according to the Berlin definition as having SLI if PaO2/FIO2 was < 200 mm Hg, and controls with PaO2/FIO2 ≥ 200 mm Hg.

**RESULTS:** Of 947 ALF patients included in this analysis, 370 (39%) had evidence of SLI while 577 (61%) did not (controls). ALF patients with SLI (ALF-SLI) had significantly worse oxygenation than controls on admission to study, (120 vs. 300 mm Hg p < 0.001) and worse biochemical derangement reflected by median bilirubin (7.3 vs. 6.3 mg/dL, p=0.04), creatinine (2.3 vs. 1.8 mg/dL, p < 0.001)
METHODS: A retrospective chart review was conducted of medical records and laboratory data of all patients who were diagnosed with T1HRS at a tertiary care teaching hospital in Winnipeg, MB between January 2015 to December 2016. These patients had all been diagnosed by their medical team with T1HRS and were concurrently started on midodrine and octreotide during this period.

RESULTS: Preliminary analysis revealed that the diagnosis of T1HRS was made 19 times over the above period. All of these diagnoses were made on a medical ward. The majority of patients had alcoholic related disease (10/19), while 84.3% (16/19) had cirrhosis. Although all patients had liver disease and ascites, 94.7% (18/19) of patients had acute kidney injury according to the ICA-AKI criteria. Only 1 of the 19 patients diagnosed with T1HRS fulfilled all of the ICA criteria published in 2015: 57.8% (11/19) had recent or current exposure to nephrotoxins, 84.2% (16/19) did not have a withdrawal of diuretics and volume expansion with albumin, and 47.3% (9/19) did not have adequate assessment to rule out macroscopic renal disease. The average duration of therapy with midodrine and octreotide was 7±5 days, with only 42.1% (8/19) of patients undergoing titration of midodrine to achieve a 10mm Hg increase in MAP. Despite inappropriate start of therapy in most patients, 31.6% (6/19) had some treatment response, while 38.4% (5/13) went on to receive renal replacement therapy. The mortality was high at 63.1% (12/19): 33.3% (2/6) amongst responders while 76.9% (10/13) amongst non-responders. Liver transplantation was pursued in 10.5% (2/19) patients.

CONCLUSION: The majority of T1HRS patients diagnosed on a medical ward did not fulfill the ICA HRS criteria. As such, the response rates to HRS therapy were not as high as expected. Further education and a quality improvement study regarding the accurate diagnosis and management of T1HRS is needed and will be performed in the future.

Patient’s perspective on early liver transplantation for alcoholic liver disease

Eric Wong, University of British Columbia; Vladimir Marquez Azalgara, University of British Columbia;
Eric Yoshida, University of British Columbia; Sigfried Erb, University of British Columbia; Charles Scudamore, University of British Columbia; Jo-Ann Ford, University of British Columbia

BACKGROUND: Liver transplant programs in Canada require a period of 6 months of alcohol abstinence before considering a patient with liver disease secondary to alcohol. Although some studies have demonstrated good outcomes in carefully selected patients transplanted before the 6 months period, arguments against a change in policy have claimed that there is a general negative perception of people with alcoholism among the public and that they are less deserving due to the behavioral component of the disease.

PURPOSE: Determine the perception of people from British Columbia regarding the possibility of liver transplantation in patients with liver disease due to alcohol who have not shown the capacity to remain abstinent.

METHODS: Cross-sectional study using self-administered questionnaire in patients recruited at a general gastroenterology practice and liver transplant clinic.

RESULTS: 219 individuals responded. The majority of patients had a form of liver disease and 54% had or were being assessed for a liver transplant. 82% of respondents agreed with a period of abstinence of 6 months. For patients who are unlikely to survive 6 months without transplant 37% were in agreement, 42% in disagreement and 21% neutral with the abstinence rule. 46% of respondents would be less trustful to the process of transplantation if an abstinence period was not required, but for the majority it will not have an impact on their decision to become organ donors. Only 29% would support abandoning the abstinence criteria. The support for abstinence was greater among patients who had a liver transplant. Alcohol consumption or history of liver disease due to alcohol did not have an impact on participant’s preference. For patients that would be unlikely to survive 6 months without a transplant, there was a shift in the perception of the abstinence rule with responders that were transplanted or currently assessed for transplant being less likely to support it.

CONCLUSION: There seems to be a consensus among respondents about supporting the 6 month abstinence rule. However, there is also an opening to ignore this criteria in patients that will be unlikely to survive the required period of abstinence. A large scale survey of all Canadian provinces would be required to assess support for a change in policy.

The treatment of patients with decompensated cirrhosis due to genotype 1 hepatitis C infection is associated with an improved quality of life

Florence Wong, Toronto General Hospital; Melissa Reyes, Toronto General Hospital

Decompensated liver cirrhosis is associated with many symptoms, some are specific to the complications of cirrhosis, others are related to the global deterioration of their health. Infection with hepatitis C virus (HCV) is also associated with chronic fatigue, and have a negative impact on the quality of life (QoL) of these patients. The advent of potent direct acting agents (DAAs) that are safe for patients with decompensated cirrhosis means that these patients can now have their HCV treated. As both the decompensated state and the presence of HCV infection contribute to the symptomatology and reduced QoL of these patients, it is not clear whether the clearance of HCV alone will improve their QoL. Therefore, the aim of this study was to assess the impact of HCV treatment on the QoL of patients with chronic HCV and decompensated cirrhosis. Methods: Patients with decompensated HCV cirrhosis were treated with sofosbuvir and ledipasvir (Harvoni) for 24 weeks. Patients were followed monthly during therapy and thereafter at 3, 6, 12 months (M) post-therapy. The Chronic Liver Disease Questionnaires (CLDQ) as a QoL instrument was administered pre-treatment, at end of treatment (EoT), and at 6 and 12M-post treatment. and the results compared. Results: 14 patients (mean age 58.8±1.6 years, 64% males) with genotype 1 HCV infection were enrolled. All had ascites, while 3 had a history of either variceal bleed or overt encephalopathy. Eight patients also had significant alcohol history. Two patients died from
complications of cirrhosis before completing treatment. Two further patients have not yet completed their courses of treatment. The preliminary results show that for the remaining 10 patients, treatment with 24 weeks of Harvoni resulted in sustained virologic response in 9 patients, associated with normalization of liver enzymes and non-significant reductions in Child-Pugh (6.9±0.4 vs. 5.7±0.3) and MELD (10.9±0.9 vs. 8.9±2.2) scores (p>0.05 for both). One patient relapsed before EoT. Five of the 6 domains of the CLDQ showed significant improvement despite persistent decompensation.

CONCLUSIONS: Despite the persistence of cirrhosis decompensation and insignificant change in the severity of liver dysfunction, HCV treatment is associated with a significant improvement in QoL in these patients, as measured by a specific chronic liver disease QoL instrument. Since there are safe DAAs that are available for the treatment of patients with HCV and decompensation, such patients should be assessed for treatment in order to improve their QoL.

Palliative care for end-stage hepatopulmonary syndrome: A systematic review
Laura Wong, University of Toronto; Samir Gupta, St. Michael’s Hospital; Madina Naimi, St. Michael’s Hospital; Jonathan Ailon, St. Michael’s Hospital; Naheed Dosani, McMaster University, University of Toronto; Anne Stephenson, St. Michael’s Hospital

BACKGROUND: The hepatopulmonary syndrome (HPS) is defined as a triad of liver disease, intrapulmonary vascular dilatation, and poor oxygenation. It is found in up to 30% of patients with cirrhosis and characterized by progressive and severe dyspnea. Liver transplantation (LT) is the only definitive treatment for HPS. However, a significant proportion of patients are not considered candidates for LT due to co-morbidities and/or addictions, or because they electively decline LT.

PURPOSE: We sought to perform a systematic literature review to identify strategies for the palliative management of HPS patients who are not LT candidates.

METHODS: We conducted a systematic literature review of MEDLINE (PubMed), Embase, Cochrane Central Register of Controlled Trials, CINAHL, and Scopus databases, with no date restrictions, using the MeSH terms/keywords “hepatopulmonary syndrome” and “hepato-pulmonary syndrome.” We included English language prospective/retrospective studies, case series/reports, and abstracts describing human subjects with HPS who were not LT candidates (all ages) who received any non-transplant intervention(s). Studies were required to report objective impact on direct or surrogate measures of dyspnea and/or quality of life. We excluded studies reporting HPS related to congenital vascular malformations or congenital heart disease, and interventions targeting the liver disease or its cause, or requiring administration and ongoing care in a monitored setting. Two reviewers independently reviewed abstracts and retrieved and reviewed full manuscripts for all abstracts definitely or possibly meeting criteria.

RESULTS: Our database search identified 3,956 studies, including duplicates. Upon review, we eliminated 2,050 (52%) duplicates, and reviewed full manuscripts for 63 (3.3%) of the remaining 1,906 abstracts. Eight of 63 (12.7%) were included. Most reports were observational. Both orally administered garlic (2 case reports; n=2) and norfloxacin (1 case report; n=1) improved hypoxemia; and pentoxifylline (one RCT; n=10) (compared to pentoxifylline plus rifaximin; n=9) improved oxygen

Table 1.

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<th>Abdominal Symptoms</th>
<th>Activities</th>
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saturation. Both curcumin and terlipressin, tested serially (1 case report; n=1) worsened hypoxemia; and neither a somatostatin analogue (1 prospective observational study; n=6) nor transjugular intrahepatic portosystemic shunt (1 case report; n=1 and 1 prospective observational study; n=2) consistently improved HPS-related outcomes. Meta-analysis could not be performed due to these small numbers and the variability of populations and outcomes across studies. No studies proposed strategies to address goals of care needs in this palliative population.

CONCLUSIONS: Although HPS is a disease associated with a high mortality and poor quality of life, there are limited data to inform palliative management of patients who are not LT candidates. Garlic, norfloxacin, or pentoxifylline might be considered for palliation in this population. Approaches could be enhanced by a review of medical treatment strategies used in all HPS patients (regardless of transplant candidacy) and of general palliative strategies used in other diseases, such as the use of opiates for dyspnea.

SESSION #3: ALLIED HEALTH

Exploring the impacts of medicalization and the limits of traditional public health approaches to HCV prevention in the spaces where people use illicit drugs

Gillian Kolla, University of Toronto; Carol Strike, University of Toronto

BACKGROUND: Making sterile injection materials easily available to people who inject drugs is key to the prevention of hepatitis C infection. The expansion of harm reduction programs, which distribute sterile injection materials while also providing education on hepatitis C, has been a key focus of public health intervention.

PURPOSE: This paper examines the impact of the “Satellite Sites,” a program in which people who use drugs are employed by a community health centre to run satellite harm reduction programs within their own homes. This paper examines the interplay of medicalization and criminalization in these sites, and its impact on HCV vulnerability among people who inject drugs.

METHOD: Using data from an ethnographic study, including observations within the Satellite Sites and interviews with key members of the program, this paper explores the process, effects and limits of medicalizing the spaces where people gather to use illicit drugs, and turning them into a formal public health intervention.

RESULTS: Turning the spaces where people gather to use drugs into sites of public health intervention has resulted in the medicalization of these sites. During their work, Satellite Site workers distribute drug use equipment and safer sex supplies, including needles and syringes, crack kits, and condoms; provide education on safer drug use; intervene in overdoses; and administer naloxone for overdose reversal. The process of medicalization has positively impacted the availability and accessibility of sterile injection equipment for people who inject drugs. The interactions between police and the Satellite Sites is also improved by medicalization. However, there are limits to the effects of medicalization under the current regime of criminalization of drug possession and distribution. Since these limits are due to the structural forces, including criminal law and the nature of illicit drug markets, it may not be possible to counteract them using traditional Public Health intervention methods.

CONCLUSION: Public Health authorities need to consider that effective HCV prevention is impeded by the effects of structural forces such as drug laws and the operation of illicit drugs markets when designing interventions. To achieve effective HCV prevention, a change in focus may be necessary, including examining the potential benefits that may stem from the decriminalization and regulation of currently illicit drug markets on the health of people who use illicit drugs and are vulnerable to HCV infection.

An economic evaluation of emergency department population-based hepatitis C screening strategies in Canada

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Isaranuwatchai, Centre for Excellence in Economic Analysis Research (CLEAR), St. Michael’s Hospital; William WL Wong, School of Pharmacy, University of Waterloo; Murray Krahn, Toronto Health Economics and Technology Assessment Collaborative (THETA), University of Toronto

BACKGROUND: An estimated 220,000 Canadians live with chronic hepatitis C viral (HCV) infection, of which 44% are unaware of their diagnosis. Of those infected, it is estimated that 1 in 4 will develop cirrhosis and 1 in 8 will die from HCV-related causes. Newly approved medications have revolutionized the treatment of HCV infection, but finding and treating cases before complications develop is difficult due to HCV’s asymptomatic nature. Emergency department (ED) patients have been associated with a higher prevalence of HCV infection when compared to the general population. Previous studies examining ED infectious disease screening have resulted in a higher prevalence of newly diagnosed infections and more cases of infection linked to timely care. Recently, the Canadian Task Force on Preventative Health Care recommended against population-based HCV screening strategies, citing a lack of evidence of their effectiveness. Although studies have analyzed wide-scale population screening, few have examined alternative screening strategies such as targeting high-risk populations including ED patients.

PURPOSE: This study aims to perform an economic evaluation of ED-based HCV screening strategies in Canada.

METHOD: A microsimulation state-transition model was developed. Two scenarios, (1) screening of the general ED population and (2) ED screening of those between 51 to 69 years of age (baby boomer cohort), were compared to no screening from the public healthcare payer perspective. Distinct measures of ED HCV prevalence, screening test uptake rate, and health utilities from published literature were used to model ED-specific screening strategies. Simulated direct-acting antiviral treatment regimens were based on treatment guidelines and effect estimates obtained from published sources. Quality-adjusted life-years (QALYs) and costs in 2016 Canadian dollars were predicted over a lifetime time horizon using a 1.5% discount rate. Sensitivity analyses were performed to characterize any uncertainties in parameter estimates and findings.

RESULTS: Preliminary results demonstrated screening and subsequent treatment of ED patients would prevent 144 and 37 HCV-related deaths per 10,000 people screened for the general population and baby-boomer scenarios, respectively. ED general population screening was associated with an average cost increase of $1,948 and a QALY increase of 0.18 relative to no screening ($10,822/QALY). Baby boomer cohort screening was associated with an average cost increase of $559 and a QALY increase of 0.03 relative to no screening ($18,633/QALY). After accounting for uncertainty, both ED screening scenarios were likely to be cost-effective when compared to no screening at willingness-to-pay thresholds greater than $20,000 per QALY gained.

CONCLUSION: ED screening demonstrates the potential to be a cost-effective strategy that can play a role in broader population-based efforts to eradicate HCV. This analysis may provide the first step towards the development of pilot studies that can further determine mechanisms of implementation, the feasibility and the acceptance of ED-based HCV screening strategies.

Values, preferences, and acceptability of hepatitis C testing and treatment in the homeless and vulnerably housed: A scoping review

Adam Palayew, McGill University; Janet Hatcher-Roberts, University of Ottawa; Kevin Pottie, University of Ottawa; Alain Mayhew, Bruyere Research Institute; Chris Greenaway, McGill University; Harneel Kaur, University of Ottawa; Olivia Magwood, University of Guelph

BACKGROUND: The WHO has called for the elimination of viral hepatitis as a public health concern by the year 2030. However, if this goal is to be met, marginalized and underserved populations, who account for a disproportionate burden of the disease, need to be tested and successfully linked to treatment and care. In Canada, at least 235,000 people experience homelessness in a year. This
Nutritional status, hepatic encephalopathy and health-related quality of life in patients with chronic liver disease

Cassandra Picinbono-Larose, l’Université de Montréal; Annie Lamoussenerie, l’Université de Montréal; Genevieve Huard, CHUM; Mélanie Tremblay, Hepatoneuro lab, Centre de Recherche du Centre Hospitalier de l’Université de Montréal; Chantal Bémeur, l’Université de Montréal; Christopher Rose, Hepatoneuro lab, Centre de Recherche du Centre Hospitalier de l’Université de Montréal; Catherine Vincent, CHUM

BACKGROUND: Malnutrition is an important prognostic factor potentially influencing clinical outcome of patients suffering from chronic liver disease (CLD; cirrhosis) and may increase the risk of developing other complications including hepatic encephalopathy (HE). Malnutrition in cirrhosis may also affect patient’s functional status and health-related quality of life (HRQOL). Management strategies focussing on nutritional status in relation to complications of cirrhosis are an unmet clinical need. We hypothesize that sub-optimal nutritional status in cirrhotic patients decreases HRQOL and increases the risk of developing HE.

PURPOSE: The primary purpose is to evaluate the impact of nutritional status on health-related quality of life in cirrhotic patients. The secondary purpose is to ascertain the presence of hepatic encephalopathy and examine its relationship with nutritional status and HRQOL.

METHOD: Hospitalized and outpatients (CHUM’s Liver Unit, Montreal, Canada) with cirrhosis as well as non-cirrhotic (NC) patients were assessed for 1) Nutritional status (Subjective Global Assessment [SGA]); 2) HRQOL (Short-Form-36 [SF-36] questionnaire); and 3) HE (presence or history).
RESULTS: 50 cirrhotic patients (72% men) of various etiologies, Child-Pugh (15A, 7B, 18C, 10 unknown), mean age 56±12 as well as 18 NC patients (33% men, mean age 42±15) were included. SGA analysis revealed that 34% of cirrhotic patients were malnourished whereas 12% of cirrhotic patients were diagnosed with HE at time of recruitment and 37% had a history of HE. Among malnourished CLD patients, 18% were diagnosed with HE. CLD malnourished patients showed a decreased HRQOL compared to well-nourished CLD patients (p < 0.01). Moreover, HE had an impact on HRQOL as cirrhotic patients with a history of HE episode(s) showed decreased physical functioning (p=0.024) and role limitations due to physical health (p=0.002). Interestingly, when compared to NC patients, CLD patients displayed a lower score in physical functioning (p < 0.0001) and general health (p=0.027).

CONCLUSION: Our data suggest that poor nutritional status does negatively influence HRQOL in cirrhotic patients but is not associated with HE. However, history of HE episode(s) does impact on HRQOL among this population. Therefore, identifying malnourished patients is of great importance and interventions for treating malnutrition remains an unmet clinical need.

REFERENCE

Undergraduate student nurses’ knowledge, attitudes and practices of Hepatitis C: Preliminary analysis of data from a community college in Vancouver, British Columbia

Denise Thomas, Langara School of Nursing; Kim Lam, Langara College

BACKGROUND: The global community has declared an ambitious goal to eradicate Hepatitis C (HCV) by 2030. Janjua et al (2016) identify the great need for British Columbians eligible for treatment to successfully access liver care and treatment for people living with HCV. Allied health care providers have an important role to play. With major changes to the treatment landscape that may not have been translated to the new healthcare force, this study aims to assess HCV knowledge, attitudes and practices among the final term of undergraduate student nurses studying at Langara College in Vancouver, BC prior to entering their clinical preceptorship in two BC health authorities.

PURPOSE: Preliminary findings have been gathered from undergraduate student nurses; to determine the pre-workforce HCV knowledge, attitudes and practice which can inform how this future workforce can participate in the eradication of HCV with the global community.

METHODS: An anonymous mixed methods qualitative study was conducted using self administered survey comprising of 15 questions on HCV knowledge, attitude and practices to the first of two cohorts.

RESULTS: The survey was administered to 66, who attended class for data collection, out of 81 nursing students; a response rate of 98.4% (n=65), 80.2% overall. Preliminary findings revealed that only 21.5% reported knowing where to find information for people living with or affected by HCV.

A significant number of students were unaware of the major routes of transmission; 46.1% (n=30) did not know if HCV is more transmissible than HIV and 30.7% (n=20) did not know if HCV is transmitted vertically.

Regarding practices, 41.5% wanted to wear two (2) pairs of gloves when caring for someone with HCV. Only 52.4% of students knew that an individual can have HCV antibodies without being currently infected with HCV. Fifty-three students (81.5%) were aware that HCV is associated with increased risk of HCC.

CONCLUSION: The overall grasp of HCV knowledge was reasonably fair however gaps need to be addressed especially about where to successfully find information and refer HCV positive people to prevention, care and treatment services.