CANADIAN LIVER MEETING

Feb 28 – Mar 1, 2020
Le Westin
Montréal

Canadian Association for the Study of the Liver
CASL ACEF
Association canadienne pour l'étude du foie

CanHepC
Canadian Network on Hepatitis C
Réseau Canadien sur l'Hépatite C

CAHN
Canadian Association of Hepatology Nurses
Association Canadienne Des Infirmieres D'Hepatologie

The Canadian Liver Meeting is a collaborative effort of the Canadian Association for the Study of the Liver (CASL), the Canadian Network on Hepatitis C (CANHEPC) and the Canadian Association of Hepatology Nurses (CAHN)

9TH CANADIAN SYMPOSIUM ON HCV—FRIDAY, FEBRUARY 28, 2020

SESSION #1: BIOMEDICAL RESEARCH

Differential gene expression of circulating CD8 T cells of cirrhotic HCV-infected individuals identifies pathways associated with lasting dysfunction

The effect of apoptosis and inflammasome-mediated pyroptosis on HCV infection

Identifying the role played by the poly(rC)-binding protein 2 (PCBP2) in the HCV life cycle

Understanding NK and T cell dysfunction in chronic HCV patients with advanced liver fibrosis by immunoprofiling of inhibitory receptors

Precision cut liver slice (PCLS) culture: a model to examine HCV interactions with the liver microenvironment

Hepatitis C virus exploits cyclophilin A to evade PKR- and IRF1-dependent antiviral responses

Neutrophils are the major producers of the pro-fibrogenic cytokine IL-17A in non-alcoholic fatty liver disease (NAFLD)

Quantifying the relative contributions of the three roles of miR-122 in the HCV life cycle

Immune restoration of hepatitis C virus-specific T cells following direct acting antiviral therapy in acute hepatitis C virus–infected patients

The use of oncolytic measles-based vectors for targeted treatment of HCV-induced liver cancer

HCV 3'UTR and the host helicases DDX1 and DDX3X

The role of community-based specialized pharmacies in provincial hepatitis C elimination

SESSION #2: SOCIAL, CULTURAL, ENVIRONMENTAL, AND POPULATION HEALTH RESEARCH

Effect of sustained virologic response and opioid agonist therapy on mortality among people living with chronic hepatitis C

Anticipated timing of elimination of hepatitis C virus in Canada's four most populous provinces

Community and corrections based point-of-care testing into a provincial hepatitis C elimination framework

Integrating community-based recruitment with data linkage to inform and enhance scale-up of HCV treatment among people who inject drugs in Canada: The VCCC study protocol

Increasing hepatitis C screening & new diagnoses in 10 British Columbia provincial correctional centres from 2010–2019

Diversity of detention patterns among people who inject drugs and the associated risk with incident hepatitis C virus (HCV) infection: Implications for hepatitis C prevention

Gender-specific associations between psychological distress and HCV risk behaviours among people who inject drugs in Montreal

Estimation of an individual-level deprivation index for HIV/HCV coinfected persons

Geographic distribution of people living with hepatitis C in British Columbia: An application of latent class analysis and disease mapping

Hepatitis C awareness, screening and linkage to care among the Pakistani community in Montreal: The Aagahi Project

Mapping the Immigrant population and cultural and community organizations to inform community outreach and HCV microelimination efforts in Montreal

Reviewing, appraising, and synthesizing observational data to inform dynamic mathematical modeling of HCV and HIV transmission among people who inject drugs in Montréal, Canada

Potential impacts of closing low-threshold overdose prevention sites on HCV and HIV prevention efforts in Toronto, Canada

Perceptions of HCV treatment and reinfection risk among HIV-positive men who have sex with men in Sydney, Australia: A qualitative study

Toward the elimination of HCV vertical transmission: A targeted, patient-informed hepatitis C engagement program in persons who use drugs in their child bearing years in southern New Brunswick

Peer led point-of-care testing: The role of Atlantic Canada's first overdose prevention site in hepatitis C elimination

Strengthening Canada's hepatitis C response by producing culturally and linguistically relevant resources for Canadian immigrants and their service providers

Estimating direct-acting antiviral impact among key populations in Ontario: A research proposal

The synthesis and integration of hepatitis C clinical practice guidelines to facilitate low threshold access to evidence-based care in the outreach setting

HCV: The neurocognitive impact in the overdose epidemic

SESSION #3: CLINICAL RESEARCH

Efficacy of sofosbuvir/velpatasvir (S/V): impact of treatment adherence

Reinfection following successful direct-acting antiviral therapy for hepatitis C infection among people who inject drugs

Non-invasive surrogates of portal hypertension predict decompensation in obese patients with compensated advanced chronic liver disease

Impact of treatment with tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) on hepatocellular carcinoma (HCC) incidence in patients with chronic hepatitis B (CHB)

Universal HCV and HIV screening in an emergency room – fewer new cases than expected

DAA treatment uptake or outcomes are not effected by alcohol use: A CANUHC analysis

SESSION #4: HEALTH SERVICES RESEARCH

Can we afford to screen and treat hepatitis C virus (HCV) infection in Canada? Latest insight from a Canadian policy model – A province-by-province analysis

HBV-HCV coinfection among immigrants in Ontario, Canada

A review of public reimbursement criteria for pan-genotypic HCV DAAs in Canada

Pilot peer-led hepatitis C screening leads to high testing uptake and rapid treatment initiation in a women's residential recovery facility

Disparities in health utilities among hepatitis C patients receiving care in different settings

Health services impact analysis of simplifying HCV diagnosis and treatment decision in Canada

Hepatitis C (HCV) re-engagement strategy after loss to follow-up

Building capacity in hepatitis C management: progress and outcomes from the ECHO Ontario liver program

Examining patient complexity in ECHO: Results from a hepatitis C telementoring education program

The Canadian network on hepatitis C virtual cascade of care cohort (VCCC) feasibility study – Saskatchewan component

CANADIAN LIVER MEETING—SATURDAY, FEBRUARY 29–SUNDAY, MARCH 1, 2020

SESSION #1: VIRAL HEPATITIS

Achieving functional cure of HBV and HBV / HDV co-infection with REP 2139: Completed follow-up in the REP 401 and REP 301-LTF studies

Micro-elimination of hepatitis C in a population of opioid substitution clients – successful task-shifting of testing and treatment to a community-based nurse/pharmacist dyad

Role of pre- and post-treatment transient elastography measurements in predicting hepatocellular carcinoma (HCC) among hepatitis C patients treated with direct acting antivirals (DAA)

Addition of peginterferon alfa 2a increases HbsAg decline in HbeAg-negative chronic hepatitis B patients treated with long-term nucleos(t)ide analogue therapy: Results from a multicenter randomized controlled trial (PAS study)

Real-world drug resistance profile of hepatitis C patients who failed direct-acting antivirals – SHARED

Hepatitis C–positive organ transplantation to negative recipients at a multiorgan Canadian transplant centre: Ready for prime time

Reducing the burden of hepatitis C-related complications through genomics-guided treatment optimization

Outcomes of hepatitis C treatment are similar in Canadian Indigenous people compared to non-Indigenous patients

Treatment differential in HCV treatment prescribers in British Columbia over time

Characteristics of resistance-associated substitutions in "unusual" hepatitis C virus (HCV) subtypes

Comparison of hepatitis C prenatal screening approaches between provinces: Seroprevalence and infection rates in universal vs risk-based screening

Factors associated with on-demand HCV screening among Canadian provincial inmates

Real world single centre experience on the efficacy of stopping long term nucleos(t)ide analog therapy in patients with chronic hepatitis B (CHB)

Reticulon-3 modulates the loading of replication competent hepatitis C virus molecules for release inside infectious exosomes

Birth cohort screening for hepatitis C during routine outpatient endoscopy

Mechanistic analysis of miR-122 promotion of HCV replication

Identification of patients with compensated cirrhosis who can safely use protease inhibitor-based therapy for HCV infection

Prenatal hepatitis C screening and diagnoses in British Columbia, 2008–2018

Targeting Hepatitis B virus cccDNA in vitro

Exploiting cccDNA's structural features to find new HBV targets

NAFLD and alcohol affect long-term liver fibrosis regression post-HCV eradication

Ethnic differences in HCV-related HCC (HCV-HCC) outcomes: Report from the real-world evidence by the Asia Pacific Rim liver consortium for HCC (REAL-HCC)

Ethnic disparities in the risk of hepatitis C virus-related diabetes in a large population-based cohort in Canada

Natural history of cirrhotic people who use drugs (PWUD) following successful HCV therapy in the direct-acting antiviral (DAA) era

Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir as a hepatitis C virus infection salvage treatment

Current opioid agonist therapy is associated with hepatitis C virus treatment uptake among people who inject drugs in a population-based data linkage study

Syndemic of viral co-infections and incident end-stage renal disease

Genotype misclassification and its impact on treatment choices, outcomes and drug resistance

Association between prescription opioids and hepatitis C virus seroconversion among people who use injection drugs in British Columbia

Evidence for a striking failure in diagnosis and linkage to care for hepatitis C-infected patients in Alberta, Canada

Prescribing trends of direct acting antivirals (DAAs) for the treatment of hepatitis C in Ontario

CD8 T cell dysfunction and cancer development in a murine model of liver fibrosis

Early peg-interferon-related ALT flares of high magnitude lead to HbsAg decline and loss. A study of 639 chronic hepatitis B patients

Population-level hepatitis C cascade of care among men who have sex with men in British Columbia, Canada

Live animal imaging of oncolytic virus infection in non-cancer cells; how this might affect therapeutic outcome

Differential hepatitis B virus (HBV) and hepatitis D virus (HDV) specific T cell response in HDV RNA positive and negative patients

Differences in surveillance for HCC in HIV infected patients with and without HCV/HBV coinfection: Insights from LIVE-HIV cohort

Long-term follow-up of people who use drugs cured of hepatitis C infection: re-infection and re-treatment

Transaminase flares during HbsAg reduction to <1 IU/mL are correlated with the establishment of virologic control and functional cure of HBV following NAP-based combination therapy

Hepatitis C virus reinfection after successful treatment with direct acting antiviral therapy in British Columbia

Glecaprevir/pibrentasvir for the treatment of hepatitis C virus infection among active drug users: The GRAND PLAN study

Overdose events among active drug users successfully treated for HCV: The impact of homelessness

Prevalence and genotype of occult hepatitis B infection in a human immunodeficiency virus (HIV) positive patient cohort in Gondar, Ethiopia

Trends in hepatocellular carcinoma survival among individuals infected with HBV and/or HCV in British Columbia, Canada (2001–2016)

A population-level latent class analysis of people living with hepatitis C virus for effective program planning and health care resource distribution

Sofosbuvir/velpatasvir (S/V) for the treatment of chronic HCV in active drug users: The CHIME study

Clinical evaluation of cholesterolic metabolism on the background of biliary insufficiency in patients with chronic hepatitis C

Who are the real transformational leaders? From peer educators to peer navigators

Transcriptomic analyses of the immune response during HCV re-infection

Association between hepatitis B virus infection and risk of non-alcoholic fatty liver disease: a meta-analytic synthesis of observational studies

MicroRNA-122 promotion of Hepatitis C Virus translation is important early in the HCV infection cycle to initiate an HCV infection

Improved linkage to care by targeting HCV RNA(+) persons in the BC-HCV network

The impact of small RNA binding on hepatitis C virus replication via structural changes within the 5' untranslated region

Can neurological weakness be the first presentation of chronic hepatitis in Immunosuppressed population? Case report and literature review

SESSION #2: GENERAL HEPATOLOGY

Differences in clonal evolution of recurrent hepatocellular carcinoma depending on the immune environment

Women likely to benefit from having a potential living liver donor compared to men

Durable response in the markers of cholestasis through 5 years of open-label extension study of obeticholic acid in primary biliary cholangitis

Preventive effect of celecoxib in sorafenib-related hand-foot syndrome in hepatocellular carcinoma patients, a single-center, open-label, randomized, controlled clinical phase III trial

Noninvasive tests (NITs) may more accurately quantify fibrosis than liver histology in patients with advanced fibrosis due to NASH

Health-related quality of life —A rapid independent predictor of hospitalizations and mortality in cirrhosis

IL-16 as a new marker for the diagnosis of AIH/PBC overlap syndrome

Hypofibrinolysis as a contributing mechanism of cirrhotic portal vein thrombosis as evidenced by rotational thromboelastometry (ROTEM)

"FIB-4 First" strategy in a NAFLD assessment pathway for HIV mono-infected patients

Combined regimen immune checkpoint inhibitor-associated hepatitis: Experience from a North American multicenter cohort

Hemojuvelin deficiency predisposes mice to hepatocellular carcinoma

Simple non-invasive prediction of advanced fibrosis in NAFLD—A stepwise approach and external validation study to reduce indeterminates and biopsy

Impaired hepatic leukocyte recruitment and increased thrombin generation during acute bacterial challenge in a mouse model of non-alcoholic fatty liver disease (NAFLD)

Modelling non-alcoholic fatty liver disease burden in Canada, 2019–2030

Lenvatinib for the first-line treatment of advanced or unresectable hepatocellular carcinoma: A cost-effectiveness analysis from a Canadian perspective

Reducing length of stay in patients following a liver transplant

The role of transferrin receptor 1 (Tfr1) in liver iron sensing and systemic iron homeostasis

A new score including anthropometric measurement for weight Improved prediction of mortality of adolescents on the liver transplantation waiting list: US nationwide study

Performance of noninvasive fibrosis tests among NAFLD patients with normal ALT: Data from a large North American primary care NAFLD pathway

Impact of repeat transient elastography within 3 years on clinical management in chronic liver disease

Evolution of autoimmune cholangitis and primary sclerosing cholangitis in a pediatric cohort

Tolerogenic effect of pregnancy in autoimmune hepatitis

Symptom burden in patients living with primary biliary cholangitis: Indigenous Canadians report significantly higher PBC-40 quality of life scores

Assessment of fibrosis and steatosis in patients and healthy volunteers

The burden of cirrhosis on the Canadian health care system: A comparison between alcoholic and nonalcoholic cirrhosis patients

Impact of depression and antidepressant use on the development of chronic liver disease: a longitudinal UK population-based study

Baseline liver function and outcomes in the phase III REFLECT study in patients with unresectable hepatocellular carcinoma (uHCC) treated with lenvatinib (LEN) vs sorafenib (SOR)

Ultrasound surface and hepatic vein nodularity as predictors of histologic advanced fibrosis in chronic liver disease

Factors associated with vibration controlled transient elastography failure in a high-volume North American liver clinic

Validation of a hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data

Retrovirus footprint in primary sclerosing cholangitis; APOBEC3 family expression

Optimising trial design in late-stage primary biliary cholangitis: evaluating options for composite clinical endpoint studies

Real-world experience with obeticholic acid (OCA) in Canada: A retrospective analysis of primary biliary cholangitis (PBC) patient characteristics and treatment patterns from the Canadian Patient Support Program

Metabolic alterations of human liver tissue occurring during biobanking procedures

Liver transplantation (LT) for hepatocellular carcinoma in Alberta: Patients assessed for LT in Calgary wait longer for listing and have increased mortality compared to those assessed in Edmonton

Serum ferritin is not associated with elevated elastography scores in non-alcoholic fatty liver disease

Test-retest reliability of hepatic venous pressure gradient: A study in 215 patients from the control arms of 17 randomized controlled trials

Preliminary results of the prevalence of fatty liver disease in the Greater Toronto population

FINCh: Fibroscan Impact on Non-alcoholic fatty liver disease in children—using randomized placebo-phase design trial

Outcomes of sarcopenic obesity and metabolic syndrome in liver transplant patients

Hepatic steatosis predicts fibrosis in long-term methotrexate use

Clinical evaluation of portal-hepatic blood flow at a low-invasive treatment of mechanical jaundice

Validation of FIB-4 scores and liver stiffness measurements (LSM) by VCTE as non-invasive modalities for detection of advanced fibrosis in NAFLD patients

Impact of depression and antidepressant usage on the clinical outcomes of chronic liver disease

Post-partum primary biliary cholangitis (PBC) after resolution of intrahepatic cholestasis of pregnancy (ICP) in First Nations patients of BC: A case series

NMR metabolic profiling can help discriminate between normal primary hepatocytes and diverging hepatic cancer cell lines

Vitamin D deficiency and its association with clinical outcomes in primary sclerosing cholangitis

Erythropoietic protoporphyria: An unusual presentation of advanced liver fibrosis during infancy

Histological characterization of muscle and adipose tissue in patients with cirrhosis receiving liver transplant

Role of glutamine in the tumorigenicity of the murine hepatocarcinoma cell line Dt81Hepa1-6

Factors associated with dialysis independence in patients with cirrhosis and acute kidney injury requiring dialysis: a population-based study

FIB4 or NFS can reliably predict fibrosis in sub-groups of NAFLD patients

Prevalence and associated factors of non-alcoholic fatty liver disease in South Asian women with polycystic ovary syndrome: A prospective study using transient elastography

Diabetes is associated with the development of hepatic encephalopathy in cirrhotic patients

Prevalence of liver diseases in referred patients of varying ethnic backgrounds within the Toronto Liver Centre

Characteristics and outcomes of patients with primary sclerosing cholangitis at a Canadian tertiary care center

New insights on the impact of sex on chronic liver disease and hepatic encephalopathy

SESSION #1: BIOMEDICAL RESEARCH

Differential gene expression of circulating CD8 T cells of cirrhotic HCV-infected individuals identifies pathways associated with lasting dysfunction

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BACKGROUND: Immune system cells in the liver are profoundly affected by chronic hepatitis, yet the impact on circulating immune cells is less well understood and may influence long term health. We reported lasting global hyperfunction of circulating CD8 T cells in HCV-infected individuals with cirrhosis. Animal models indicate irreversible CD8 T cell gene expression changes in chronic infection. Whether bulk CD8 T cell gene expression is associated with the severity of liver fibrosis in HCV infection is not known.

PURPOSE: To determine if the gene expression profiles of bulk CD8 T cells from HIV-infected individuals differ on the basis of liver disease severity.

METHODS: RNAseq analysis of blood CD8 T cells from treatment naïve, HCV-infected individuals with minimal (Metavir F0-1 ≤ 7.0 kPa) or cirrhosis (F4 ≥ 12.5 kPa) was performed, as well as after antiviral therapy. Functional and gene set enrichment analyses compared gene expression profiles between groups. Culture of CD8 T cells probed identified pathways in flow cytometry-based immunoassays.

RESULT(S): Principal component analyses determined robust differences in 444 gene expressed by CD8 T cells from HCV$^+$ (F0-1) compared to HCV$^+$ (F4) individuals and suggests this remains relatively stable after viral clearance. Gene ontology analyses identified upregulated phospholipase, phosphatidyl-choline/inositol activity and second-messenger-mediated signaling while nuclear processes, RNA transport and actin nucleation were reduced. Gene Set Enrichment Analysis identified decreased expression of genes regulated by the cMyc and E2f transcription factors in cirrhotics, compared to F0-1, as well as reduced oxidative phosphorylation, mTOR signaling, and more. Up-regulated gene sets in cirrhotics included genes in IFN-α, -g, TGF-β responses, apoptosis and apical surface pathways, among others. The top featured gene set was the hedgehog signaling pathway, wherein hallmark genes Gli1 and Ptch1 ranking highly.

CONCLUSION(S): This is the first analysis of bulk CD8 T cell gene expression profiles in HCV infection in the context of liver fibrosis severity, and suggests cirrhosis significantly reprograms CD8 T cells. Increased Hh Hh signaling in CD8 T cells in cirrhosis is a novel finding and may relate to generalized CD8 T cell hyperfunction in cirrhotic HCV-infected individuals. Understanding the lasting nature of immune cell dysfunction may help mitigate remaining clinical challenges after HCV clearance and more generally, improve long term outcomes for individuals with severe liver disease.

The effect of apoptosis and inflammasome-mediated pyroptosis on HCV infection

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BACKGROUND: It is well-known that non-inflammatory caspase-3-mediated apoptosis contributes to the liver pathology associated with chronic HCV infection. Pyroptosis is an inflammatory form of programmed cell death mediated by caspase-1 that is induced after activation of an inflammasome, ultimately resulting in pore formation and cell lysis. Our lab has found both apoptosis and pyroptosis occurring in Huh-7.5 cells infected with HCV.

PURPOSE: This study aims to identify cellular mechanisms utilized by HCV to induce these forms of cell death and potentially impact disease.

METHODS: A cell culture-adapted strain of HCV JFH-1 ($JFH1_T$) was cultured in Huh-7.5 cells and virus infection and cell death was monitored. To test for the involvement of various cell death pathway components, CRISPR-Cas9 knockout cell lines were generated lacking either caspase-3, NLRP3 or gasdermin-D (GSDM-D). FAM-FLICA probes or antibodies were used to visualize active caspase-1 and caspase-3, and HCV core protein. Virus titers were measured by limiting dilution focus-forming assays. Virus-induced cell death was analyzed by Western blotting, flow cytometry and confocal microscopy.

RESULT(S): We observed decreased HCV titer in CRISPR knockout cells when compared to wild-type Huh-7.5 cells. Increased levels of active caspase-1 were consistently observed in infected cells compared to uninfected cells and these levels increased with subsequent days post-infection (p.i.). Caspase-1 activation was first observed on day two p.i., whereas activation of apoptosis began on day three. NLRP3 and GSDM-D knockout cell lines showed differential activation of caspase-1 and caspase-3, displaying a trend towards higher levels of activated caspase-3, indicative of apoptosis. Inhibition of NLRP3 resulted in a substantial but not complete omission of caspase-1 activation. Flow cytometry results revealed a small subset of cells positive for both caspase-1 and caspase-3, apparently undergoing pyroptosis and apoptosis simultaneously.

CONCLUSION(S): These data confirm the occurrence of pyroptosis earlier than apoptosis during the progression of virus infection. The results demonstrate involvement of the NLRP3 inflammasome, although other inflammasome sensors may be involved in pyroptosis induction. Since inhibition of one cell death pathway resulted in increased activation of the other, along with the presence of double-positive cells, there may be cross-talk between apoptotic and pyroptotic pathways. The impact of cell death inhibition on virus titer indicates that cell death promotes HCV replication, likely through enhancement of viral spread. These findings will aid in understanding the mechanisms surrounding inflammation and liver pathology associated with chronic HCV infection.

Identifying the role played by the poly(rC)-binding protein 2 (PCBP2) in the HCV life cycle

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BACKGROUND: 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. One particular cellular RNA-binding protein, the poly(rC)-binding protein 2 (PCBP2), is known to mediate the stability and expression of a number of cellular transcripts and is 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 the 5′ and 3′ untranslated regions, which are known to play important roles in viral translation and replication. However, the exact mechanism(s) by which PCBP2 affects HCV replication still remain to be elucidated.

PURPOSE: We aimed to identify the specific step(s) of the viral life cycle affected by PCBP2.

METHODS: We used the HCV cell culture system to assess how viral protein expression, viral RNA accumulation, and the production of infectious viral particles is affected by siRNA-mediated knockdown of PCBP2. To examine PCBP2's effects on specific steps of the viral life cycle, we carried out luciferase reporter assays for viral entry, translation, genome stability and RNA replication. Viral entry was assessed using the HCV pseudoparticle (HCVpp) system. Viral translation and genome stability were assessed using a RNA replication-deficient luciferase reporter virus (full-length J6/JFH-Renilla-GNN). RNA replication was assessed using packaging-deficient luciferase reporter viruses (full-length J6/JFH-Δcore-p7-Renilla and J6/JFH-ΔE1-p7-Renilla).

RESULT(S): Knockdown of PCBP2 leads to ~2-fold reductions in HCV protein expression, RNA accumulation, and infectious particle production. Using the HCVpp system, we ruled out a role for PCBP2 in HCV entry. Using a RNA replication-deficient

luciferase reporter virus, we found that PCBP2 knockdown did not alter viral translation nor the rate of viral genome decay. When we assessed RNA replication using a subgenomic replicon, which allows replication but not packaging, we found that PCBP2 knockdown only lead to a reduction in luciferase activity when we used constructs that contained the HCV core gene. Specifically, the ΔE1-p7 construct displayed impaired viral RNA accumulation, while the Δcore-p7 construct was unaffected by PCBP2 knockdown. Assessment of intracellular and extracellular infectivity revealed that PCBP2 knockdown decreased both viral titers, suggesting that it affects a step of the viral life cycle preceding infectious particle packaging.

CONCLUSION(S): PCBP2 knockdown disrupts the HCV life cycle in Huh-7.5 cells. While the exact mechanism of PCBP2-mediated regulation is unclear, we have found that it does not promote viral entry, translation, genome stability or egress - but, that it is necessary for optimal RNA accumulation of viral constructs that contain the core gene. We anticipate that further clarifying this PCBP2-HCV interaction will provide a model for the PCBP2-mediated regulation of viral RNA accumulation.

Understanding NK and T cell dysfunction in chronic HCV patients with advanced liver fibrosis by immunoprofiling of inhibitory receptors

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BACKGROUND: Liver fibrosis is the buildup of scar tissue in the liver due to sustained insults. One of the major causes of liver fibrosis is chronic infection with HCV, which promotes inflammation leading to the release of TGFβ. This activates hepatic stellate cells that produce and deposit collagen, and continual scar tissue buildup causes chronic HCV patients to progress along fibrosis stages from no fibrosis to cirrhosis. Immune cells, specifically NK and T cells are crucial for the antiviral and tumor response in hosts and dysfunction of these cells contributes to their susceptibility to chronic infections and cancer. Increased surface expression of inhibitory receptors is a pronounced phenotype of immune cell dysfunction, and recently, a study showed that the surface expression of Galectin-9 (Gal-9), a ligand for Tim-3, modulates the function of NK cells.

PURPOSE: As liver fibrosis progresses to advanced fibrosis and cirrhosis, patients experience increased susceptibility to infection, poor response to vaccination as well as increased susceptibility to HCC. There is, therefore, a need to characterize the level of immunosuppression in these patients to create targeted therapies to improve their immune function.

METHODS: We divided 30 chronic HCV patients into 2 groups based on their fibrosis score. Stages F0-F2 were group 1 (n = 15) and F3-F4 group 2 (n = 15). Using flow cytometry analysis, we measured the surface expression of inhibitory receptors (PD-1, CTLA-4, Lag-3, TIGIT, and Tim-3) as well as Gal-9 on $CD8^+$ and $CD4^+$ T cells; $CD56^{Bright}CD16^-$ NK cells (immature NK cells) as well as $CD56^{Dim}CD16^+$ NK cells (mature NK cells). T-Distributed Stochastic Neighbor Embedding (t-SNE) analysis was used to dimensionally reduce flow data to analyze co-expression of multiple inhibitory receptors on immune cells.

RESULT(S): Group 2 patients had increased PD-1 expression on their mature NK cells; decreased CTLA-4 expression on T cells but increased expression on mature NK cells; increased Lag-3 expression on NK cells; increased TIGIT expression on CD4 T cells; increased Tim-3 expression on immature NK cells and increased Gal-9 expression on T cells and NK cells. Group 2 patients also had an increased frequency of $CD25^+$ cells, a regulatory T cell subset, among the $CD4^+$ T cells. Upon t-SNE analysis, T and NK cells showed a subset with high co-expression of Gal-9 and Lag-3, and this subset also had low or no Tim-3 expression and high expression of PD-1.

CONCLUSION(S): Chronic HCV patients in advanced fibrosis and cirrhosis have higher expression of inhibitory receptors when compared to patients with lesser fibrosis. They also have an increase in the frequency of immune cells with high

co-expression of Gal-9 and Lag-3. Taken together, my results would provide an insight into developing biomarkers for the dysregulation of immune cells, and treatments to reverse the immune suppression.

Precision-cut liver slice (PCLS) culture: a model to examine HCV interactions with the liver microenvironment

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BACKGROUND: Hepatitis C Virus (HCV) infects 71 million individuals worldwide and is one of the leading causes for hepatocellular cancer, end-stage liver disease and liver transplantation. While direct acting antivirals (DAA) therapies have revolutionized the way we treat HCV infection, they are unable to protect against HCV reinfection. The development of a model able to recapitulate the complex liver microenvironment, including cell-to-cell interactions and to preserve hepatocyte polarity, coupled with standard-of-art technologies will allow us to thoroughly understand the key immunological players associated with HCV infection and clearance and direct the design and testing of preventive and therapeutic strategies against HCV.

PURPOSE: We propose to 1) develop and validate a Precision-Cut liver slice (PCLS) culture system as a way to characterize HCV interactions with the human liver tissue, and 2) test the effects of nanoparticles (NPs) on the hepatic microenvironment and responses against HCV. Resident macrophages are key determinants of the liver microenvironment. We hypothesize that reprogramming or deleting hepatic immunoregulatory macrophages can help promote host anti-HCV immunity.

METHODS: Liver cores of 6 mm diameter are obtained from the caudate lobe excised from healthy livers during the liver transplant (LT) procedure and prepared for automatic slicing using a vibrating microtome under sterile conditions. Tissue culture conditions are being optimized based on specific liver cells' requirements. Specialized parenchymal and non-parenchymal cells, including immune cells, are closely monitored with regards to their viability and function, spatial positioning, cell-to-cell interactions, and frequency using liver function, flow cytometric and immunohistochemistry assays. Liver slices cultured in the optimal condition will be examined by single cell RNA-sequencing and compared to the healthy liver with regards to key immune populations and pathways.

RESULT(S): Preliminary data shows the presence of viable macrophages, T cells and hepatocytes up to day 7 of culture—an improvement to the 4-day period usually reported for this model. We are working to optimize media exchange, to reduce accumulation of toxic metabolites, and to provide biological factors required by different liver cell populations all aimed at mimicking in vivo conditions. Next, we will expose PCLS culture to HCV and monitor both HCV replication in hepatocytes and phenotypic changes in tissue cellular landscape. We will examine links between the level of HCV replication and the degree of cellular dysfunction, using our established flow cytometry phenotyping protocols. By targeting macrophages with previously identified NPs, we expect to favor a pro-inflammatory phenotype able to boost host immunity and reduce HCV replication.

CONCLUSION(S): By successfully creating an ex vivo platform for the study of liver tissue we will be able to characterize HCV interactions with the hepatic microenvironment and guide the design of interventions aimed at eliciting protective HCV-specific immune responses.

Hepatitis C virus exploits cyclophilin A to evade PKR- and IRF1-dependent antiviral responses

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BACKGROUND: Counteracting innate immunity is essential for successful viral replication. The cyclophilin (Cyp) family of proteins have been implicated in the regulation of viral innate immune evasion and innate immune signalling. In the case of hepatitis C virus (HCV), clinical trials demonstrated that pharmacological inhibition of CypA suppressed HCV replication and increased expression of type I interferon (IFN) in patients, although the mechanisms underlying the latter are still unclear. CypA binds to the HCV NS5A protein, which contributes to HCV innate immune evasion by several key mechanisms, including formation of the protective viral replication organelle (RO)and inhibition of the antiviral effector protein kinase R (PKR).We hypothesized that CypA regulates NS5A-mediated viral immune evasion.

PURPOSE: We sought to characterize the mechanisms through which CypA contributes to HCV immune evasion, focusing on NS5A-mediated evasion strategies.

METHODS: We synthesized a diverse panel of novel Cyp inhibitors (CypI) and used them alongside CRISPR/RNAi genetics approaches to probe the role of innate immune signaling pathways. We treated HCV-replicating or HCV-infected human hepatoma cells with CypI. We evaluated viral replication by luciferase reporter activity, and expression of IFN-β and other antiviral genes by qPCR.

RESULT(S): Using electron microscopy, we showed that CypI disrupt formation of the HCV RO. Interestingly, CypI were ~10-fold more potent in innate immune competent Huh7 cells than in RIG-I-deficient Huh7.5 cells, which corresponded to an induction in IFN-β expression observed only in Huh7 cells. Furthermore, silencing CypA expression abrogated HCV replication in Huh7 cells, but had only a minor effect in Huh7.5 cells. We hypothesized that disruption of RO formation by CypI exposes replicating viral RNA to cytoplasmic sensors such as RIG-I, thus triggering classical RNA sensing pathways. However, CypI were equally potent and still led to induction of IFN-β in MAVS knockout Huh7 cells, suggesting that the RIG-like receptor/MAVS signaling pathway is not involved in CypA-mediated innate immune evasion. Rather, the phenotype was dependent on PKR. Pharmacological inhibition of CypA triggered PKR-dependent IRF1 antiviral responses, leading to expression of IFN-β and other IRF1-dependent antiviral genes. Notably, IRF1 was recently shown to drive intrinsic hepatocyte resistance to RNA viruses.

CONCLUSION(S): HCV co-opts CypA to evade PKR and IRF1-dependent antiviral responses that would otherwise restrict viral replication in hepatocytes. CypA inhibition counteracts this evasion strategy, leading to restoration of cell intrinsic antiviral responses that suppress virus replication. Our findings advance understanding of CypA-virus interactions in hepatocytes, and open perspectives for the development of novel CypA-targeted therapies that engage cell intrinsic antiviral responses to combat infection.

Neutrophils are the major producers of the pro-fibrogenic cytokine IL-17A in non-alcoholic fatty liver disease (NAFLD)

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BACKGROUND: Due to the rise in obesity among adults, NAFLD-related liver fibrosis has become a major health challenge with a complex pathogenesis and limited therapies. Liver fibrosis occurs via the production of collagen by activated hepatic stellate cells (HSC) in response to persistent tissue damage and inflammation. This response can be modulated by pro-inflammatory cytokines such as IL-17A that is produced by intrahepatic leucocytes (IHL) and hence can influence liver fibrosis progression (Frideman S.L. et al. 2015). We have demonstrated that IL-17A promotes fibrosis by sensitizing HSCs to the suboptimal doses of TGF-β via increasing cell surface expression of TGF-β-RII (Fabre T. et al. 2014). Furthermore, IL-17A producing cells, primarily neutrophils, were enriched in

livers with advanced fibrosis (F3-F4) irrespective of the aetiology. This finding was validated *in vivo* in CCl_4 model of chronic liver injury (Fabre T. et al. 2018). In this study, we wanted to extend our findings to a more physiological model such as NAFLD.

PURPOSE: We hypothesize that IL-17A producing cells enhance NAFLD-related fibrosis. Our main goal is to define the cellular sources of IL-17A implicated in this process.

METHODS: We employed a mouse model of NAFLD using male and female C57BL/6N mice (age 6–8 weeks) fed high fat diet (HFD, 40% Kcal fat+ 40% Kcal carbohydrate (including fructose) +2%cholesterol)) vs chow diet (18%Kcal fat+ 24% Kcal protein) for 15 or 30 weeks (Wk). IL-17A+ cells were characterized in liver tissue sections using immunofluorescence (IF). Visiopharm software was used for IF image analysis and quantification. H&E and Sirius red staining were used to evaluate liver inflammation, steatosis and fibrosis, respectively. NAFLD activity score (NAS) and fibrosis stage were blindly evaluated by an expert pathologist. Characterization of IHL in human NAFLD biopsies is currently in progress.

RESULT(S): HFD mice had mean NAS score of 3.778 at 15 wk that increased to 4.273 at wk 30. This was accompanied by an increase in NAFLD-related fibrosis (fibrosis stage and/or sirius red +ve area quantification) and increased infiltration of IL-17A+ IHL. Neutrophils were the major IL-17A producers and the density of IL-17A producing neutrophils correlated with both fibrosis stage and NAS score at 30 Wk ($r = 0.8032$ and 0.8611, $P < 0.0001$, respectively).

CONCLUSION(S): Our data suggest an active role for IL-17A+ neutrophils in pathology of NAFLD and fibrosis progression in NAFLD.

Quantifying the relative contributions of the three roles of miR-122 in the HCV life cycle

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BACKGROUND: The liver-specific microRNA, miR-122, is an essential host factor for optimal replication of HCV and its contribution to the viral life cycle depends on its binding to two sites in the 5′ UTR of the viral genome: Site 1 (S1) and Site 2 (S2). Three functions are attributed to miR-122 in the context of HCV infection: 1) stabilization of the viral genome by protecting it from pyrophosphatase activity and subsequent exoribonuclease-mediated decay, 2) riboswitch activity to promote formation of the functional IRES structure, and 3) promotion of translation mediated by Site 2-bound Argonaute (Ago)-IRES interactions. Notably, recent studies have revealed several resistance associated variants (RAVs) of HCV that are able to accumulate in the absence of miR-122. Notably, one of these, the G28A RAV, allows formation of the functional IRES even in the absence of miR-122.

PURPOSE: We hypothesize that the three roles miR-122 plays in the HCV life cycle have different relative contributions to the overall impact of the microRNA on the viral life cycle. We plan to quantify the relative contributions of these three functions in the HCV life cycle using viral RAVs and luciferase reporter assays.

METHOD: To study riboswitch activity and translation promotion function of miR-122, we generated Renilla luciferase (RLuc) reporters whose translation is directed by the HCV IRES, including those with the complete 5′ UTR of WT and G28A, as well as reporters that contain S2 only (begins at nt 28, which does not contain stem-loop I or the first miR-122 binding Site). The reporters contain a S2:p3 (C41A) mutation which ablates WT miR-122 binding, but allows binding of exogenously provided complementary miR-122p3U molecules. This allows us to study miR-122 binding at either site independently by exogenous addition of wild-type and/or miR-122p3U in miR-122 knockout Huh-7.5 cells. We are using luciferase assay and ribonucleotide protection assay (RPA) to quantify the riboswitch and translational promotion activities of miR-122 using this system. We will also measure the RNA stability effect using this system.

RESULT(S): Our preliminary results suggest that the G28A mutant, which is precited to be 'riboswitched' has a 1.2-fold increase in luciferase activity over the WT HCV-RLuc reporter. Moreover, when both the WT and G28A reporters are

complemented with miR-122p3U, they have enhanced luciferase activity (1.7-fold for WT and 1.5-fold for G28A) suggesting an enhancement of translation.

CONCLUSION(S): Thus far, we have established a reporter assay system to quantify the relative contributions of each of the miR-122 activities to the viral life cycle. Our preliminary data suggests a similar magnitude of the riboswitch and translational enhancement activities; however, this will need to be verified by RPA. We anticipate that this study will help to reveal the importance of each of miR-122's roles in the HCV life cycle and provide novel insight into this unique mechanism of RNA regulation that may be applicable to other human and veterinary pathogens as well as cellular RNAs.

Immune restoration of hepatitis C virus-specific T cells following direct acting antiviral therapy in acute hepatitis C virus–infected patients

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BACKGROUND: Chronic hepatitis C virus (HCV) infection is defined by an exhausted immune phenotype. Exhaustion develops in a step-wise and progressive manner, varies in severity, and results in ineffective HCV-specific antiviral T cell responses. Previous data demonstrate that cure of chronic infection with direct-acting antivirals (DAA) leads to partial reversal of T cell exhaustion in some patients. We hypothesize that treatment of acute infection with DAA will further improve immune restoration, leading to responses similar to those seen with spontaneous HCV clearance, which may increase protection against reinfection.

PURPOSE: Characterize the HCV-specific immune response before, during and after treatment of acute infection with both interferon (IFN) and DAA regimens and compare to responses after treatment of chronic infection and spontaneous clearance of HCV infection.

METHODS: We assessed the impact of DAA and IFN-based therapies on HCV-specific T cell responses in peripheral blood during treatment of acute HCV infection using enzyme-linked immunospot (ELISPOT) and flow cytometry. We evaluated the strength and breadth of T cell responses to overlapping HCV peptides using ELISPOT to quantify IFNγ cytokine secretion by HCV-specific T cells. Responses were compared at baseline to those at Sustained Virologic Response (SVR) and between treatment type (IFN vs DAA). Evolution of responses after the course of therapy and follow-up are compared to individuals treated during chronic HCV infection and responses in individuals who spontaneously cleared HCV infection without treatment.

RESULT(S): Broad and strong HCV-specific responses were seen in spontaneous clearers (n = 13). To date, ELISPOT data are available for 7 patients treated with DAAs during chronic HCV infection, 11 treated with DAAs during acute infection and 12 treated with IFN-based therapy during acute infection. Some general emerging patterns are a more common increase in breadth and strength of HCV-specific immune responses from baselines to SVR when DAAs were administered during acute infection compared to treatment during chronic infection or with IFN-based regimens.

CONCLUSION(S): DAA therapy administered during acute infection may improve immune restoration compared to IFN treatment administered during acute infection and DAA therapy after the establishment of chronic HCV infection. Flow data describing the frequency and phenotype of HCV-specific T cells as well as clinical correlates will also be presented.

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, HCV clearance does not necessarily prevent the occurrence of hepatocellular carcinoma (HCC), especially in those who have developed liver cirrhosis, and therapeutic options for HCC 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 epithelial-derived malignancies 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 in 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.

METHODS: 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 are validated in the HCC cell lines and their derivatives containing HCV subgenomic RNA. The role 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.

RESULT(S): Oncomine online dataset analysis reveals that nectin-4 is upregulated in HCC specimens, including those with HCV infection, compared to normal liver tissue. Preliminary results indicate that several HCC cell lines express nectin-4 and are susceptible to oncolytic MV infection. Additionally, hepatoma cells harboring replicating HCV subgenomes exhibit better MV infectivity and spread compared to the HCV-negative parental cells.

CONCLUSION(S): We have shown that nectin-4 is upregulated in 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 influence on the infectivity of the 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.

HCV 3'UTR and the host helicases DDX1 and DDX3X

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BACKGROUND: Hepatitis C virus (HCV) chronically infects approximately 71 million people worldwide, including >240,000 Canadians, all of whom are at increased risk of developing hepatocellular carcinoma. While great progress has been made in direct-acting-antiviral therapies, many questions remain regarding the interaction of this virus with the host's cellular proteins and their link with liver pathology and oncogenesis.

Upon cellular invasion, host proteins, including the host helicases, DDX1 and DDX3X, are recruited for viral propagation. DDX1 is strongly implicated in aiding replication in many viruses including HIV. DDX3X has been shown to be essential for HCV viral replication and is linked to HCV-associated hepatic steatosis through influences on lipid metabolism pathways. Interestingly, all of these processes are mediated by host protein interaction with the 3'-UTR of HCV. Furthermore, elevated levels of DDX1 and DDX3 are associated with oncogenesis highlighting these host proteins as important targets.

PURPOSE: Through the rigorous study of the key host protein interactions with HCV 3′-UTR RNA, the precise structural features necessary for this interaction will be determined, that will enable downstream inhibitor development and pathogenesis studies.

METHOD: We designed triple-host (expressible in *E. coli*, HEK293 or sf9 cells) cDNA constructs of DDX1 and DDX3X that can express full-length protein and individual domains. Protein products were purified through affinity and size-exclusion chromatography. The HCV 3′-UTR was cloned in segments—the full length, X-region and variable+X region fragments and produced using *in vitro* transcription. Electrophoretic mobility shift assays and microscale thermophoresis were employed to study interactions between DDX1 and DDX3X and the 3′-UTR of HCV RNA to identify which domains are responsible for mediating the interaction. As well, small-angle X-ray scattering will be performed on the individual fragments and the interacting partners to inform solution structure models.

RESULT(S): Ten cDNA constructs were designed for expression and purification of each of DDX1 and DDX3X proteins. In vitro transcription protocols have been optimized for purification of HCV RNA fragments. We show data on low-resolution structures of HCV RNA and are collecting that on DDX1- and DDX3X-HCV RNA. We will also evaluate binding affinities between RNA and protein using various biochemical assays.

CONCLUSION(S): A detailed structural assessment of the DDX1- and DDX3X-HCV-3′-UTR interaction will improve our understanding of HCV replication and HCV-associated liver pathogenesis and possibly aide the development of inhibitors to selectively disrupt these pathologic processes.

The role of community-based specialized pharmacies in provincial hepatitis C elimination

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BACKGROUND: Hepatitis C virus (HCV) elimination requires contemporaneous scale-up of both diagnostics and therapeutics, including approaches to facilitate adherence and treatment completion in challenging to reach populations. Specialized pharmacies can extend traditional pharmacy services to include: drug approval; medication delivery to home/designated address (for underhoused); on-demand side effect and safety phone consultations for both HCV care providers and patients. A collaborative approach with specialized pharmacies augmenting adherence may be beneficial, however there is little data.

PURPOSE: Assess the impact of task shifting medication related interactions to specialty pharmacies on overall patient engagement and HCV cure.

METHOD: A publicly funded provincial HCV elimination approach was developed in Nova Scotia, Canada. Two specialized pharmacies provided community care, including real-time reports on patient interactions over 17 months for those prescribed hepatitis C treatment. If there was clinical suspicion of adherence difficulty, a specialized pharmacy prospectively called patients, and recorded all patient contacts. Patients were encouraged to contact the pharmacy for medication or other HCV provincial program related inquiries. Reports document call source, as well as reason for the call. We conducted a thematic analysis of these data, including six major themes emerged related to: number of patient and pharmacy initiated calls; number of calls associated with side effects; drug-drug interactions; medication delivery; follow-up engagement (e.g. treatment initiation, adherence, bloodwork) and; other (e.g. HCV transmission inquiries).

RESULT(S): 68 calls for 37 patients were reported by two specialized pharmacies in the province over 17 months. 26/68 (38.2%) were patient generated (PtG) calls and 42/68 (61.8%) were pharmacy generated (PhG) calls. 15/68 (22.1%) were HCV treatment side effect inquires (10 PtG, 5 PhG).7/68 (10.3%) were for drug-drug interactions (3 PtG, 4 PhG). 20/68 (29.4%) were related to medication

delivery (6 PtG, 14 PhG). 23/68 (33.8%) were related to follow-up engagement (5 PtG, 18 PhG). Lastly, 3/68 (4.4%) were related to other issues (2 PtG, 1 PhG). In those without a fixed address or changing contact information (3 individuals) there were 5 calls (2PtG, 3 PhG). There were 6 individuals in the specialty pharmacy group who have not reached end of treatment.

CONCLUSION(S): These data highlight the safety and effectiveness of task-shifting on-treatment adherence (calls and patient-centered medication delivery) to specialized community based pharmacies. This model may be an important tool to augment the core HCV care team in difficult to reach populations.

SESSION #2: SOCIAL, CULTURAL, ENVIRONMENTAL AND POPULATION HEALTH RESEARCH

Effect of sustained virologic response and opioid agonist therapy on mortality among people living with chronic hepatitis C

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BACKGROUND: People living with hepatitis C virus (HCV) infection often have co-occurring substance use which increases their reinfection risk after treatment-based cures, and elevates their risk of dying. Sustained virologic response (SVR) following HCV treatment has been shown to reduce mortality, liver cancer and other complications; opioid agonist therapy (OAT) also reduces opioid related mortality. However, their individual and combined effects have not been assessed.

PURPOSE: To evaluate the combined effect of SVR and OAT on liver-related, drug-related and all-cause mortality.

METHODS: We used data from the British Columbia Hepatitis Testers Cohort (BC HTC), a dynamic cohort consisting of approximately 1.7 million individuals tested for HCV or HIV, or reported as a case of HBV, HCV, or HIV at the British Columbia Centre for Disease Control, linked to administrative health care and mortality data. The study population included all HCV positive individuals in the BC HTC from January 1, 1990 to June 30, 2017. SVR and OAT were the main exposures of interest and were categorized as: 1) No SVR and off OAT; 2) On OAT only; 3) SVR only; 4) SVR and on OAT. The outcomes of interest were time to all cause, drug and liver-related death, as noted in the BC Vital Statistics registry until December 31, 2018. Cox proportional hazards models with time updated OAT exposure were used to estimate the independent and combined effects of SVR and OAT on liver-related, drug-related and all-cause mortality, adjusting for sex, urbanicity, ethnicity, birth cohort, HCV genotype, alcohol misuse, cirrhosis, material and social deprivation, injection drug use, major mental illness, chronic kidney disease, hypertension, HIV coinfection and other comorbidities.

RESULT(S): Of 72,268 HCV-positive individuals who met inclusion criteria, 19,335 (26.8%) were treated with either interferon or direct acting antivirals, 7,767 (10.8%) were on OAT at some point, and 64,501 (89.1%) never received OAT. Of those who received HCV treatment, 14,396 (74.5%) achieved SVR, 2,014(10.4%) did not achieve SVR and 2,925(15.13%) were unknown/missing. In the multivariable model, *SVR only* was associated with a 92.7% reduction in liver-related mortality risk compared to the *no SVR and off OAT* group (aHR = 0.07, 95% CI: 0.06, 0.09). However, *SVR and on OAT* was associated with 98% reduced liver-related mortality compared to the *no SVR and off OAT* group (aHR: 0.02, 95% CI: 0.01, 0.04). Similarly, *SVR only* was associated with 72.3% reduced drug-related mortality compared to the *no SVR and off OAT* group (aHR = 0.28, 95% CI: 0.21, 0.37), *SVR and on OAT* was associated with 83.8% reduced

drug-related mortality compared to the *no SVR and off OAT* group (aHR: 0.16, 95% CI: 0.10, 0.27). *SVR only* was associated with 86.0% reduced all-cause mortality compared to the *no SVR and off OAT* group (aHR = 0.14, 95% CI: 0.12, 0.15), *SVR and on OAT* was associated with 94% reduced all-cause mortality compared to *no SVR and off OAT* group (aHR: 0.06, 95% CI: 0.04, 0.08).

CONCLUSION(S): Harm reduction interventions such as OAT, in addition to cure from HCV treatment, would be necessary to improve overall survival among individuals with substance use disorder and HCV infection.

Anticipated timing of elimination of hepatitis C virus in Canada's four most populous provinces

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BACKGROUND: While direct-acting antiviral therapy for hepatitis C virus (HCV) infection has made HCV elimination an attainable goal, current diagnosis and treatment levels in many high-income countries are insufficient to reach World Health Organization's (WHO) 2030 elimination targets.

PURPOSE: This study examines timing of HCV elimination in Canada's four most populous provinces which account for 86% of total population.

METHODS: A previously published model of HCV progression was populated with reported data for Alberta (AB), British Columbia (BC), Ontario (ON), and Quebec (QC). For British Columbia, chronic prevalence and diagnosis data from 2018, and average annual treatments over 2015–2018 were used. For Alberta, Ontario, and Quebec, prevalence and diagnosis data from 2007 and 2011, respectively, and peak number of treatments in Canada, prorated for each province, were used. As base case, diagnosis (from 2017) and treatment levels were assumed constant, optimistically, to determine year of achieving WHO's 2030 HCV elimination targets for reduction in incidence (80%) and mortality (65%), and diagnosis (90%) and treatment (80%) coverage. The impact of 5% and 10% annual reductions in diagnoses and treatments were explored as less optimistic scenarios. The minimum annual reduction in diagnoses and treatments for delaying HCV elimination beyond 2050 was also calculated.

RESULT(S): Under base case, British Columbia would reach WHO's HCV elimination targets by 2028, Ontario by 2030, Alberta by 2031 and Quebec by 2035. At 5% annual reduction in diagnoses and treatments, British Columbia would be on track to eliminate by 2030, Alberta and Ontario by 2040, and Quebec by 2050; at a 10% reduction, only British Columbia and Ontario would eliminate by 2050. At 14% annual reduction in diagnoses and treatments, no province would eliminate HCV by 2050 (Table).

CONCLUSION(S): Assuming that the current levels of diagnosis and treatment are maintained, only British Columbia and Ontario are on track towards WHO's 2030 HCV elimination targets among Canada's four most populous provinces. With many of the currently diagnosed individuals already being treated, increasing and maintaining diagnosis

Table: Progress towards HCV elimination targets

Province	Anticipated year of HCV elimination			Annual treatments needed over 2020–2030 for HCV elimination by 2030
	Base case (0% reduction)	5% reduction*	10% reduction*	
Alberta	2031	2035	–	1,300
British Columbia	2028	2030	2033	3,900
Ontario	2030	2033	2044	5,300
Quebec	2035	2043	–	2,100

** Reduction in HCV screening and treatment*
– No HCV elimination before 2050

levels is critical for achieving the treatment levels that would make timely HCV elimination a reality in Canada.

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Community and corrections based point-of-care testing into a provincial hepatitis C elimination framework

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BACKGROUND: Hepatitis C virus (HCV) elimination requires novel approaches to care for vulnerable people. Best practices remain unclear, and further pragmatic implementation research is required. Embedding HCV point-of-care (POC) testing into both community and correctional settings has the potential to improve diagnosis, decrease spread of infection, and rapidly engage people in care.

PURPOSE: We assessed the development of implementing community and correctional-based HCV POC testing pathways for a provincial hepatitis C elimination program.

METHODS: A multi-disciplinary team of experts across Nova Scotia, Canada informed community and correctional-based HCV POC testing framework development and implementation. The expert team included physicians, healthcare providers, laboratory medicine managers, community-based harm reduction directors, health researchers, public health officers, correctional facility health teams, and patient advisors. A hybrid effectiveness-implementation type I mixed methods study design prospectively evaluated implementation of HCV POC testing in a provincial HCV elimination program. Barriers, facilitators, and strategies for embedding the community were recorded. Four community sites implemented HCV POC testing and provided feedback. These data were reviewed, analyzed for themes, and integrated pragmatically in the implementation framework. Future work will be focused on embedding and assessing these measures within the correctional population.

RESULT(S): The HCV POC testing implementation framework was developed. Major themes included simplified diagnostic algorithms, increased patient engagement processes, and HCV care capacity building in the community. Framework implementation evaluation was conducted at four community sites with 163 HCV POC tests. 58/163 (35.6%) were antibody positive. 28/58 (48.3%) had a positive viral load and were immediately engaged in care, 9 of whom were previously disengaged in care and 19 were new HCV infections. 12/58 (20.7%) did not have a detectable HCV viral load. 18/58 (31.0%) were lost to follow up at the time of submission.

CONCLUSION(S): Multi-disciplinary collaboration across front-line workers, laboratory medicine staff, public health, corrections staff, and community partners is fundamental for effective design of HCV POC testing. Community and corrections embedded research with pragmatic and iterative designs is critical to developing complex models for provincial HCV elimination. These data support ongoing efforts to scale-up provincial HCV elimination implementation and evaluation efforts, and highlight the need for cross-discipline and lived experience voices for successful program buy-in and implementation.

Integrating community-based recruitment with data linkage to inform and enhance scale-up of HCV treatment among people who inject drugs in Canada: The VCCC study protocol

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BACKGROUND: People who inject drugs (PWID) are the principal group at risk of hepatitis C virus (HCV) infection in Canada and bear a disproportionate amount of the HCV disease burden.Highly effective direct-acting antiviral therapies have been available in Canada since 2014, with many provincial health plans expanding coverage in 2018. Rapid scale-up among PWID is essential to Canada's commitment to eliminate HCV by 2030, but uptake remains low. Challenges include the need to adapt strategies to a geographically and socially diverse group of individuals.

PURPOSE: The Virtual Cascade of Care Cohort (VCCC) study is a CIHR-funded pan-Canadian observational cohort study that seeks to improve understanding of how diverse groups of PWID achieve HCV treatment and cure, with the overall goal of informing treatment scale-up. Specific aims are to:

1. Document the HCV cascade of care in diverse Canadian settings and understudied subpopulations, namely female and Indigenous PWID, and examine its evolution between periods following (i) introduction of DAA therapies (2014–18) and (ii) coverage changes (2018–22).
2. Characterise use of broader health, social, and community services in these populations.
3. Identify stable and modifiable determinants of progress through the HCV cascade of care, applying a conceptual framework developed in the pilot phase.

METHODS: VCCC employs a hybrid methodology combining in-person data collection with 'virtual' follow-up via data linkage. The target population includes adults who have ever injected drugs and are at risk of unmet health care needs, as defined by illicit drug or hazardous alcohol use in the past six months. Recruitment will take place in community-based harm reduction or addiction service sites in BC, SK, ON, QC, and an Atlantic province (four sites per province, n = 100 per site) using sampling quotas to ensure adequate representation of women, Indigenous people, and smaller urban/rural populations.

The study protocol comprises a single baseline visit to enrol participants and obtain consent for health administrative database linkage. Baseline visits comprise on-site rapid HCV antibody testing and dried blood spot sampling for RNA detection, and a short study questionnaire to characterise patterns of service use, unmet need for HCV care, and attributes that may facilitate or impede access to HCV care. Recruitment and baseline data collection procedures were piloted in three regions of Québec (Montréal Island, Mauricie, Estrie) during a 2018–19 feasibility study (n = 508 enrolled). A pilot study focused on Indigenous communities in Saskatchewan is ongoing.

Periodic linkages to federal/provincial databases will provide individual-level outcome data informing on the HCV care cascade (antibody testing, RNA testing, linkage to care, treatment) as well as health care utilisation and outcomes (physician visits, emergency department use, hospitalisations, liver-related outcomes, attributable & non-attributable deaths). Both retrospective (to 1990) and prospective (up to 10 years post-enrolment) data will be obtained.

RESULT(S): Identification of research sites is currently underway, with data collection scheduled to commence in fall 2020. Insights and baseline data from the Québec feasibility study will be discussed.

CONCLUSION(S): 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 will provide a rich pan-Canadian data source to study HCV care in a population hard to capture through traditional clinical cohorts or population-based studies.

Increasing hepatitis C screening & new diagnoses in 10 British Columbia provincial correctional centres from 2010–2019

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BACKGROUND: Screening and treatment of hepatitis C virus (HCV) infection among people who are incarcerated (PWAI) is key for elimination efforts to be successful. HCV testing in corrections is frequently risk-based or on-demand only, resulting low numbers of PWAI receiving HCV tests. Responsibility for health services in all 10 provincial correctional centres (housing people on remand or with sentences <2 years) in British Columbia (BC) was transferred from BC Corrections to the Provincial Health Services Authority (PHSA) in October 2017. Since then, efforts have been made to increase HCV screening among PWAI in BC Corrections, with the goal of universal offer of HCV screening to all PWAI at intake.

PURPOSE: To evaluate efforts to increase HCV screening in BC provincial corrections after the transfer of health services from BC Corrections to PHSA in October 2017.

METHODS: BC Centre for Disease Control Public Health Laboratory (BCCDC PHL) does >95% of all HCV testing in BC, so data from BCCDCPHL were used to estimate the number of HCV antibody, HCV RNA and HCV genotype tests that were ordered from provincial correctional centres in BC from Jan 1 2010 to Aug 11 2019. The number of people who received a new HCV diagnosis while incarcerated was assessed by counting the number of HCV tests ordered from BC provincial correctional centres from Jan 1 2010 to Aug 11 2019 that returned a positive result, where this was the first time that the client had a positive HCV test result through BCCDC PHL.

RESULT(S): In 2017, the number of HCV antibody, RNA, and genotype tests ordered from BC provincial correctional centres was 440, 164 and 40 respectively (Figure 1); with 65 people receiving a new HCV diagnosis from a test that was ordered while incarcerated. Compared to 2017, HCV antibody, RNA, and genotype tests ordered increased by 191% (n = 1278), 238% (n = 554) and 315% (n = 166), respectively, in 2018. In 2018, 176 people received a new HCV diagnosis from a test that was ordered during incarceration, a 171% increase compared to 2017. As the 2019 calendar year is not yet complete, data presented for this year are not comparable with the previous full calendar years; however, tests ordered and new HCV diagnoses in BC provincial corrections up to Aug 11 2019 are already greater than in 2017 (Figure).

CONCLUSION(S): Transfer of health services from BC Corrections to the PHSA led to a precipitated

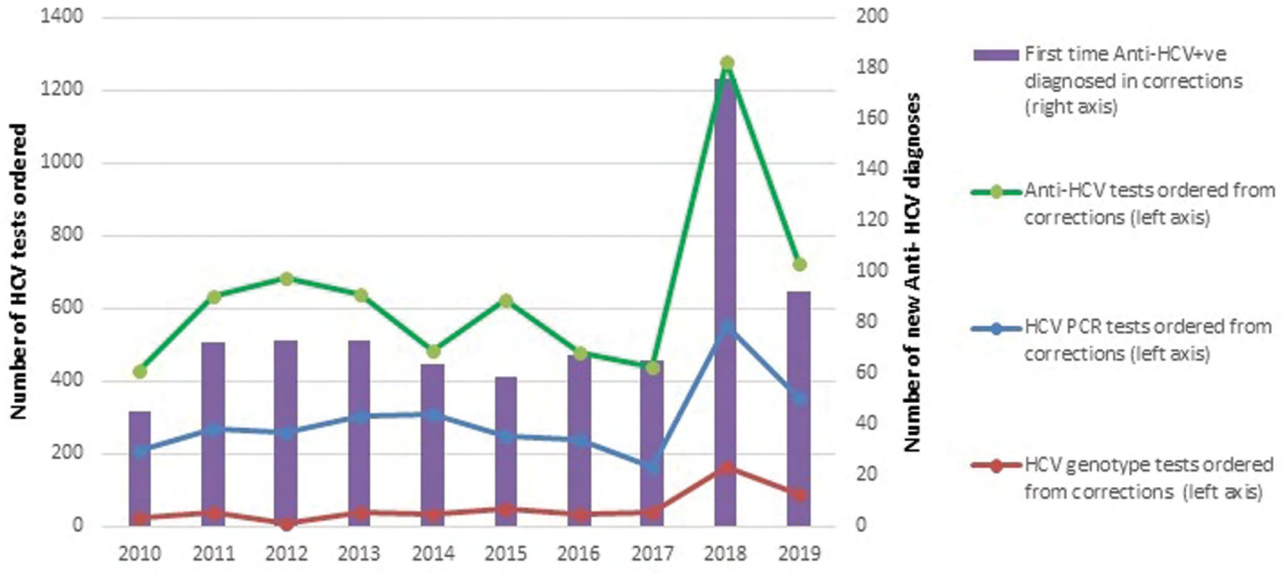

Figure: HCV testing and new HCV diagnoses in BC provincial corrections from Jan 1 2010 to Aug 11 2019

large increase in the volume of HCV tests ordered from BC provincial correctional centres, with concomitant increases in the number of new Anti-HCV diagnoses among PWAI in BC. Higher percentage of positivity detected among PWAI highlights potential impact on identification of people with undiagnosed infection and treatment needs, hence may be an effective strategy to reach Canada's goal of eliminating HCV as a public health threat by 2030.

Diversity of detention patterns among people who inject drugs and the associated risk with incident hepatitis C virus (HCV) infection: Implications for hepatitis C prevention

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BACKGROUND: Recent incarceration has been linked to a high risk of hepatitis C virus (HCV) infection among people who inject drugs (PWID). Although research surrounding this topic mainly focused on long-term incarceration, many PWID frequently experience short-term detention episodes—a context where access to care and harm-reduction is particularly limited. Whether or not any recent episode of detention is associated with a greater risk of HCV infection remains to be examined.

PURPOSE: In view of the diversity of detention patterns among PWID, our aim was to examine associations between (i) detention setting and (ii) time spent in custody, and risk of HCV infection in this population.

METHODS: Between November 2004 and June 2019, 712 HCV RNA- (Ab+/-) active PWID were enrolled in HEPCO, a prospective cohort study in Montreal. At 6- or 3-month intervals, participants were tested for HCV Ab or RNA and completed behavioural questionnaires, self-reporting any recent (past 6/3-month) detention, including the setting (local jail or prison) and the time spent in custody. Time-updated Cox regression models were fit for each exposure separately, adjusting for gender, age, recent income obtained through criminal or prohibited activities, homelessness and injection frequency.

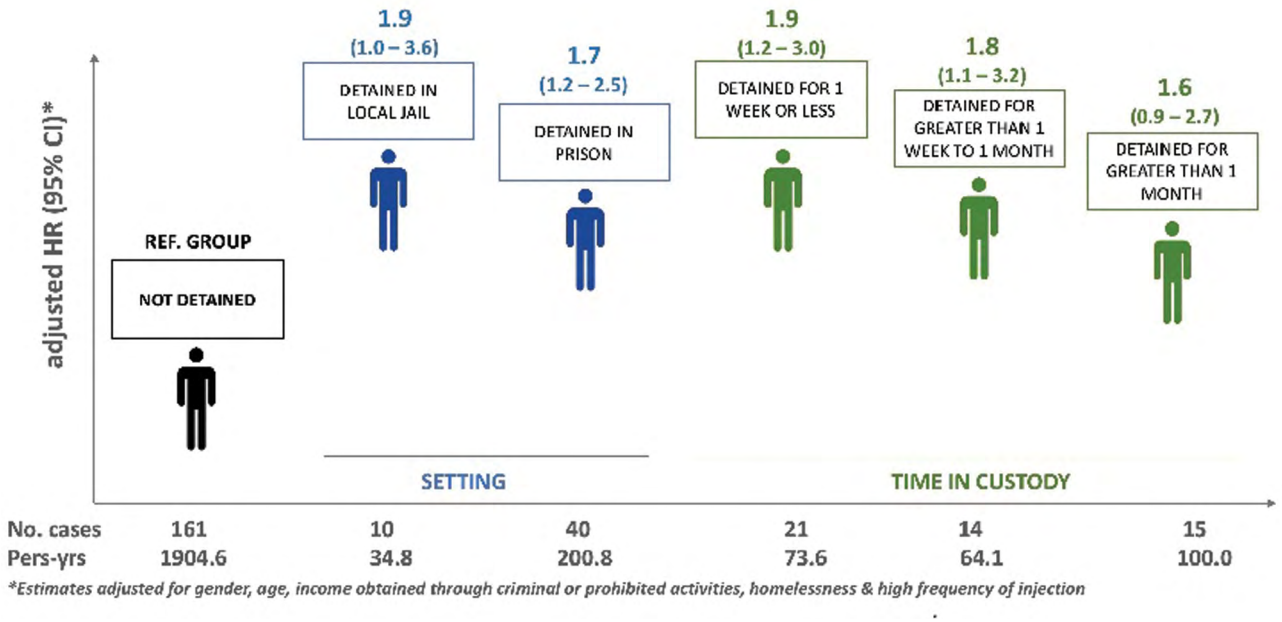

Figure: Associations between patterns of detention and risk of HCV infection among people who inject drugs

RESULT(S): At baseline, the median age of PWID was 37 and 81% were male. 520 detention episodes were reported over 5507 study visits (setting: 18% jail, 82% prison; time in custody: 35% ≤1 week; 28% >1 week and ≤1 month, 38% >1 month). Overall, 211 participants acquired HCV over 2142.2 person-years [HCV incidence: 9.8/100 person-years (95% confidence interval (CI): 8.6–11.3)]. Compared to those reporting no recent detention, PWID had a nearly two-fold greater risk of HCV infection if detained in a local jail [adjuster hazard ratio (aHR): 1.9 (95% CI: 1.0–3.6)] or prison [1.7 (95% CI: 1.2–2.5)]. Similarly, compared to no recent detention, HCV infection risk was higher among PWID detained ≤1 week [(aHR: 1.9 (95% CI: 1.2–3.0)], >1 week and ≤1 month [(aHR: 1.8 (95% CI: 1.1–3.2)] and >1 month [(aHR: 1.6 (95% CI: 0.9–2.7)]. Injection drug use during detention was uncommon (<3% of all detention episodes). (Figure)

CONCLUSION(S): Any recent detention episode appears to raise the risk of HCV infection among PWID, regardless of the setting and the time spent in custody, possibly reflecting poor access to harm reduction programs. Findings suggest that detention and the period surrounding release from local jails and prisons are key targets for HCV prevention efforts.

Gender-specific associations between psychological distress and HCV risk behaviours among people who inject drugs in Montreal

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BACKGROUND: Mental illness is a common and understudied problem among people who inject drugs (PWID), the primary group at risk of HCV acquisition in Canada. In this population, periods of high psychological distress may be associated with increased HCV risk behaviours, and may constitute opportunities for preventive intervention. Female gender has previously been associated with increased vulnerability to HCV infection and associated risk behaviours, as well as mental illness and psychological distress in both PWID and general population cohorts.

PURPOSE: To estimate associations between psychological distress and outcomes of i) binge drug injection and ii) receptive sharing of injection material, and evaluate effect modification by gender.

METHODS: Data were drawn from HEPCO, a longitudinal cohort of PWID recruited in Montreal and followed every 3 months (eligibility: age ≥18, drug injection in the past 6 months). At each visit, interviewers administer questionnaires to collect data on drug use patterns, HCV risk behaviours, health service utilization, and life events. The Kessler Psychological Distress Scale (K10) was used to assess psychological distress in the past month, and was categorized for analysis using pre-established cut-offs (low [score 10–15], moderate [16–21], high [22–29], very high [30–50]). Binge drug injection was assessed by asking participants whether they had, in the past 3 months, injected large quantities of drugs until they ran out or they could no longer physically continue (y/n). Injection material sharing was defined as using needle-syringes or ancillary injection equipment previously used by someone else, in the past 3 months (y/n). Generalized estimating equations were used to estimate associations of interest, adjusting for age (years), recent incarceration (y/n), living in the street/shelter in the past month (y/n), and past-month cocaine injection (y/n). Analyses were stratified by self-reported gender (m/f).

RESULT(S): 760 individuals (82% male, median age at baseline [Q1–Q3]: 41 [32–48] y, 68% HCV Ab+) contributed 6,363 observations over the study period (03.2011–08.2017). High to very high levels of psychological distress were commonly reported (40% of observations) and were more frequent among women (57% vs. 38% among men). Among men, we observed a gradient in the odds of both binge drug injection and sharing across levels of

psychological distress (aORs [95% CI] relative to low distress, for binge: moderate = 2.01 [1.34–3.02], high = 3.35 [2.26–4.95], very high = 3.62 [2.38–5.51]; for sharing, moderate = 1.24 [0.93–1.64], high = 1.49 [1.09–2.03], very high = 1.73 [1.23–2.42]). Among women, associations with binge followed a similar gradient but were less pronounced (aORs [95% CI] relative to low distress: moderate = 1.00 [0.45–2.24], high = 1.40 [0.66–2.95], very high = 2.37 [1.00–5.59]). Meanwhile, sharing was associated with psychological distress in a non-linear fashion, with the greatest risk among women experiencing moderate distress (aORs [95% CI] relative to low distress: moderate = 1.70 [1.05–2.76], high = 1.52 [0.85–2.74], very high = 1.24 [0.65–2.38]).

CONCLUSION(S): Psychological distress was associated with greater propensity to engage in HCV risk behaviours in this study. Point estimates suggest a more pronounced effect among men than women for binge, and differing gradients of risk for sharing. Assessment of psychological distress using common screening tools, with interventions adapted to gender-specific coping styles and strategies, may provide opportunities for HCV prevention among PWID.

Estimation of an individual-level deprivation index for HIV/HCV coinfected persons

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BACKGROUND: HIV/HCV coinfected individuals are often marginalized, and of lower socioeconomic status, which plays an important role in health outcomes. These factors are difficult to measure and are often constructed using aggregated data, which fails to capture individual heterogeneity. Furthermore, traditional indices that try and capture this information are often designed for the general population and are not generalizable to more marginalized populations. We developed an individual-level index that encapsulates social, material, and lifestyle variables for participants in the Canadian Coinfection Cohort (CCC), a publically funded prospective cohort of 1842 HIV/hepatitis C co-infected individuals actively recruiting from 18 centres across Canada.

PURPOSE: To use the rich and individual-level data of the CCC to better quantify the spectrum of deprivation in HIV/HCV co-infected individuals. To do this by creating a single individual score for every HIV/HCV co-infected individuals. To do this by creating a single individual score for every participant by aggregating information from multiple variables.

METHOD: We fit a Bayesian factor analysis model based on 8 dichotomous variables: income >$1500 per month, education >high school, employment, identifying as homosexual, unstable housing, injection drug use in last 6 months (IDU6m), past incarceration, and self-reported depression measured at baseline CCC visit for all participants. Variables included in the model were selected based on an exploratory data analysis, which consisted of significance testing with chi-squared tests set an alpha of 0.05 and multiple joint correspondence analyses to examine the grouping of the responses to the variables visually. For the variables included in the model, we estimated a severity parameters, which considers how likely an item was to be reported, and discriminatory parameters, denoting the ability of a variable to distinguish between levels of the index. Additionally, we estimated an individual parameter for every subject, which is the index.

RESULT(S): We analyzed 1642 complete cases (of 1842 enrolled participants) for the 8 variables. In the full model, we found incarceration, education, income, and employment had the highest absolute values of the discriminatory parameter, suggesting that these variables were more likely to distinguish between different levels of the index. Furthermore, we found that past history of incarceration, depression, and IDU6m were the variables with the highest severity parameter meaning that those 3 items were the most likely to be reported. The person with the highest score had: education ≤ high school, a history of incarceration, IDU6m, was

heterosexual, unemployed, with income <$1500, reported depression, and was unstably housed. In contrast, those with the lowest score had the entirely opposite profile.

CONCLUSION(S): We estimated a novel individual-level index incorporating social, material, and lifestyle components which may be useful in studying access to treatment and other health outcomes in HIV/HCV co-infected Canadians.

Geographic distribution of people living with hepatitis C in British Columbia: an application of latent class analysis and disease mapping

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BACKGROUND: Hepatitis C virus (HCV) impacts various populations, including baby boomers, people who inject drugs (PWID), and immigrants from endemic countries. However, there is limited information on the geographic distribution of people living with HCV, their overlap, and proximity to health services. Understanding where people with HCV live, can assist in service delivery, provision of care, resource allocation and targeted interventions for control and prevention of HCV infection.

PURPOSE: We employed geographic mapping to understand the distribution of people living with HCV in British Columbia (BC) using the BC Hepatitis Testers Cohort (BC-HTC) during 1990–2018.

METHODS: The BC-HTC includes all BC residents tested for HCV (~1.7 million), linked to administrative healthcare databases. We used Latent Class Analysis (LCA) to group people diagnosed with HCV based on attributes associated with HCV acquisition, transmission, or treatment uptake (age, gender and sexual orientation, ethnicity, urbanicity, social/material deprivation, history of injecting drug use or opioid agonist therapy, problematic alcohol use, mental illness, HBV/HIV co-infections, and liver disease). Multiple models were fitted using 1–10 classes. The best fitting model had 6 classes and was selected on the basis of goodness-of-fit statistics, epidemiological plausibility, and maximisation of posterior probability for class assignment. The resultant latent classes were named according to defining characteristics. Then, the proportion of each class was mapped by creating thematic maps at the Canada Census Dissemination Area level.

RESULT(S): The best fitting model's 6 classes were: 1) Younger people who inject drugs (PWID), 2) Men who have sex with men (MSM), 3) Other—healthier people, 4) People born <1964, 5) People from Asian backgrounds, and 6) Older PWID. A higher proportion of Younger PWID were concentrated around urban centres such as Vancouver city, Surrey, Langley (Metro Vancouver [MV]), Abbotsford (Fraser Valley [FV]) Duncan (Vancouver Island [VI]), Prince George (Northern BC [NBC]), and Kelowna (Interior BC [IBC]). MSM were mostly concentrated around the West End of Vancouver city (MV), and Prince George (NBC). As expected, no specific pattern was observed for other—healthier people; but, most of this population also lived in urban areas. Similarly, no particular pattern was seen for people born before 1964. However, people of Asian background were mostly concentrated in urban centres such as Vancouver city, Burnaby, Richmond, Surrey (MV) and Abbotsford (FV), with very low proportions in other areas of BC. A higher proportion of Older PWID were clustered in North/West Vancouver, Coquitlam, South Surrey (MV), Port Alberni (VI), Prince George (NBC), and Kelowna (IBC).

CONCLUSION(S): Our study identified several areas where populations with HCV were clustered. These areas could be used for placement of services tailored for each population, targeted resource allocation and interventions aimed at prevention and control of HCV infection. Our study demonstrates the use of combining statistical and disease mapping techniques as a tool to guide HCV program planning and implementation.

Hepatitis C awareness, screening and linkage to care among the Pakistani community in Montreal: the Aagahi Project

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BACKGROUND: Immigrants bear a disproportionate burden of hepatitis C virus (HCV) in Canada, accounting for 35% of all cases and have a 2–4-fold higher risk of developing cirrhosis and liver cancer than the Canadian-born population. This is likely due to delayed diagnosis, resulting from lack of routine HCV screening, barriers in accessing health care, and low HCV knowledge. Canada is home to approximately 200,000 Pakistani immigrants who may be at increased risk for HCV acquired in their country of origin (Pakistan HCV prevalence = 5.6%) and could benefit from HCV screening and treatment.

PURPOSE: To increase HCV awareness, screening and linkage to care among the Pakistani population in Montreal.

METHOD: Partnerships with key representatives of the Pakistani community were made and enabled access the community through cultural events. A community outreach program that provided culturally adapted HCV education in Urdu and English by Pakistani team members and offered point of care anti-HCV screening during six community events in the Montreal area (July-September 2019) was conducted. First- and second-generation Pakistani immigrants over the age of 18 living in Montreal area were eligible. Participants competed a questionnaire administered by research staff that included demographic information, HCV knowledge, risk factors, and prior screening and underwent a point of care anti-HCV antibody test (OraQuick®). Results were provided within 20 minutes and those with a positive test were referred to a specialist for confirmatory testing and treatment as needed. Standard descriptive analyses were used.

RESULT(S): Event organizers and study participants appreciated the opportunity to access HCV screening. Among 142 participants, the median age was 48 years (IQR, 36–60) and 67% (n = 95) were males. Participants had resided in Canada for a median of 14.5 years (IQR, 3.1–20.2). Two participants (1.4%) screened anti-HCV positive; and one was found to have active viral infection. A total of 88% of participants had at least one HCV risk factors; body piercing was most common among females (38% vs 0%) and males were more likely to have visited a barber (73% vs 34%). Two-thirds of participants (n = 90) reported visiting Pakistan since their arrival to Canada, 4 times on average [median travel time 6 months (IQR, 3–12.5)]. The majority of participants (73%) were aware of HCV however only 40% accurately identified the route of transmission. Although 65% had a family doctor, only 13% had been previously tested for HCV.

CONCLUSION(S): Accurate HCV knowledge was low and despite a large proportion having a family doctor a minority had been previously screened for HCV. HCV seroprevalence was lower than expected. These results highlight the importance to educate both physicians and patients about the need to screen for HCV, and to conduct larger HCV seroprevalence studies among the Pakistani population.

Mapping the Immigrant population and cultural and community organizations to inform community outreach and HCV microelimination efforts in Montreal

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BACKGROUND: New effective hepatitis C virus (HCV) therapies that cure >95% of people treated

led the World Health Organization (WHO) to call for the elimination of HCV as a public health threat by 2030. Microelimination strategies that tailor efforts to the specific needs of sub-populations at risk, have been proposed as a pragmatic approach to achieve WHO elimination targets. Immigrants are a key HCV risk population who face unique barriers in accessing healthcare including difficulties navigating the healthcare system, lack of culturally and linguistically adapted services, and socio-economic factors. Partnerships with community leaders, cultural organizations and community organizations involved with newly arriving immigrants will be required to engage the immigrant population in microelimination efforts.

PURPOSE: In the context of "Montreal sans HepC", an ambitious project to eliminate HCV in Montreal, we aimed to map the density of immigrants from HCV endemic countries and to identify cultural and community organizations to partner with in the area of Montreal to inform community outreach efforts.

METHOD: We used 2016 census data and published country-specific anti-HCV prevalence to estimate the number of ever and currently HCV infected immigrants in the Montreal Agglomeration (Island). Using country specific 2016 census data we evaluated the density of immigrants originating from a country with ≥2% anti-HCV prevalence living in Montreal. Maps of the density and numbers of these immigrants in each by census tract and each of the 35 borough subdivisions in Montreal were constructed with ArcGIS. Community organizations providing services for immigrants were identified through key sources: *Table de concertation des organismes au services des personnes refugiées et immigrantes* (TCRI), and the Québec Immigration site [*Immigration, Francisation et Integration (MIFI)*]. Organizations that match the linguistic and cultural needs of each group will be geocoded on the maps created.

RESULT(S): In 2016, the total population in the Montreal Agglomeration was 1,942,044 with 644,685 (33%) foreign-born individuals: 2.32% (N = 14,940) were estimated to be anti-HCV positive. Immigrants originating from countries with ≥ 2% anti-HCV prevalence made up 59% (N = 8,834) of all immigrants and originated from 30 countries in the Middle East, Africa and Asia. Four boroughs were home to 37% (N = 240,555) of all immigrants in Montreal. A total of 95 organizations that provide various services (social support, integration, etc.) in different languages to new immigrants in Montreal were identified. Twelve of these organizations were located in these four boroughs and offered services in more than 25 different languages.

CONCLUSION(S): Immigrants are concentrated in certain boroughs of Montreal in which there are organizations providing services for immigrant with concordant linguistic services. This will be an ideal starting point to begin outreach activities for immigrant community partners for the Montreal sans HepC project.

Reviewing, appraising, and synthesizing observational data to inform dynamic mathematical modeling of HCV and HIV transmission among people who inject drugs in Montréal, Canada

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BACKGROUND: Canada is not on track for eliminating the hepatitis C virus (HCV) as a public health threat by 2030. Pursuing micro-elimination among people who inject drugs (PWID) living with HIV is key to meeting this goal. Dynamic mathematical models of disease transmission can evaluate the potential impact of prevention and treatment intervention scenarios prior to scale-up. There has been no such modeling performed for HCV-HIV co-infected PWID in Canada. The wealth of surveillance and epidemiological data available in Montréal represents an opportunity to fill these research gaps. One challenge to modeling is the synthesis of multiple primary and secondary data sources to inform model parametrization.

PURPOSE: We aim to i) identify the parameters to estimate; ii) determine observational data availability and gaps; iii) appraise the potential biases inherent to these data and assess their impact on parameter estimates; and iv) elicit appropriate prior distributions for model parameters.

METHODS: Model parameters from four domains will be estimated: demography, biology, behaviours, and the public health response. We will systematically search for bio-behavioural data collected among PWID in Montréal between 2000–2019 by conducting reviews of the peer-reviewed literature and reports from provincial and federal health authorities. Some parameters will be directly estimated from individual-level data (primary data sources), and others from published sources (secondary data sources). Both types of estimates will include quantification of random error. Epidemiological studies are also subject to systematic error, and this is particularly true among hard-to-reach populations for which sampling frames are generally not available. For each parameter value estimated from one/several data source(s), we will conduct probabilistic bias analyses to estimate the direction, magnitude, and uncertainty arising from potential uncontrolled confounding, selection bias, and measurement error. The quantitative evidence generated on random and systematic error will allow us to then elicit appropriate prior distributions for the model parameters, thereby resolving potential conflicts between different data sources and weighting these sources of information based on their relative quality.

RESULT(S): The 22 parameters to estimate are listed in Table 1. To date, we have identified three data sources for parametrization: the Canadian co-infection cohort (2003–), a prospective study of health outcomes among 1,983 HIV-HCV co-infected individuals across Canada for which we have individual-level data; SurvUDI (1995–), repeated cross-sectional bio-behavioural surveys of HIV and HCV among PWID in Quebec; and the Saint-Luc Cohort (1998–), a longitudinal study of HIV and HCV determinants among 1,451 Montréal PWID. Parameters that cannot be estimated using local data will be gathered from public health reports or peer-reviewed literature involving populations in comparable contexts. Additional expected results include detailed outcomes of the bias analyses, as well as the elicited prior distribution for each parameter (Table).

CONCLUSION(S): Dynamic epidemic modeling requires integrating information from multiple data sources. We provide one of the few examples of data synthesis, accounting for sources of random and systematic error in primary and secondary data sources, in order to parametrize a dynamic, deterministic, compartmental model of both HCV and HIV transmission among Montréal PWID.

Table 1. Model parameters† to be estimated, and their potential sources

Parameter	Symbol	Units	Potential source(s)
Recruitment rate (varies by HIV, HCV, and injecting status)	$\theta(t)$‡	people per year	Peer-reviewed literature; public health reports
Background mortality rate	$\mu(t)$	per 100 PY¶	SLC¶, public health reports
Coverage of needle and syringe programs	$cov(t)$	%	CCC¶; SurvUDI; SLC
HCV¶ transmission			
HCV-related mortality	μ_1	per 100 PY	SLC, peer-reviewed literature
Spontaneous HCV clearance rate (varies by HIV status)	α_v	%	Peer-reviewed literature
Duration of the HCV acute phase	D_a	year	Peer-reviewed literature
HCV testing rate	$\tau(t)$	per 100 PY	SLC
HCV treatment rate	$\sigma(t)$	per 100 PY	CCC; SLC
HCV treatment efficacy (varies by HIV status)	$\varepsilon_v(t)$	%	CCC; SLC
Duration of HCV treatment	$D_T(t)$	year	CCC; SLC
HIV transmission			
HIV-related mortality	μ_2	per 100 PY	SLC, peer-reviewed literature
Progression rate from >350 CD4 count to 200-350 CD4 count (varies by HCV status)	π_1	per 100 PY	Peer-reviewed literature
Progression rate from 200-350 CD4 count to <200 CD4 count (varies by HCV status)	π_2	per 100 PY	Peer-reviewed literature
HIV treatment rate among individuals with >350 CD4 count	$\psi_1(t)$	per 100 PY	SLC, peer-reviewed literature
HIV treatment rate among individuals with 200-350 CD4 count	$\psi_2(t)$	per 100 PY	SLC, peer-reviewed literature
HIV treatment rate among individuals with <200 CD4 count	$\psi_3(t)$	per 100 PY	SLC, peer-reviewed literature
HIV treatment cessation rate among individuals with >350 CD4 count	$\nu_1(t)$	per 100 PY	SLC, peer-reviewed literature
HIV treatment cessation rate among individuals with 200-350 CD4 count	$\nu_2(t)$	per 100 PY	SLC, peer-reviewed literature
HIV treatment cessation rate among individuals with <200 CD4 count	$\nu_3(t)$	per 100 PY	SLC, peer-reviewed literature
Injection dynamics			
Duration of "injecting career"	δ_0	year	SurvUDI, SLC
Opioid agonist therapy coverage	$\delta_1(t)$	%	SurvUDI, SLC
Rate of retention in Opioid agonist therapy	$\omega(t)$	per 100 PY	SLC, peer-reviewed literature

† The parameters of the HIV and HCV forces of infection are not listed in this table.
‡ (t) indicates time-varying parameters.
¶ CCC: Canadian co-infection cohort; HCV: hepatitis C virus; PY: person-year; SLC: Saint-Luc Cohort.

Potential impacts of closing low-threshold overdose prevention sites on HCV and HIV prevention efforts in Toronto, Canada

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BACKGROUND: In response to the devastating opioid overdose crisis in Canada, overdose prevention sites (OPS) have opened across the country. OPS allow for illicit drugs to be used under the supervision of trained personnel who are available to provide harm reduction materials and education, and who intervene in case of overdose. The primary purpose of OPS is to intervene when overdose occurs. Less attention has been paid to the role of OPS in the prevention of HCV and HIV transmission, and facilitating access to treatment. Following a change in government in 2018, the Ontario provincial government amended the operational and funding model, resulting in several OPS losing provincial funding.

PURPOSE: To examine the potential impacts on HCV and HIV prevention and treatment efforts among people who inject drugs if two OPS in Toronto are forced to close.

METHODS: An evaluation of two Toronto-area OPS that had their funding cut but remained open under federal exemption was conducted in 2019. Program statistics were collected, complemented by one-on-one qualitative interviews with front-line staff and management (n = 12) and four focus groups with OPS clients (n = 24). Thematic analysis was used to examine potential impacts of OPS closure.

RESULT(S): Participants anticipated that closure of these two OPS would result in increased drug use and overdose in public spaces in the areas surrounding the sites. Clients reported having used drugs in public spaces prior to OPS opening, and that they would return to consuming drugs in public spaces if the OPS were forced to close. Participants also reported injecting fentanyl more frequently (in comparison to when the illicit opioid market consisted of longer-acting heroin), leading to a need for more sterile injection equipment. Closure of OPS would increase the risk of health-related harms due to using in areas lacking sterile equipment. Staff highlighted that they could better connect with vulnerable drug users since opening the OPS, increasing their ability to connect people to health services, including specialized HIV and HCV treatment services. They worried that closing the OPS would result in feelings of abandonment for OPS clients, and that they would lose their ability to connect clients to much-needed health and social services.

CONCLUSION(S): Forced closure of OPS from funding cuts may lead to multiple negative impacts, including: local increases in overdose deaths due to loss of supervised spaces to use drugs; increased difficulty in accessing sterile injection equipment; loss of an entry point to health and social services; and the severing of relationships of trust that had been built with clients. Increased injection frequency due to fentanyl's short duration of action holds the potential for increased HCV and HIV transmission, particularly in the context of a loss of supervised spaces providing sterile injection equipment if OPS were forced to close.

Perceptions of HCV treatment and reinfection risk among HIV-positive men who have sex with men in Sydney, Australia: A qualitative study

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BACKGROUND: Globally, treatment uptake for hepatitis C virus (HCV) infection among HIV-HCV coinfected men who have sex with men (MSM) has substantially increased since the advent of interferon-free direct-acting antivirals (DAA). However, HIV-positive MSM may be at an increased risk of HCV reinfection following treatment given continued engagement in high-risk behaviours. There is currently limited research on HCV reinfection risks post-DAA in HIV-positive MSM.

PURPOSE: The aim of this qualitative study was to investigate the experience of HCV treatment and perceptions of reinfection risk among HIV-positive MSM who engage in drug use and/or high-risk sexual behavior in Sydney, Australia.

METHODS: Participants were recruited from the Control and Elimination within AuStralia of HEpatitis C from people living with HIV (CEASE) cohort (n = 402) who reported engaging in drug use and/or high-risk sexual behavior for the transmission of HCV infection. Semi-structured, in-person interviews took place at the participant's clinic site between April and September 2019. Participants were asked about their HCV diagnosis and treatment experience, risks of HCV reinfection—i.e. past/current injection drug use and sexual behaviour—and utilisation of healthcare services. Interview data was transcribed, coded, and analyzed thematically.

RESULT(S): Of 33 participants interviewed (mean age 49 years), most had injected drugs (often methamphetamine) within six months of enrollment. Many participants were 'shocked' by their HCV diagnosis—especially those who engaged in limited drug use—with some participants reducing their level of sexual activity while HCV RNA positive to avoid disclosure to sexual partners for fear of stigmatising responses. Participants expressed high satisfaction with their HCV treatment experience due to long-standing, trusting therapeutic relationships with their HIV specialists and the simplicity of adding HCV treatment to their antiretroviral regimen. Given this, most participants stated that they would seek out the same services if they became reinfected with HCV. Many participants expressed a firm understanding of how to prevent HCV reinfection from injection drug use yet most were unsure or unwilling to reduce their high-risk sexual activity with such discussions occurring less frequently with healthcare practitioners. As drug use and sexual activity often occurred concurrently, some participants ceased or limited their sexual activity as a strategy to reduce their drug use.

CONCLUSION(S): Overall, participants were content with their HCV treatment experience and felt comfortable discussing their drug use with healthcare practitioners due to long-standing, trusting therapeutic relationships. Some participants were uncertain on how to reduce the risk of HCV reinfection related to high-risk sexual behaviours with more targeted education needed in this area. Moreover, MSM who wish to reduce their stimulant drug use require additional information on services available, including services in non-urban regions.

Toward the elimination of HCV vertical transmission: A targeted, patient-informed hepatitis C engagement program in persons who use drugs in their child bearing years in southern New Brunswick

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BACKGROUND: Substance use disorders (SUD) have been well-documented in Canada to be rising, particularly among younger adults. Estimated prevalence of SUD in the 15–39-year age range is thought to be between 1.3% and 6.4% with higher prevalence in younger ages. Along with the high prevalence of SUD, rates of HCV in Canada have steadily risen in all age groups within that range. The incidence rates of HCV between 2011 and 2017 have seen increases of 28.6% in those aged 30–39 years, and 62.3% in those aged 25–29 years. This rise in HCV incidence among those considered to be in their primary child-bearing years raises concern for an increasing number of babies born to HCV-positive mothers and the potential for vertical HCV transmission.

PURPOSE: Using structured feedback from our target population, the purpose of this project is to lessen or eliminate HCV prevalence among adults in their prime child-bearing years. The goal is to decrease the number of babies born at risk for HCV.

METHODS: A qualitative study was undertaken to identify primary modes of information gathering and motivations and barriers to HCV treatment engagement of persons who use drugs (PWUD) aged 20–39 years who had an unknown HCV status, or known HCV infection but not connected to

care. The findings of the qualitative study are the foundation of the 12-month Hepatitis C Engagement Program (HEP) to increase screening and engagement in care in the target population.

RESULT(S): The qualitative review identified word-of-mouth and posters/pamphlets as the most common ways of obtaining information. Systemic barriers and stigmatization were the two most common themes cited as barriers to accessing HCV care. The HCV engagement program was initiated June 28, 2019. As of October 31, 2019, a total of 91 patients in our target population accessed HEP. Of those, 31.9% (n = 29) were HCV-positive with 51.7% (n = 15) of those being new diagnoses. Mean age was 29.9 years and 31.9% (n = 29) were female. Engagement was highest when clinics were conducted in the setting of community organizations (i.e. shelters, soup kitchens). Injection drug use (IDU) was reported by 58.2% (n = 53), snorting in 76.9% (n = 70), and 36.7% were on opiate agonist therapy (OAT). Among HCV-positive persons, 62.0% were not on OAT. Word of mouth was the most common way of learning about outreach clinics. Among females, 55.2% (n = 16) reported having one or more children, and 28.6% may have had children born to them when HCV-positive and as such may require screening to assess for vertical HCV transmission.

CONCLUSION(S): The first four months of this HEP program saw one-third of all those accessing the program to be HCV positive with high prevalence of both IDU and snorting. The majority were not on OAT. Next steps for HEP is expanding screening to children at-risk and improving methods of attracting patients to HEP outreach clinics.

Peer led point-of-care testing: The role of Atlantic Canada's first overdose prevention site in hepatitis C elimination

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BACKGROUND: The HaliFIX Overdose Prevention Society is an organization dedicated to reducing the harms associated with substance use. Recently, we opened Atlantic Canada's first overdose prevention site (OPS). Our site is peer led and employs former or current substance users. The goal of the OPS is not only to provide a safe space for people who use substances (PWUS) but also to offer services and connection to services needed by PWUS, including hepatitis C (HCV) testing and treatment.

PURPOSE: In Atlantic Canada, point-of-care-testing (POCT) for HCV has only recently begun to be employed and remains largely limited to testing conducted by healthcare providers. The purpose of this initiative is to demonstrate proof-of-concept that with appropriate preparation and supports, peer-led HCV POCT has the potential to significantly expand access to screening, diagnosis and treatment. Through peer-led POCT events we hope to reduce the structural, social and self-directed stigma that comes with injection substance use and/or being infected with HCV while increasing the capacity amongst the peers to feel comfortable performing POCT.

METHODS: Peers will lead 6 POCT events through the OPS while linking the participants to care through our integrated model of housing an OPS in a low-barrier opioid agonist therapy (OAT) clinic. After each testing event we will hold a focus group for participants and peers conducting the sessions to provide feedback and input. The results of these focus groups will be used to create a presentation about HCV elimination for people who use substances by people who use substances (PWUS).

RESULT(S): In 2019, one of our arm's length organization Mainline Needle Exchange in advance to HaliFIX OPS opening in the fall of this year, expanded use of POCT at dedicated events was explored and over 100 POCTs have been performed. These events represented the first major community-located effort at HCV testing with support provided by an infectious disease physician and other healthcare providers for testing. The first peer conducted POCT event will take place in January 2020.

CONCLUSION(S): In order to reach the World Health Organization 2030 goal of viral hepatitis elimination we must get as many tests in the hands of community-based organizations that are serving the priority populations that are at risk of HCV. Through this initiative we hope to demonstrate that peer conducted POCTs are a safe and effective way to reach a larger group of at-risk PWUS.

Strengthening Canada's hepatitis C response by producing culturally and linguistically relevant resources for Canadian immigrants and their service providers

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BACKGROUND: Immigrants from countries where HCV is common bear a large burden of Canada's HCV epidemic. Of all the HCV infections in Canada, 35% are in foreign-born Canadians.(1) Hep C prevalence in Canadian immigrants is double the national average.(2) The '*Blueprint to Inform Hepatitis C Elimination Efforts in Canada*' identifies immigrants as a priority population and gives specific recommendations to educate immigrants and service providers about offering linguistically and culturally sensitive hepatitis C education and services.

PURPOSE: CATIE addresses the information needs of large immigrant communities and their service providers by creating culturally relevant in-language HCV resources. Our key resources:

1. A web portal for service providers to find the latest resources on hepatitis C among Canadian immigrants.
2. A multilingual website with up-to-date, basic hepatitis C information in 11 common immigrant languages: English, French, Arabic, Bengali, Hindi, Punjabi, Simplified Chinese, Spanish, Tagalog, Tamil, Thai, Urdu and Vietnamese.
3. A print brochure with up-to-date, basic hepatitis C information on testing, treatment, and transmission in Chinese, Tagalog, Urdu and Punjabi, with English or French.

METHOD: The process of creating culturally-relevant resources is a highly participatory. CATIE works closely with separate advisory committees for each cultural community to ensure that cultural differences between these communities are reflected in the messaging.

All resources are translated by native speakers, who have professional training in health or medicine. CATIE engages our translators on long-term basis and offers training to keep their HCV knowledge up-to-date. All translations undergo community and medical reviews to ensure that the language is accessible, unbiased and accurate.

RESULT(S): From Nov. 2018–Oct. 2019, 14,850 print resources were distributed across Canada in the following provinces: Ontario, British Columbia, Quebec, Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia and Saskatchewan. CATIE's multilingual website has been visited by 108,377 unique users who spent 122,043 sessions with 209,520 page views.

Testimonials from users from British Columbia, Quebec and Ontario:

"CATIE's ethnocultural program has contributed more to raising awareness of HCV among immigrants than any other organization in Canada."

"CATIE's resources have supported our work and training efforts to Urdu-English and Urdu-French cultural communities."

"We have worked cooperatively in bringing multilingual hepatitis C education to thousands of newcomers through CATIE resources and presentations."

CONCLUSION(S): CATIE is strengthening Canada's hepatitis C response by producing these culturally-relevant and in-language resources. They are key to help Canada fulfill recommendations from the *Blueprint to inform hepatitis C elimination efforts in Canada*.

Estimating direct-acting antiviral impact among key populations in Ontario: a research proposal

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BACKGROUND: Hepatitis C virus (HCV) is responsible for a major healthcare burden in Canada, leading to more years of life lost than any other infectious agent. If untreated, chronic HCV can progress to cirrhosis, liver cancer [hepatocellular carcinoma (HCC)], liver failure, and death. Among the estimated 250,000 Canadians living with HCV infection, key groups at risk include people who inject drugs (PWIDs), migrants originating from HCV-endemic regions, and baby boomers (born 1945–65). Since 2014, safe and effective all-oral direct-acting antiviral (DAA) treatments (curing >95% of cases) have been available in Canada, offering the potential to reduce HCV-related morbidity and mortality. However, there is limited evidence available at present to describe DAA treatment impact at a population-level and among key risk groups.

PURPOSE: We aim to measure DAA treatment impact on rates of HCV-related hospitalizations, HCC, liver-related mortality, and all-cause mortality by risk groups, and address the question "Does DAA treatment equitably reduce HCV-related illness and death among key risk groups at risk?" We will use a health equity lens to support a critical investigation of disparities in health outcomes among risk groups.

METHOD: The study dataset is comprised of HCV cases linked to health administrative data (physician billing, hospitalization, pharmacy, laboratory, cancer registry, vital statistics, and immigration) in Ontario. Participants eligible for DAA treatment (active infection on/after January 2014) will be included and followed up to December 2018. Risk groups will be identified via birth year (baby boomers), immigration data linkages (migrants), and through the development of an algorithm to estimate injecting drug use based on ICD codes and opioid agonist therapy dispensation (PWIDs). Time-dependent Cox proportional hazard models stratified by risk groups will be used to estimate the impact of DAA treatment on health outcomes (all-cause mortality, liver-related mortality, HCC diagnosis, and HCV-related hospitalizations). Models will be adjusted for age, sex, liver state, co-morbidities associated with HCC, treatment year, and neighbourhood-level socioeconomic status. Follow-up time will be measured from cohort entry (*unexposed*) or DAA start date (*exposed*) up to outcome date or censored at the end of follow-up (December 31, 2018).

RESULT(S): Data linkages are ongoing at present, and analysis is expected to begin in fall 2020.

CONCLUSION(S): Population-level data to assess the real-world impact of DAA treatment will help identify populations requiring additional interventions to ensure DAA treatment benefit, such as increased engagement in care and follow-up, and harm reduction services. In doing so, this research has the potential to change how HCV treatment and healthcare are delivered for key risk groups in Ontario, creating positive change and improving health outcomes for people affected by HCV.

The synthesis and integration of hepatitis C clinical practice guidelines to facilitate low threshold access to evidence-based care in the outreach setting

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BACKGROUND: Saskatchewan continues to lead the country in rates of new HCV infections. In 2016, the numbers of new HCV infections were double the national average. Intravenous drug use (IDU) has been identified as the predominant risk factor for acquiring HCV infection.

Although effective treatment is available there are challenges with accessibility and engagement of the population. Substance use is one of the most stigmatized conditions in the health care setting and it is often associated with criminalization and poverty. Effective delivery of care, including DAAs to people who use and inject drugs (PWUD) requires low threshold access to care that is adaptable, patient centered and incorporates a holistic model of care.

PURPOSE: HCV treatment modalities and models of care vary across Canada and internationally. The HCV Patient Pathway Clinical Guidelines were developed to offer point-of-care clinicians the accessibility, portability and universality to initiate

testing, assessment and rapid access to HCV care and treatment.

METHODS: The development of the HCV pathway guidelines was completed by reviewing, comparing and critiquing the Canadian, American and European HCV clinical practice guidelines (CPG). Each recommendation or decision point within the guidelines were evaluated by the level of supporting evidence based on the grade of strength of evidence and recommendation.

Utilizing the three CPG recommendations the HCV patient pathway was then developed as a comprehensive guideline to allow for high utility, while ensuring consistency in practice, resulting in fluid, best practice care being provided at the community level. A focus on patient centered, non-judgemental language and a harm reduction care approach are infused and integrated throughout the pathway.

The guidelines have been reviewed by various stakeholders and revised numerous times. RNSP documents and protocols have been developed to support a nurse led model of care, which will further facilitate the implementation of the pathway into practice.

RESULT(S): The HCV pathway will operationalize standards of practice in the clinical setting, so patients experience seamless, timely and evidence-based care. The guidelines are designed to allow for HCV care to be delivered in the community and outreach setting by clinicians already established and working in the community. The guidelines are comprehensive in nature and were created to assist in bringing care to the community level, while ensuring practice standards are adhered to.

As peer led models of care begin to be implemented, the pathway will also be available as a comprehensive teaching and resource guide to peers who take on an active role in HCV care.

CONCLUSION(S): Numerous system and individual-level barriers to HCV care and treatment exist among the population, especially in PWID. The pathway offers support and guidance to front line clinicians who have already established therapeutic helping relationships with the population in need of HCV care. By taking the care to the population it will aid in overcoming some the barriers of accessibility and engagement that prevent the population from accessing care.

While some of the population are aware of their current infection, they have not been retained in the HCV cascade of care, while still others remain unaware of their HCV infection. Targeted interventions to improve frequency and uptake of HCV testing and models of care that strengthen retention and engagement in care and promote uptake of treatment, while ensuring CPG are upheld are essential to reach the WHO target of HCV elimination by 2030.

HCV: The neurocognitive impact in the overdose epidemic

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BACKGROUND: The hepatitis C virus (HCV) belongs to the family Flaviviridae, along with several well-known neurotropic viruses.

Spontaneous clearance rates of hepatitis C virus (HCV) have been revised upwards to 35%–40%.

This cohort may have higher rates of cognitive dysfunction that persist after SVR, and recent BC CDC data also suggests a 17-year reduction in life expectancy.

PURPOSE: To consider the burden of cognitive dysfunction resulting from HCV to our social safety net, with a particular focus on the overdose crisis.

METHOD: A review of HCV literature from 2015 to present combined with a two-year patient-oriented surveillance of social media.

RESULT(S): HCV causes inflammation in the frontal white matter and in the basal ganglia which has critical schema functions, especially procedural categorization processes that are important in making choices and dementia.

Hepatitis C induced brain inflammation has significant impacts on delay discounting and inhibition, mood, learning, memory (anomic aphasia), and other critical functions that can reduce health related quality of life for many individuals at any level of cognitive function.

CONCLUSION(S): The significance of HCV on potential years of life lost (PYLL) has not kept pace with recent findings.

HCV elimination would likely reduce the burden of addictions and mental health costs.

HCV is likely an under-estimated contributor to the overdose crisis.

Eradication of HCV would contribute to a long-term reduction of mortality from addiction, reduce mental health services costs, and reduce confounds in mental health diagnosis.

SESSION #3: CLINICAL RESEARCH

Efficacy of sofosbuvir/velpatasvir (S/V): Impact of treatment adherence

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BACKGROUND: Current all-oral regimens offer the promise of cure for nearly all Canadians living with chronic HCV infection. This is particularly true with the availability of simple pan-genotypic regimens such as sofosbuvir/velpatasvir (S/V), administered as one tablet once a day for 12 weeks for the treatment of all HCV genotypes and all levels of fibrosis. Clinical trial results suggest these regimens are associated with very high cure rates, even in the setting of sub-optimal adherence. There is limited real-world evidence to substantiate these findings.

PURPOSE: To examine the real-world efficacy of sofosbuvir/velpatasvir in a setting of sub-optimal adherence and subsequent SVR12.

METHODS: Accessing the national observational Canadian Network Undertaking Against Hepatitis C (CANUHC) database, we evaluated all patients receiving S/V for the treatment of chronic HCV infection. The endpoint of this analysis was the achievement of a cure of HCV infection (undetectable HCV RNA levels 12 or more weeks after the end of therapy, SVR12) as a function of the reported level of adherence to therapy that was achieved.

RESULT(S): A total of 152 individuals were included in this analysis, with an overall SVR12 rate of 98.7% (150/152). Overall adherence >90% was reported in 142 (93.4%) participants, with 10 (6.6%) reporting adherence below 90%, 3 of which (2%) were below 75%. Of those with <90% adherence, all achieved SVR12. Subjects with sub-optimal adherence (n = 10) differed slightly from the entire cohort by mean age (46.5 vs 50.4 years), sex (30% vs. 41% female), HCV genotype (50% vs. 45% GT3) HIV co-infection status (20% vs. 14%), history of injection drug use (70% vs. 47%) and mean fibrosis score (10.9 vs. 9.3 kPa). Two individuals did not achieve SVR12 (both virologic relapses), both within the >90% adherence group. Non-SVR subjects were 69 and 44 years old, both were female, fibrosis scores were 4.5kPa and 8.2 kPa, one each GT2 and GT3. One individual had a history of injection drug use and neither had any documentation of treatment interruption >7 days or premature treatment discontinuation.

CONCLUSION(S): Within the CANUHC cohort, self-reported adherence was generally high, as was the rate of achievement of SVR12 with the use of S/V. Suboptimal adherence was rare and not associated with treatment failure nor with any specific demographic profile. These data endorse the relative robustness of the S/V regimen in clinical practice and is reassuring as the use of S/V is expanded into populations facing multiple obstacles to treatment adherence.

Reinfection following successful direct-acting antiviral therapy for hepatitis C infection among people who inject drugs

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BACKGROUND: The advent of highly effective interferon-free direct-acting antivirals (DAA) for hepatitis C virus (HCV) infection has resulted in significant progress towards HCV elimination in many settings. DAA therapy is safe and effective among people who have recently injected drugs and people on opioid agonist therapy (OAT), including in "real-world" settings. However, reinfection following successful DAA therapy remains a concern and may compromise HCV elimination efforts.

PURPOSE: The aim of this analysis was to calculate the incidence of HCV reinfection and associated factors among two clinical trials of HCV DAA treatment in people with recent injecting drug use or currently receiving OAT.

METHODS: Participants who achieved an end-of-treatment response in two clinical trials of people with recent injecting drug use or currently receiving OAT (SIMPLIFY and D3FEAT) enrolled between March 2016 and February 2017 in eight countries were assessed for HCV reinfection, confirmed by viral sequencing. Incidence was calculated using person-time of observation and associated factors were assessed using Cox proportional hazard models.

RESULT(S): Seventy-three percent of the population at risk for reinfection (n = 177; median age 48 years, 73% male) reported ongoing injecting drug use. Total follow-up time at risk was 254 person-years (median 1.8 years, range 0.2–2.8). Eight cases of reinfection were confirmed via viral sequencing for an incidence of 3.1/100 person-years (95% CI 1.6–6.3) overall, 17.9/100 person-years (95% CI 5.8–55.6) among those who reported sharing needles/syringes, and 1.7/100 person-years (95% CI 0.5–5.2) among those on OAT. Younger age and needle/syringe sharing were associated with HCV reinfection.

CONCLUSION(S): The population-level effects of widespread treatment scale up will be improved by the prevention, early detection, and retreatment of reinfection cases; therefore, it is important that HCV treatment is nested within a framework that encompasses harm reduction, ongoing testing, and access to retreatment if elimination is to be achieved.

Non-invasive surrogates of portal hypertension predict decompensation in obese patients with compensated advanced chronic liver disease

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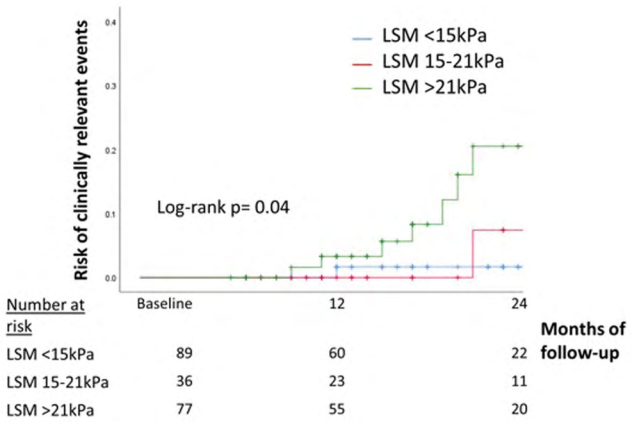
BACKGROUND: Portal hypertension (PH) is a major driver of progression to clinical decompensation in compensated advanced chronic liver disease (cACLD), as such it should be identified as soon as possible and treated as needed. In patients with cACLD requiring the use of extralarge (XL) probe for liver stiffness measurement (LSM)

due to overweight/obesity, the prognostic value of simple non-invasive surrogates of PH and controlled attenuation parameter (CAP) for predicting first clinical decompensation has not been fully assessed.

PURPOSE: We designed the present study to evaluate the vaue of LSM, CAP and other simple non-invasive tests to predict first clinical decompensation and other clinically relevant events (severe bacterial infections) in patients with cACLD with overweight/obesity requiring the use of XL probe. As secondary endpoint, we aimed at specifically analyzing the prognostic performance of these non-invasive tests in patients with cACLD due to NAFLD/NASH.

METHODS: Consecutive patients with cACLD (LSM ≥10 kPa by XL probe) observed between 2015 and 2018 in two large academic centers, University of Bern and McGill University Health Centre, were included. Clinically relevant events including classical decompensation (ascites, PH bleeding, jaundice, hepatic encephalopathy) and severe bacterial infections were recorded on follow-up. The association between these events and LSM, CAP, LSM*spleen size/platelet count (LSPS) and Portal Hypertension (PH) Risk score (based on LSM, sex, spleen diameter and platelets) was studied. The Cox proportional hazards model was used for multivariate analyses. The log-rank test was used to compare time-to-event curves between patients with and without steatosis and among LSM categories. To assess the performance of the different non-invasive methods to predict clinical decompensation, area under the receiver operating characteristic (AUROC) curves were calculated.

RESULT(S): 274 patients (NASH 57%, viral hepatitis 25%; BMI 33.8±6.5 kg/m^2; median Child score 5; median LSM 16.8 kPa; CAP 318±66 dB/m) were followed up for a median of 17 months (IQR 11–75). 30 patients (15%) were on non-selective beta-blockers at inclusion. 18 developed clinically relevant events (13 classical decompensation, 5 severe bacterial infections). LSM, LSPS and PH risk score showed a high prognostic discriminative ability (AUROC) for classical decompensation: LSM 0.849 (95% CI, 0.730–0.968, p <.0001), PH risk score 0.876 (95% CI, 0.799–0.954, p <.0001), and LSPS 0.849 (95% CI, 0.730–0.968, p <.0001) and for clinically relevant events. LSM category by XL probe also predicted clinically relevant events (see Figure). NASH patients showed similar results as patients with viral hepatitis etiology. By multivariate Cox regression analysis, LSPS remained independently associated with decompensation and with clinically relevant events in the whole population (HR 1.144; 95% CI, 1.035–1.265, p <0.001). In the subgroup of patients with NASH, PH Risk score (HR 1.256; 95% CI, 1.144–1.378, p <0.001) and CAP remained independently associated with decompensation and clinically relevant events, being CAP ≥ 220 dB/m protective (HR 0.063; 95% CI, 0.012–0.336, p = 0.001).



CONCLUSION(S): In obese patients with cACLD, simple and readily available non-invasive surrogates of PH help identifying those at increased risk of developing first clinically relevant events and classical decompensation. The results of the present study also validate the use of XL probe for LSM and CAP to stratify the risk of clinical decompensation.

Impact of treatment with Tenofovir Alafenamide (TAF) or Tenofovir Disoproxil Fumarate (TDF) on hepatocellular carcinoma (HCC) incidence in patients with chronic hepatitis B (CHB)

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BACKGROUND: Potent antivirals can reduce HCC incidence in CHB. TDF and TAF are first-line treatments, and in Phase 3 studies through 3 years, TAF has shown antiviral efficacy similar to TDF, higher rates of ALT normalization, and no resistance.

PURPOSE: We evaluated HCC incidence in patients participating in these ongoing studies.

METHOD: HBeAg-positive (n = 1039) and -negative (n = 593) patients with HBV DNA ≥20,000 IU/mL and ALT >60 U/L (males) or >38 U/L (females) recruited from 190 sites in 20 countries were randomized (2:1) to TAF 25 mg QD or TDF 300 mg QD for up to 3 years, followed by open-label TAF through Year 8. Patients with hepatic decompensation, co-infection with HCV/HDV/HIV, or evidence of HCC were excluded. HCC was assessed at 6 monthly intervals by hepatic ultrasonography beginning after Week 96 and by local standards of care. The standardized incidence ratio (SIR) for HCC was calculated for observed cases relative to predicted cases using the REACH-B model.

RESULT(S): 1632 patients were followed for up to 4 years; HCC was seen in 16 patients (0.98%; 7 TAF; 9 TDF); median (Q1, Q3) time to onset was 568 (316, 855) days. At baseline HCC patients were older (median age 53 vs 40 y; $p < 0.001$), had lower median HBV DNA (6.2 vs 7.3 $\log_{10}$ IU/mL; $p = 0.041$) and were more likely to have cirrhosis (FibroTest score ≥0.75; 31% vs 10%; $p = 0.004$). For study patients, the overall SIR was significantly reduced with TAF or TDF treatment 0.45 (95% CI 0.278–0.740) [Table]. HCC incidence was significantly reduced (SIR 0.42, 95% CI 0.23 to 0.75) in noncirrhotic patients (n = 11 vs 26.5 predicted), but not for cirrhotic patients (n = 5 vs 8.1 predicted). The SIR was also significantly reduced in noncirrhotic patients receiving TAF (n = 5), but not in those treated with TDF (n = 6).

CONCLUSION(S): In CHB patients treated with TAF or TDF for up to 4 years, HCC incidence was reduced, particularly in noncirrhotic patients. Additional follow up is needed to further characterize the impact of longer term treatment on HCC risk reduction.

Universal HCV and HIV screening in an emergency room – fewer new cases than expected

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BACKGROUND: According to the Public Health Agency of Canada, 44% of HCV-infected and 14% of HIV-infected Canadian patients are unaware of their status. Contrary to the USA, universal HIV screening in the emergency room and HCV baby-boomer screening are not recommended in Quebec, in part due to the lack of data regarding cost-effectiveness in our epidemiological context.

PURPOSE: The aim of this project was to determine the prevalence of undiagnosed HCV and HIV cases in a population sample tested in the emergency room of the University of Montreal hospital centre, a tertiary care hospital of downtown Montreal, and to evaluate linkage-to-care.

METHOD: Between July 2018 and May 2019, patients aged between 18 and 73 years old were offered HCV and HIV screening on an opt-out basis in the emergency room without regards to their risk factors. Patients were asked by nurses if they were known to be positive for HCV and/or HIV and, if not, were informed they would be tested unless they refuse the test. HCV and HIV serology tests were performed on the ARCHITECT (Abbott) and, when required, confirmation tests were performed at the provincial reference laboratory. Overall and undiagnosed cases prevalence were calculated. Linkage-to-care was defined as completion of pre-treatment evaluation and treatment prescription three months after diagnosis.

RESULT(S): Overall, 6,350 unique eligible patients were informed of the screening program and 62.1% of patients were tested for at least one virus (HIV: 3,905; HCV: 3,910). Reasons for not testing were as follows: 25% patients opted out, 12% patients did not opt-out but were not tested for various reasons, largely organizational (e.g.: left emergency room before being seen by physician), 0.3% (18) patients were HIV-HCV co-infected. Nine patients were newly diagnosed with HCV and two with HIV. Overall prevalence of HCV and HIV cases were 1.9% and 1.2%, respectively. We were able to communicate the diagnosis to 67% and 100% of new HCV and HIV-infected patients, respectively. All patients had recognized risk factors for HCV or HIV. Only 2 (22.2%) HCV-infected and 1 (50%) HIV-infected patients were linked to care 3 months post-diagnosis (Table).

CONCLUSION(S): Universal screening at the emergency room allowed identification of 9 new HCV and 2 new HIV-infected individuals, which is important in the context of disease elimination in Montreal. Nevertheless, identification of new cases of HCV and HIV and linkage-to-care were low.

DAA treatment uptake or outcomes are not effected by alcohol use: A CANUHC analysis

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BACKGROUND: Alcohol use accelerates HCV liver disease and precludes initiation of interferon-based treatment. There are limited data on the influence of alcohol use on DAA treatment initiation and outcome.

PURPOSE: There are limited data on the influence of alcohol use on DAA treatment initiation and outcome.

METHODS: The Canadian Network Undertaking against Hepatitis C (CANUHC) Cohort contains prospectively collected demographic information and HCV DAA treatment information collected at 10 Canadian sites. Self-reported alcohol (define as: (a) any use, (b) number of drinks per day/week/

Table:

	New diagnosis	Declared being positive	Tested, but previously diagnosed	Prevalence of undiagnosed cases	Overall prevalence
HCV	9	59	50	0.14% (95% CI: 0.07–0.27%)	1.9% (95% CI: 1.6–2.2%)
HIV	2	71	5	0.03% (95% CI: <0.01–0.12%)	1.2% (95% CI: 1.0–1.5%)

month) is collected. Patient characteristics and SVR outcomes were compared by past and present alcohol use.

RESULT(S): 725 HCV-infected patients under assessment for DAA therapy were enrolled in CANUHC (mean age: 53 (SD 12.7); 66% male; 78% White). Any past and present alcohol use was reported by 37% and 30%, respectively. Mean age was older in those with [54.5 (SD 11.9)] vs without current alcohol use [51.9 (SD 12.9), $p < 0.01$]. A similar proportion of males (31%) and females (27%) reported current alcohol use ($p = 0.27$). The mean baseline fibrosis measures were similar [(10.8 kPa (SD 10.0) vs 10.9 kPa (SD 9.2)] in current alcohol users and non-users. The proportions initiating treatment were similar in current alcohol (42%) and non-users (39%, $p = 0.52$). SVR rates of 92.3% and 92.0% were achieved ($p = 0.93$).

CONCLUSION(S): DAA antiviral therapy is highly curative irrespective of past or current self-reported alcohol use. Alcohol use should not be considered an absolute preclusion to DAA consideration.

SESSION #4: HEALTH SERVICES RESEARCH

Can we afford to screen and treat hepatitis C virus (HCV) infection in Canada? Latest insight from a Canadian policy model – A province-by-province analysis

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BACKGROUND: Managing chronic hepatitis C (CHC) is challenging because majority of those infected are asymptomatic. In Canada, the uncertainty of budget-impact, among other factors, has led to conflicting recommendations on screening.

PURPOSE: The objectives of this study are to 1) generate high-quality evidence on the current CHC-related costs estimates and prevalence estimates using health-administrative data; and 2) develop a policy model that integrate the up-to-date evidence to estimate the cost-effectiveness and the budget-impact of a one-time HCV screening program.

METHODS: Three studies were conducted: 1) A retrospective analysis of health-administrative data from a cohort with CHC to generate population-level diagnosis statistics and health-states specific costs for modelling; 2) A back-calculation mathematical model to project recent prevalence and undiagnosed proportion using data obtained from the retrospective analysis; and 3) A state-transition model to evaluate the cost-effectiveness and budget-impact between a no-screening strategy and a screen-and-treat strategy for birth-cohort born between 1945–1964 for each of the ten Canadian provinces. Cost and prevalence data were obtained from study 1 and 2 respectively. Progression and utility data were based on two systematic reviews published in 2019. We used a provincial payer-perspective, life-time time horizon and a 1.5% discount rate for the cost-effectiveness analysis, and used a provincial payer-perspective, 10-year time horizon and no discount for the budget-impact analysis.

RESULT(S): Our retrospective analysis showed that current CHC-related costs estimates were roughly three-times higher than the previously reported estimate in 2005, with an average 30-day cost ranging from $798 for patients diagnosed with non-cirrhotic CHC to $8,753 for patients diagnosed

Table 1: Direct medical cost per 30 days by health states

Health State	Average direct medical cost per 30 days ($)
No cirrhosis	$798
No cirrhosis (SVR)	$660
Compensated Cirrhosis	$1,487
Decompensated Cirrhosis (DC)	$3,659
Hepatocellular carcinoma (HCC)	$4,238
DC and HCC	$8,753
Liver transplant	$4,539

with decompensated cirrhosis and hepatocellular carcinoma (Table 1). Among the birth-cohort born between 1945–1964, the prevalence of CHC was estimated at 1.77%-2.31% with an undiagnosed proportion of 21.1%-32.6% across different provinces. The incremental-cost-effectiveness-ratio (ICER) of no-screening versus screen-and-treat varied from $35,217 per quality-adjusted-life-year (QALY) to $48,197 per QALY across different provinces (Table 2). Screen-and-treat would cost an additional $30 million for British Columbia, $23 million for Alberta, $7 million for Saskatchewan, $8 million for Manitoba, $61 million for Ontario, $54 million for Quebec, $5 million for New Brunswick, $1 million for PEI, $6 million for Nova Scotia, and 4 million for Newfoundland for the next 10 years.

CONCLUSION(S): Our retrospective analysis provided population-derived, granular diagnosis statistics and up-to-date cost estimates for CHC health states that were used for prevalence estimation and economic modelling. Our cost-effectiveness analysis suggested that a one-time HCV screening program in Canadian provinces remained cost-effective. Contrasting the budget impact of this HCV screening program with other recommended health services and technologies, we can conclude that HCV screening should be considered affordable. In conclusion, these findings provide vital evidence to help Canada develop appropriate policies to achieve the WHO elimination targets.

HBV-HCV coinfection among immigrants in Ontario, Canada

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BACKGROUND: Viral hepatitis B and hepatitis C are important causes of chronic liver disease globally, and coinfection is not uncommon. Numerous studies provided evidence that coinfection accelerates liver disease progression and increases the risk of adverse health outcomes. However, the epidemiology of co-infections is poorly defined among migrant groups.

PURPOSE: To describe the epidemiology of HBV and HCV mono- and co-infections among immigrant groups in Ontario, Canada.

METHODS: We use linked laboratory results from a public laboratory to their health administrative data in Ontario, Canada, and defined HBV and HCV mono- and co-infected groups using serology and nucleic acid test results. Individuals were considered HBV infected if they had HbsAg reactive, HbeAg reactive, or HBV DNA detected laboratory results, and HCV infected if they had HCV Ab reactive or HCV RNA detected laboratory results.

Table 2: Province-by-province results for birth cohort born between 1945–65

Province	CHC Prevalence estimates (%)	Undiagnosed Proportion (%)	ICER of no-screening versus screen-and-treat ($/QALY)	Budget-impact ($)
AB	2.11	32.6	$46,723	$22,913,869
BC	2.31	21.2	$35,217	$29,616,954
MB	2.11	32.6	$41,718	$7,554,160
NB	1.77	25.0	$39,354	$5,273,472
NL	1.77	25.0	$48,197	$3,762,147
NS	1.77	25.0	$41,998	$6,463,108
ON	1.93	21.1	$39,816	$61,513,127
PE	1.77	25.0	$46,901	$970,865
QC	1.67	30.7	$37,424	$53,626,065
SK	2.11	32.6	$41,145	$6,519,459

We investigate the associations between immigrant status and infection using Poisson regression models with a robust sandwich estimator to produce relative risk estimates and examined time to death from first test using Kaplan-Meier survival curves.

RESULT(S): Of 2,000,756 individuals included in this study, 650 were co-infected, 57,913 were HCV mono-infected, 41,714 were HBV mono-infected, and 1,900,479 were tested and found to be non-infected. Immigrants overall were more likely to be HBV mono-infected (aRR 4.7 [95% CI: 4.6, 4.8]) and co-infected (aRR 1.7 [95% CI: 1.4, 2.0]) as compared to long term residents, but were less likely to be HCV mono-infected (aRR 0.7 [95% CI: 0.6, 0.8]). Similar trends were observed when looking at immigrants born in HBV endemic countries, albeit with a greater magnitude. Those from HCV endemic countries were more likely to be HBV mono-infected (aRR 1.9 [95% CI: 1.8, 9.2]), HCV mono-infected (aRR 1.4 [95% CI: 1.3, 1.5]), and co-infected (aRR 1.9 [95% CI: 1.3, 2.7]), as compared to long term residents.

CONCLUSION(S): Immigrants are an at-risk group for HBV/HCV co-infection and should be given special consideration when it comes to screening and surveillance efforts.

A review of public reimbursement criteria for pan-genotypic HCV DAAs in Canada

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BACKGROUND: Pan-genotypic direct-acting antivirals (DAAs) offer the opportunity to broadly treat HCV patients to ultimately eliminate the disease. However, despite the potential of these DAAs to reduce pre-treatment testing (i.e. genotyping, baseline viral load, baseline resistance-associated variants) and drive quicker access to care while reducing the risk of patients being lost to follow-up, Canada significantly lags in progress toward eliminating HCV by the WHO target of 2030.

PURPOSE: The aim of this qualitative review is to identify differences across Canadian publicly-funded drug programs' reimbursement criteria for pan-genotypic HCV DAAs to find opportunities to simplify the journey for HCV diagnosis and treatment for patients and physicians.

METHOD: Reimbursement criteria for pan-genotypic HCV DAAs (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) were retrieved from provincial, territorial, and federal drug programs. Comparisons between programs included (1) restrictions on prescribers, (2) genotype testing, (3) HCV RNA testing, and (4) fibrosis score reporting requirements.

RESULT(S): All public programs had at least one pan-genotypic HCV DAA reimbursed, with most programs funding both treatments. Only Quebec and the Non-Insured Health Benefits (NIHB) program had no prescriber restrictions, while Alberta offered case-by-case exemptions for patients living in geographic areas without access to hepatologists, gastroenterologists, or infectious disease specialists.

Despite evidence of efficacy across genotypes, only Alberta and Quebec had optional or no requirement of genotype testing. Alberta and Quebec were also the only jurisdictions with optional fibrosis score reporting.

Most programs only require one quantitative HCV RNA test to be completed within the past 6 months; with British Columbia, Yukon, and NIHB requiring the test to have occurred within the past 12 months. Ontario is the only program which requires two RNA tests, with the test occurring at least 6 months apart, and one test occurring within the last 6 months prior to initiation of treatment. RNA testing is optional in Quebec for chronic HCV.

CONCLUSION(S): Pre-treatment testing requirements are not identical across the public drug programs in Canada. Compared to simplified diagnostic pathways observed in Alberta and Quebec, the pre-treatment laboratory testing requirements in most Canadian jurisdictions may create unnecessary administrative barriers that increase the likelihood of losing the most vulnerable patients to follow-up.

Pilot peer-led hepatitis C screening leads to high testing uptake and rapid treatment initiation in a women's residential recovery facility

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BACKGROUND: Integrated community-based centers which offer treatment services for hepatitis C have been shown to increase access to care through incentivized education programs, mental health support, peer or harm reduction staff, and outreach. Importantly, in 2015, the Toronto Community Hepatitis C Program published a study which demonstrated that improvements in non-HCV outcomes also occur as a result of engagement in HCV services. Despite these successes, treatment initiation in community continues to be challenging among difficult-to-reach populations in smaller urban centers in Ontario where funding for HCV care is limited. Peer-led approaches to engaging individuals has been shown to be effective in community and facility settings, however women's-specific HCV peer-led programming is not well described in Ontario.

PURPOSE: Over a six month period, we evaluated a peer-led approach to engaging women in HCV care who have experienced violence, and struggle with complex trauma and substance use. In this residential addictions treatment facility in Ontario, women are engaged in on-site trauma-informed addictions recovery programming for approximately one-month before transiting to community.

METHODS: On day 3–5 of each program cycle, a peer-leader with lived experience co-facilitated a brief hepatitis C education event with specific emphasis on testing modalities, treatment access and eligibility, and cure rates. Immediately following, women were offered point-of-care (POC) antibody testing, and if this test was positive were then offered viral nucleic acid testing by dried blood spot (DBS). For those who were HCV RNA positive, a community phlebotomist attended the facility to complete required pre-treatment blood work, and a healthcare provider completed an HCV intake. Outcomes during the pilot phase include: testing uptake, antibody positivity rates, and time to treatment.

RESULT(S): Each month 17–19 women initiated the recovery program, with a 30%–40% drop-out rate. Over six, one month cycles, 98.7% of women who attended the education session approached the team for POC testing. Anti-HCV antibody positivity was 14.1% (total tested n = 78), with a 63.6% RNA positivity rate. All individuals who were eligible for HCV treatment initiated before discharge from the recovery program (treatment initiation maximum = 27 days post-RNA testing). Those who were not yet eligible for treatment, i.e. known acute infection or pregnant, continue to be followed by the HCV team following discharge.

CONCLUSION(S): Our data demonstrate that a women's peer-led test and treat model leads to very high HCV POC testing uptake in a residential addictions recovery setting. As a result of the immediate access to nucleic acid testing by DBS, subsequent HCV RNA testing uptake was 100%. Most importantly, all women who were RNA positive and eligible for treatment initiated therapy before being discharged from the recovery centre. Thus, our pilot shows that residential recovery programs may be an opportune environment to engage women with complex trauma and multiple mental health comorbidities in HCV testing and treatment.

Disparities in health utilities among hepatitis C patients receiving care in different settings

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BACKGROUND: Health utility is a preference-based global measure of health-related quality of life that can be used to quantify disease burden and conduct cost-utility analysis. Utilities are anchored at 0 (dead) and 1 (perfect health).

Although chronic hepatitis C virus (HCV) infection disproportionately affects marginalized individuals, most utility studies are conducted in

hospital settings which may not reflect the population living with HCV.

PURPOSE: To compare health utilities in two populations of HCV patients: patients receiving HCV care at academic hospital-based clinics, and patients receiving HCV care through a community-based HCV program.

METHODS: We recruited patients from 3 hospital-based clinics at the University Health Network (UHN) and 3 sites of the Toronto Community Hep C Program (TCHCP) in Toronto, Canada.

TCHCP is a community-based program that provides HCV treatment, support, and education to marginalized patients who have difficulty accessing mainstream healthcare due to barriers such as low income, substance use, and mental health issues.

We elicited EQ5D-3L utilities from all patients and collected sociodemographic and clinical information.

We used the Wilcoxon rank-sum test to compare utilities between community and hospital patients. An initial regression model examined whether differences in utility between settings remained after adjusting for age, sex, liver disease severity, and Charlson Comorbidity Index (CCI). A second model examined whether socioeconomic factors accounted for any differences found.

RESULT(S): We recruited 211 eligible patients (UHN: 113; TCHCP: 98). Hospital patients were older (mean age: 57 vs. 51) and more likely to be female (46% vs. 32%) and cirrhotic (32% vs. 22%). Community patients had more comorbidity (mean CCI: 1.3 vs. 1.1), unemployment (87% vs. 61%), history of injection drug use (88% vs. 48%), and history of mental health problem(s) (79% vs. 51%).

Unadjusted mean ± standard error utilities were substantially lower in community patients (community: 0.722 ± 0.209; hospital: 0.806 ± 0.195; p = 0.0002) (Table 1).

Multivariable regression showed that this difference between settings persisted after adjusting for age, sex, liver disease severity, and CCI (community coefficient = –0.075, p = 0.018) (Table 1).

The second regression model demonstrated that much of the difference attributed to the community setting could be explained by unemployment (coefficient = –0.092, p = 0.007) and a history of mental health problem(s) (coefficient = –0.106, p = 0.001) (Table 1).

Table 1. EQ5D-3L health utilities in chronic hepatitis patients and results of regression analyses

Unadjusted Utilities	**Estimate**	**Standard error**	**p-value**†
All patients			0.0002*
Hospital setting (n = 113)	0.806	0.195	
Community setting (n = 98)	0.722	0.209	
No cirrhosis			0.0001*
Hospital setting (n = 77)	0.835	0.157	
Community setting (n = 76)	0.732	0.200	
Compensated cirrhosis			0.1901
Hospital setting (n = 36)	0.744	0.250	
Community setting (n = 22)	0.686	0.238	
Regression Model 1	**Estimate**	**Standard error**	**p-value**
Age	0.000	0.001	0.780
Sex (female)	–0.005	0.029	0.876
Liver disease severity: compensated cirrhosis	–0.066	0.032	0.040*
Charlson Comorbidity index			
1	–0.072	0.038	0.062
2	–0.058	0.047	0.224
3+	–0.110	0.055	0.048*
Setting: community	–0.075	0.031	0.018*
Regression Model 2	**Estimate**	**Standard error**	**p-value**
Age	0.000	0.001	0.735
Sex (female)	–0.011	0.028	0.685
Liver disease severity: compensated cirrhosis	–0.051	0.031	0.094
Charlson Comorbidity index			
1	–0.046	0.038	0.226
2	–0.046	0.045	0.301
3+	–0.090	0.053	0.091

Unadjusted Utilities	Estimate	Standard error	p-value†
Education: less than high school	−0.011	0.031	0.723
Unemployed	−0.092	0.034	0.007*
History of injection drug use	−0.004	0.032	0.907
History of mental health problem(s)	−0.106	0.032	0.001*
Setting: community	−0.024	0.032	0.450

†*Wilcoxon rank-sum test*

CONCLUSION(S): HCV patients receiving care in the community have lower health utilities than those who attend hospital clinics. This disparity is associated with socioeconomic differences between patients who attend these settings—particularly, differences in employment and mental health history.

Cost-utility analyses informed by hospital-based utility studies may over- or underestimate the benefits of HCV screening and antiviral therapy. Longitudinal research on the impacts of antiviral therapy on utilities in marginalized populations is needed, as well as research on the costs and utilities associated with providing mental health and employment services alongside antiviral therapy in the community.

Health services impact analysis of simplifying HCV diagnosis and treatment decision in Canada

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BACKGROUND: Pan-genotypic direct-acting antivirals (DAAs) offer the opportunity to broadly treat HCV patients to ultimately eliminate the disease. However, despite the potential of these DAAs to reduce pre-treatment testing Canada significantly lags in progress toward eliminating HCV by the WHO target of 2030. While the benefits of simplifying the pathway to treatment have been acknowledged, including the potential reduction in patients lost to follow-up, the short-term financial benefits are unknown.

PURPOSE: The aim of this health services impact analysis is to quantify the financial savings associated with simplifying provincial pre-treatment funding criteria requirements for pan-genotypic HCV DAAs.

METHODS: Real-world claims data for pan-genotypic HCV DAAs (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) were retrieved from the IQVIA PharmaStat database for January 2018 through June 2019 to estimate the total number of HCV patients treated. Provincial, territorial, and federal drug program reimbursement criteria were gathered from publicly-available formularies and reviewed to identify the number of pre-treatment testing requirements. Two scenarios were compared to estimate potential savings: (1) pre-treatment testing costs as defined by current reimbursement criteria and (2) pre-treatment testing costs assuming provincial adoption of a simplified treatment pathway. Sensitivity scenarios were evaluated comparing a simplified treatment pathway requiring only one mandatory RNA test and an alternative scenario where quantitative RNA testing is optional.

RESULT(S): Over the evaluation period, public drug plans had the opportunity to save approximately $2.3-million on laboratory testing and physician consultations associated with genotype testing (and a second RNA test in Ontario) of patients who were ultimately prescribed a pan-genotypic DAA. In a scenario where both RNA testing and genotype testing were made optional, a savings of $4.4-million is estimated.

CONCLUSION(S): Pre-treatment testing requirements are not identical across the public drug programs in Canada. By simplifying the pre-treatment testing requirements and removing potentially unnecessary administrative barriers, public drug programs have an opportunity to save financial resources in the short-term, while reducing the long-term risk of patients being lost to follow-up.

Hepatitis C (HCV) re-engagement strategy after loss to follow-up

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BACKGROUND: Prior to 2015, HCV treatment was interferon-based. Many marginalized patients were unable or unwilling to take the treatment due to the side effects. After the introduction of direct acting antiviral (DAA) therapy with minimal side effects, there were restrictions on fibrosis level for reimbursement. Thus, there were many people who could not access treatment and who often disengaged from HCV care. All DAA reimbursement criteria were subsequently removed in Alberta in April 2019.

PURPOSE: Provide access to HCV care for people who had previously engaged at the CUPS Liver Clinic, but who had been unable or unwilling to pursue treatment at that time and who had not followed up with the clinic.

METHODS: CUPS is an inner-city non-profit organization which helps people facing proverty build resilient lives, offering medical care along with multi-faceted help with social determinants of health. A list of 424 clients lost from the cascade of care between 2007-2018 had previously been compiled. We obtained funding from Gilead Sciences for a summer student for 80 hours in the summer of 2019 to reconnect with these people via telephone calls, electronic medical record searches, and calls to other providers in order to re-engage them in HCV care. This was done under the supervision and assistance of the clinic nurse.

RESULT(S): Due to time constraints, contact attempts were only made for 347 patients (82% of the list). Of these, 46 (11%) were deceased. For 2013 alone, thirteen people (33 % of the list for that year) had died. The cause of death was not easily ascertained from electronic medical records. Ninety people (21%) had already been treated for HCV. We spoke with 55 people (13%) and voicemails were left for another 58 (14%). Twenty-three (42 % of those who were reached) were interested in re-engagement. People often told the student that they were unaware of newer drug treatments and indicated that they were grateful to be contacted. We were unable to contact 170 people (40%). We will reach out to the remaining 77 people in the future.

CONCLUSION(S): Telephoning patients who had disengaged from the cascade of care allowed us to re-engage 23 patients. We found that 21 % of people had already accessed HCV treatment in the interim. People were grateful to have been contacted. We plan to attempt to contact the remainder of the people on the list and to continue to track the impact of this simple intervention to offer access to the new DAA therapies.

The rate of death in this cohort far exceeds the expected rate. This underscores the importance of addressing other aspects of health, rather than merely HCV, in this marginalized population.

Building capacity in hepatitis C management: Progress and outcomes from the ECHO Ontario liver program

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BACKGROUND: Despite effective, well-tolerated treatment, rates of diagnosis and treatment for chronic hepatitis C virus (HCV) infection remain low in Ontario. The cascade of care for a patient from initial testing to diagnosis and treatment is complex and at each step along the way, individuals drop off. Approaches to improve the cascade of care by involving primary care providers are needed. The ECHO model provides an ideal platform to improve HCV management in the province of Ontario.

The **E**xtension for **C**ommunity **H**ealthcare **O**utcomes Model™ is a telementoring education program that runs weekly sessions, connecting providers from rural and underserved areas to an interprofessional specialist team. Each session includes a short didactic lecture and a case presentation, followed by a structured case discussion and interprofessional management recommendations.

ECHO Ontario Hepatitis C ('ECHO') launched in January 2017 and expanded to ECHO Liver in February 2018. The goal of ECHO was to disseminate best practices in hepatology appropriate for primary care and to improve providers' knowledge and self-efficacy.

PURPOSE: This study aims to evaluate the impact of ECHO on providers' self-efficacy, knowledge, and practice in Ontario.

METHODS: We conducted a mixed methods program evaluation with health care providers who attended ECHO sessions from January 2017 to November 2019. Quantitative assessment included pre-post questionnaires on self-efficacy and knowledge. Qualitative assessment included semi-structured phone interviews with providers regarding their experience and impact of ECHO on their practice.

Descriptive statistics were calculated for baseline variables and provider characteristics. Paired sample t-tests were used to analyze differences pre-post ECHO. All interviews were recorded, transcribed, and analyzed using thematic content analysis.

RESULT(S): Between January 2017 to November 2019, 111 ECHO sessions have been provided and 133 cases presented. Of 192 providers who attended ≥1 session of ECHO, 128 (66.7%) completed the Pre-ECHO questionnaire, and 65 (50.7%) completed the Post-ECHO questionnaire. 37 (56.9%) were physicians 20 (30.8%) nursing professionals, and 8 (12.3%) other allied health.

All 10 items on providers' assessment of self-efficacy demonstrated a statistically significant increase, where the total mean self-efficacy score increased from 3.3 (SD 1.1) pre-ECHO to 5.0 (SD 1.1) post-ECHO (effect size = 1.7, $p < 0.0001$). Of the 9 knowledge questions, there was no significant change pre-post ECHO, with the mean score pre-ECHO = 8.1 (SD 1.9) and post-ECHO = 8.4 (SD 2.0).

Twenty-five interviews were conducted. Thematic analyses revealed that providers valued their time participating in ECHO. Many described ECHO as an enriching experience, not only to fill a knowledge gap on HCV management but also to better understand the important public health measures of screening birth cohorts. In terms of impact on patient care, several providers described how they were now treating patients with HCV whereas they would have referred their patient before.

CONCLUSION(S): ECHO increased capacity for HCV management in Ontario. These results demonstrated that ECHO increased provider self-efficacy and impacted practice behaviour. Changes in knowledge may not have been captured accurately due to high pre-ECHO test scores. Future research will aim to link knowledge with provincial healthcare administrative databases to better understand the implementation barriers along the HCV cascade of care.

Examining patient complexity in ECHO: Results from a hepatitis C telementoring education program

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BACKGROUND: Hepatitis C patients are complex, often presenting with comorbid addictions and medical issues. Management of these patients can be complicated due to poor adherence to medications, limited access to treatment, and lack of education in patients and their health care providers regarding care.

Education remains an effective solution to combat these difficulties in hepatitis C management. One such education solution is Project **E**xtension for **C**ommunity **H**ealthcare **O**utcomes, a telehealth model aimed at increasing access and building capacity within primary care. ECHO Ontario Hepatitis C ('ECHO') launched in January 2017. Our program connects an interprofessional group of specialists to providers across the province of Ontario via weekly teleconference sessions. Each session consists of a didactic lecture and a patient case presented by a provider from the community, followed by a guided discussion and recommendations for management.

PURPOSE: The aim of this study is to characterize and discuss the complexity of patient cases and recommendations that were presented during weekly ECHO sessions.

METHODS: We conducted a retrospective descriptive study using administrative patient health data. Data were extracted from ECHO patient case presentation forms and recommendations forms. The patient case presentation form was adapted from The ECHO Institute version and is separate from a patient's chart; here, providers extract information on their patient's relevant health history as well as data from labs, investigations, and medications. The recommendation form captures all recommendations on the management of this patient broken down into two broad sections: diagnoses and management and recommendations. Descriptive statistics were calculated for each patient and provider outcome variable and thematic analysis on content.

RESULT(S): 133 patients were presented from January 2017 to August 2019 by 56 individual providers. 67 (50%) of patients were male, 52 (39%) female, 1 (1%) trans female and 13 (10%) unknown. The majority of patients were diagnosed with either genotype 1 (45%) or genotype 3 (23%). 54 (41%) of patients presented were baby boomers and 102 (69%) had a comorbid diagnosis of addiction disorder.

The majority of patient cases (66%) were presented by physicians. Of the reasons why providers presented, queries were mainly about management. Questions about diagnoses, drug therapy, and system navigation were less common.

Based on the cases presented, recommendations were given by the community of providers participating and hepatology specialists at the hub. For the majority of cases, further investigations were recommended to help clarify the patient diagnosis, serology, or status. While most recommendations made supported the provider to manage the patient in their own clinic, 4% of patient cases were for a referral to a specialist.

CONCLUSION(S): This study characterized the diagnoses, comorbidities, and medical histories of patients, as well as the demographics of the presenting provider. The patients presented at ECHO Ontario Hepatitis C are complex and representative of those managed in primary care clinics in the community. Future research aims to focus on linking the recommendations provided with provincial healthcare administrative databases and better understanding the barriers to implementation along the cascade of care.

The Canadian network on hepatitis C virtual cascade of care cohort (VCCC) feasibility study – Saskatchewan component

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BACKGROUND: Hepatitis C virus (HCV) is associated with considerable morbidity, mortality and health-related costs. In addition, modeled estimates of HCV prevalence shows about a 3-fold higher prevalence among Indigenous populations compared with non-Indigenous Canadians.A majority of HCV disease burden in Canada is attributable to injection drug use (IDU) with 94% of seropositive individuals self-reporting IDU as a risk factor since reporting began in Saskatchewan. Treatment scale-up presents a promising avenue to reduce prevalence among people who inject drugs (PWID) but requires improved diagnosis and linkage to care.

PURPOSE: This Virtual Cascade of Care Cohort (VCCC) study will document and analyze the HCV cascade of care among current or former PWID to inform on the factors linking harm reduction, primary care, treatment, and reinfection. The goal of the SK component, with enhanced focus on Indigenous participants, is to provide insight towards the reduction of the public health burden of HCV in Indigenous communities in Canada. We aim to identify ways to predict engagement and empowerment in Indigenous people with drug use experience and the critical elements to make health care more responsive to them by including a health system transformation lens in the analysis.

METHODS: The study is a multi-centre observational prospective cohort feasibility study with the Saskatchewan sites located in both rural and urban communities. It combines in-person data collection at baseline with virtual prospective follow-up through health administrative databases. The SK component is peer-designed and -led with Indigenous CBPR principles applied through implementation and knowledge synthesis. Unique to its protocol is an additional qualitative interview to better understand the nuances involved in the barriers and enablers to care. The SK protocol also includes dried blood spot (DBS) collection for HCV RNA detection and optional testing for HIV, syphilis and hepatitis B to promote diagnosis and linkage to care.

RESULT(S): Periodic linkages to health administrative data are expected to inform on multiple

outcomes including HCV testing and diagnosis, physician visits, hospitalizations, treatment access and interruptions, liver-related and other comorbidities and cause of death over the next five years. Baseline data collection (qualitative interview, questionnaire, and DBS) will provide information on barriers and facilitators to care not available in health administrative databases and enable preliminary detection of HCV and other diseases outside a clinical setting.

CONCLUSION(S): The results of this feasibility study will serve to fine-tune the protocol, collate preliminary data, and provide an Indigenous-specific lens to the research. This will guide the planning and implementation of a recently CIHR-funded, peer-reviewed large-scale investigation with expansion throughout Canada. This study will also help to provide unique insights into Saskatchewan-specific HCV-related health system utilization and augment Saskatchewan's data mapping capabilities. Recommendations will be made regarding the need for, design, and implementation of tailored services and policies within a national HCV strategy to better meet the needs of PWID and especially Indigenous people with drug use experience.

SESSION #1: VIRAL HEPATITIS

Achieving functional cure of HBV and HBV/ HDV co-infection with REP 2139: Completed follow-up in the REP 401 and REP 301-LTF studies

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BACKGROUND: Nucleic acid polymers (NAPs) inhibit the assembly and secretion of HBV subviral particles and interact with small and large forms of the hepatitis delta antigen. The REP 401 study (NCT02565719) examined the safety and efficacy of tenofovir disoproxil fumarate (TDF), pegylated interferon alfa-2a (pegIFN) and two NAPs (REP 2139 and REP 2165) in HbeAg negative chronic HBV infection. The REP 301-LTF study (NCT02876419) is an ongoing long-term follow-up study of previous treatment of HbeAg negative chronic HBV/ HDV co-infection with pegIFN and REP 2139 (REP 301: NCT02233075).

PURPOSE: To evaluate the long-term stability of control of HBV and HDV infection and normalization of liver function persisting after finite, NAP-based combination therapy with pegIFN.

METHOD: In REP 401 study, 40 participants were treated with 48 weeks of triple combination therapy (TDF + pegIFN + NAPs), 20 of whom were crossed over to this therapy after demonstrating poor HbsAg response to 24 weeks of TDF + pegIFN. In the REP 301 study, 12 participants received 15 weeks of REP 2139, followed by 15 weeks of REP 2139 + pegIFN, followed by 33 weeks of pegIFN. After removal of all therapy, 48 weeks of follow-up have been completed in the REP 401 study and 3.5 years of follow-up have been completed in the REP 301-LTF study.

RESULT(S): The bioequivalence of REP 2139 and REP 2165 were demonstrated in the REP 401 study. On therapy effects of NAP-based combination therapy in the REP 301 and REP 401 studies have been previously described and include high rates of HbsAg clearance and loss (<0.05 IU/mL), HbsAg seroconversion (up to 255,055 mIU/mL), clearance of HBV DNA (in mono-infected participants) and clearance of HBV RNA, HbcrAg and HDV RNA (in co-infected participants) and otherwise asymptomatic transaminase flares having no impact on liver function throughout (normal bilirubin, INR and albumin). Complete HBV RNA and HbcrAg results in the REP 401 study are still pending.

In the REP 401 study, 36 participants completed therapy and at least 24 weeks of follow-up, with 32 of these completing 48 weeks of follow-up. In these participants, 79% had virologic control (HBV DNA ≤2000 IU/mL, normal ALT), with 39% additionally with functional cure (HBV DNA target not detected, HbsAg <LLOQ, normal ALT) with HbsAg seroconversion. Liver function remains normal in 89% of participants.

In the REP 301-LTF study,all participants have completed 3.5 years of follow-up. In these participants, 7/11 remain HDV RNA target not detected, 4 with functional cure of HBV with HbsAg seroconversion and 3 with virologic control of HBV. Liver function remains normal in 8/11 participants.

CONCLUSION(S): NAP-based combination therapy achieves high rates of HbsAg clearance and seroconversion (and HDV RNA clearance in co-infection) during therapy, leading to high rates of virologic control and functional cure of HBV infection with sustained HbsAg seroconversion, sustained undetectability of HDV RNA and normalization of liver function stable during prolonged follow-up.

Micro-elimination of hepatitis C in a population of opioid substitution clients – successful task-shifting of testing and treatment to a community-based nurse/ pharmacist dyad

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BACKGROUND: Saskatchewan remains in the midst of a unique hepatitis C (HCV) epidemic driven by high rates of injection drug use in marginalized populations. The Infectious Diseases Clinic (ID Clinic) at Regina General Hospital serves as a tertiary referral center for southern Saskatchewan. Given a lack of physician capacity, the ID Clinic has successfully task-shifted HCV care to nurse-led protocolized models in a variety of community settings. Significant additional treatment capacity is needed to eliminate HCV in Saskatchewan by 2030.

PURPOSE: We postulated that task-shifting the management of HCV therapy to a trained community pharmacist in collaboration with a dedicated nurse clinician, all under protocol with remote physician supervision, would be both effective and safe. To determine this, we created a dedicated HCV nurse/ pharmacist 'dyad' in the setting of a community pharmacy serving a moderate number of opioid substitution therapy (OST) clients and sought to systematically micro-eliminate HCV from this population using this model.

METHOD: We identified a long-established community pharmacy in inner-city Regina serving an OST population of roughly 100 clients. Informed consent was obtained by the pharmacist for patients receiving OST to allow advance access to electronic health records to determine testing requirements and avoid unnecessary testing for persons with recent results. All persons with no record of blood-borne infection testing in the previous year were targeted for updated testing. Individuals attending the pharmacy not on OST who wished testing and treatment were also engaged. A trained nurse-clinician in collaboration with the community pharmacy provided consistent on-site presence and facilitated all aspects of the HCV cascade of care. Assessment of liver fibrosis was carried out through a combination of non-invasive markers (APRI and FIB-4), nursing assessment, and Fibroscan. All persons were discussed with the physician prior to initiating HCV therapy. On-treatment monitoring was provided by the pharmacist.

RESULT(S): Over the initial 7-month period of the pilot project from May 1/19 to November 17/19, a total of 128 persons were engaged in care by the nurse/ pharmacist dyad. 67 were receiving opioid substitution therapy. 69/128 (53.9%) were female, 83/128 (64.5%) were of Indigenous ethnicity, and the mean age was 40.5 years. 42/128 (32.8%) were identified with detectable HCV RNA. One individual was newly diagnosed with HIV. 23/42 (54.8%) of persons with HCV viremia have been initiated on HCV therapy to date. 22 of these received a pan-genotypic regimen, 4 have completed therapy and are awaiting SVR-12, and 19 remain on therapy. No adverse events have occurred for persons on therapy. Updated HCV cascade and treatment outcome data will be presented at the meeting.

CONCLUSION(S): Traditionally difficult-to-engage persons can be successfully tested and treated for HCV by a trained nurse/pharmacist dyad working under protocol in the community with remote physician supervision. Similar HCV micro-elimination approaches delivered by qualified non-physician health care providers can be replicated in similar care settings and will be important for both Saskatchewan and Canada to achieve WHO HCV elimination targets by 2030.

Role of pre- and post-treatment transient elastography measurements in predicting hepatocellular carcinoma (HCC) among hepatitis C patients treated with direct acting antivirals (DAA)

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BACKGROUND: Current guidelines recommend regular lifelong HCC screening in HCV patients with advanced fibrosis or cirrhosis. However, no study has evaluated the impact of early changes in liver stiffness measurement (LSM) by transient elastography (TE), which may reflect DAA-induced improvement in liver inflammation, on subsequent HCC risk after successful eradication of HCV.

PURPOSE: To evaluate the association between LSM measured by TE pre- and early post-DAA treatment, and HCC occurrence.

METHOD: All electronic medical records of HCV patients treated with DAA at the University of Calgary Liver Unit (UCLU) between January 2014 and December 2017 were reviewed (n = 1,161) to identify those patients who developed HCC after completing treatment. Patients were excluded if they were treated for HCV while having HCC, or developed HCC during or immediately after (within 3 months) therapy. Baseline LSM was defined as TE within 6 months before starting DAA therapy, and post-treatment LSM was defined as TE within 36 months post-DAA therapy. We used Cox regression analysis to evaluate the association between pre- and post-HCV treatment TE measurements and HCC occurrence. We adjusted for age, sex, HCV genotype, and Charlson comorbidity index in our models.

RESULT(S): We identified 524 patients with a valid TE assessment obtained both at pre- and post-DAA treatment. In our cohort, median TE pre-DAA treatment was 12.1 kPa (IQR: 8.3–21.1 kPa), while post-DAA TE was 8.4 kPa (IQR: 5.8–14.1 kPa), $p < 0.001$. Therefore, the majority of our cohort (65.1%, n = 341) had advanced fibrosis or cirrhosis (TE >9.5 kPa) pre-DAA treatment, compared to 43.5% (n = 228) post-treatment. Within a median follow-up of 26 months (IQR: 14–36) 18 patients (3.4%) developed HCC. In our cohort, sustained viral response (SVR) was 98.6% and all HCC patients had achieved SVR. Patients who developed HCC were similar to those not developing HCC according to sex (male 72.2% vs. 61.0%), age (median: 61 vs. 59 year), HCV genotype (1a: 38.9% vs. 49.4%), and having >2 comorbidities (66.7% vs. 58.3%), respectively; $p > 0.05$ for all comparisons. However, patients who developed HCC had a higher median TE pre-treatment (29.2 vs. 12.0 kPa, $p < 0.001$) and post- treatment (15.8 vs. 8.1 kPa, $p < 0.001$), respectively. All patients who developed HCC had TE >9.5 kPa at pre-treatment, while one (5.6%) patient had a post-treatment TE <9.5 kPa. In our adjusted Cox regression models, pre-treatment TE >9.5 kPa accurately predicted HCC (all HCC patients had pre-treatment TE >9.5 kPa), while post-treatment TE of >9.5kPa was a strong predictor for HCC (HR: 18.70, 2.46–141.92).

CONCLUSION(S): In our large DAA-treated HCV cohort, pre- and post-treatment TE indicating advanced fibrosis or cirrhosis were strong predictors for HCC development post-treatment. Future studies should examine utility and cost effectiveness of measuring LSM post-HCV therapy on HCC occurrence.

Addition of peginterferon Alfa-2a increases HbsAg decline in HbeAg-negative chronic hepatitis B patients treated with long-term nucleos(t)ide analogue therapy: Results from a multicenter randomized controlled trial (PAS study)

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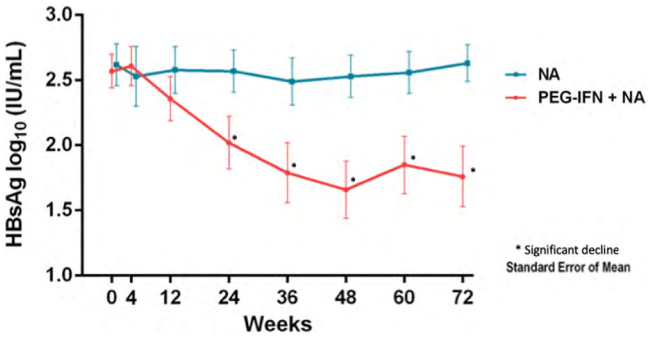
BACKGROUND: Pegylated-interferon (PEG-IFN) treatment has been associated with higher hepatitis B

surface antigen (HbsAg) decline rates in chronic hepatitis B (CHB). It is essential to assess this decline as PEG-IFN add-on to NA is increasingly used in new regimens aiming for a functional cure. In addition, PEG-IFN add-on therapy may help to reach HbsAg loss allowing to stop NA.

PURPOSE: We investigated in a randomized, controlled trial the dynamics of HbsAg in HbeAg-negative CHB patients on long-term NA therapy who received add-on PEG-IFN.

METHOD: In this investigator-initiated randomized controlled trial conducted in Europe and Canada, HbeAg-negative patients with compensated liver disease treated with NA therapy >12 months and had HBV DNA <200 IU/mL were enrolled. Patients were randomized 2:1 (baseline) to 48 weeks of add-on PEG-IFN alfa-2a (180 µg per week) or continued NA monotherapy with subsequent follow-up to week 72. The primary endpoint was HbsAg decline >1 log IU/mL at week 48 from baseline and HbsAg loss was a secondary endpoint.

RESULT(S): Of the 88 patients in the modified intention-to-treat analysis, 58 patients received PEG-IFN add-on, and 30 continued NA monotherapy. At baseline, the mean age was 48 years, 86% male, 66% Asian, and 25% Caucasian. Median baseline HbsAg level was 2.6 $\log_{10}$IU/mL. At week 48, 18 (31%) patients achieved HbsAg >1 $\log_{10}$decline in the add-on arm compared to none on NA monotherapy (P <0.0001) and HbsAg clearance was observed in 6 (10.3%) of patients who received PEG-IFN add-on therapy versus none of the NA monotherapy. Compared to NA monotherapy, PEG-IFN add-on resulted in significant HbsAg decline at week 48 (mean [SD]: -0.57 [1.1] vs. -0.05 [0.1] $\log_{10}$, p = 0.001; see Figure). PEG-IFN



was well-tolerated in the majority of patients. Severe adverse events were reported in four patients.

CONCLUSION(S): At week 48, the addition of PEG-IFN to long term NA is associated with substantial HbsAg decline and limited HbsAg clearance in HbeAg-negative CHB patients. Therefore, the future role of PEG-IFN add-on appears to be mainly in new regimens aiming for a functional cure of CHB.

Real-world drug resistance profile of hepatitis C patients who failed direct-acting antivirals – SHARED

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BACKGROUND: Hepatitis C patients (pts) who failed Direct-Acting Antivirals (DAA) often selected viruses with drug resistance-associated substitutions (RAS), which limits treatment options. High response rates from DAA therapy make it challenging to study HCV drug

resistance. SHARED, the Surveillance of Hepatitis C Antiviral Resistance, Epidemiology and Methodology, is an international consortium with the goal of better understanding and avoiding HCV drug resistance and transmission through the development, application, and sharing of HCV genomic data, methods, software and technologies.

PURPOSE: To characterize HCV resistance after unsuccessful DAA in real-world settings.

METHOD: HCV sequences and clinical data from >1900 DAA-failures were collected from Australia, France, Germany, Israel, Italy, Netherlands, Argentina, Portugal, Slovenia, Turkey, Israel, Luxembourg, Russia, Slovenia, Spain, Sweden. Variants within NS3, NS5A, and NS5B were examined for resistance-associated substitutions (RAS) at positions according to the 2018 EASL guideline.

RESULT(S): Of the 1543 patients who failed NS5A inhibitor (NS5AI)-containing regimens, 83% selected RAS following therapy. Notably, 63% of pts with RAS had intricate patterns with >2 NS5A RAS suggesting a high level of resistance.

In the 244 pts treated with a combination of NS5AI and protease inhibitor (PI), 63% had RAS in both drug-targets, and only 6% failed with no RAS. There was no difference in the frequencies of RAS selected between the first generation NS5AI+PI regimens versus glecaprevir/pibrentasvir after treatment failure.

The prevalence of NS5A-RAS was lower in genotype (GT) 1a (77%) but higher in GT2 (100%) and GT4 (99%). Each genotype/subtype had distinct RAS patterns, usually at positions 28, 30, 31, and 93. In general, GT2a virologic failures selected L31M while non-GT2 selected T24S+F28C; none of them harbored Y93H. In GT3, Y93H was most prevalent (61%) followed by mutations at position 62 (45%) and A30K/S (17%). Intriguingly. All GT3b/g harbored A30K+L31M mutations without Y93H.

Overall, the prevalence of an unfit sofosbuvir mutation, S282T, was low in GT1a (2%), GT1b (1%), GT2 (3%) and GT3 (1%), but high in GT4 (18%).

CONCLUSION(S): Drug resistance is complex and new RAS are emerging. SHARED provides an opportunity to study HCV drug resistance adequately.

Hepatitis C–positive organ transplantation to negative recipients at a multiorgan Canadian transplant centre: Ready for prime time

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BACKGROUND: Organ transplantation offers better survival for patients with end stage organ disease compared to no transplant. Hepatitis C virus (HCV) positive donor organ transplantation to negative recipients is a novel adopted strategy that may potentially increase the donor pool.

PURPOSE: The aim of this study is to evaluate our multiorgan transplant centre experience with transplanting HCV positive organs.

METHOD: This study was conducted at London Health Sciences Centre in London, Ontario, Canada. All transplants with HCV nucleic acid testing (NAT) positive and negative organs were included from 2018 to present. Our primary outcome was the rate of sustained virologic response at 12 weeks after the end of treatment (SVR12) in patients that developed viremia. Secondary outcomes were the rate of transmission of HCV in both NAT positive and negative recipients, treatment adverse events, and graft failure rate.

RESULT(S): A total of 27 organ transplantations with hepatitis C positive organs were performed including 19 kidneys (70.4%), 4 livers (14.8%), 2 kidney-pancreas (7.4%), 1 liver-kidney (3.7%), and 1 heart (3.7%). The mean age of recipients was 48 ± 12 years. 54% of them were male. NAT positive HCV organs were 20 (74%) of the organs used and viremia was transmitted in 90% of these patients while no transmission occurred in NAT negative HCV organs. HCV genotype was 1a in 76%, 1b in 6%, 2 in 6%, and 3 in 12%. The most common direct acting antiviral (DAA) used for treatment was Ledipasvir/Sofosbuvir in 13%, Velpatasvir/Sofosbuvir in 62%, and Glecaprevir/Pibrentasvir in 25 %. SVR12 was 100% in all patients that completed HCV therapy. Treatment was tolerated by all patients, there were no significant treatment adverse events, and there were no graft failures.

CONCLUSION(S): Using HCV positive organs is safe and may further expand the donor pool. In patients that have HCV transmission post-transplant DAAs are efficacious with no significant adverse events, intolerance, or graft failure.

Reducing the burden of hepatitis C–related complications through genomics-guided treatment optimization

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BACKGROUND: The World Health Organization has identified viral hepatitis as a public health threat, with an estimated 71 million people living with chronic hepatitis C infection globally. In 2015, approximately 400,000 deaths worldwide occurred due to complications of chronic hepatitis C infection. A new wave of highly effective drugs first introduced in 2011, collectively called direct acting antivirals (DAAs), promise the elimination of hepatitis C–related complications with reported cure rates over 95%, yet these rates may not adequately represent real-world patients with difficult-to-cure infections. Both clinical and genomic factors influence the likelihood of curing hepatitis C, but the role of genomic differences in predicting DAA-based treatment failure has not been thoroughly investigated.

PURPOSE: Discover and replicate genomic predictors of treatment failure for DAA-based regimens.

METHOD: We recruited patients treated with sofosbuvir-containing regimens from five Canadian sites and collected comprehensive clinical and genomic data. Logistic regression was used to uncover genomic predictors of sofosbuvir-based treatment failure. Approximately 700,000 variants across the genome were assessed, including variants in genes previously linked to treatment success (e.g., the interferon–λ gene, *IFNL4* – previously *IL28B*), genes playing important antiviral roles (e.g., *IL10RB* – a receptor component acting downstream of interferons) and genes involved in sofosbuvir biotransformation (e.g., *CES1* – required for its activation).

RESULT(S): 401 sofosbuvir-treated patients were recruited. Of the 360 patients who have completed therapy, 34 failed to eradicate the hepatitis C virus, representing a cure rate of 91% in our real-world cohort. We have replicated associations between *IFNL4* variants, including rs8099917 ($P = 0.0056$; OR = 2.53), rs12979860 ($P = 0.0101$; OR = 2.13) and rs74597329 ($P = 0.0217$; OR = 2.01). Furthermore, we have discovered novel associations with *CES1* rs2302719 ($P = 0.0271$; OR = 1.97) and *IL10RB* rs2284552 ($P = 0.0349$; OR = 1.89), which remain significant after adjusting for *IFNL4* rs8099917 (*CES1* rs2302719; $P = 0.022$; OR = 2.01 and *IL10RB* rs2284552; $P = 0.013$; OR = 2.17).

CONCLUSION(S): Although several variants in *IFNL4* have been shown to predispose patients to treatment failure in regimens without DAAs, their role in DAA-based regimens remains largely unexplored. Our work suggests that variation in *IFNL4*, *CES1* and *IL10RB* is relevant for sofosbuvir-treated patients. Overall, understanding how genomic differences contribute to sofosbuvir-based treatment failure could help identify patients at high risk for treatment failure prior to therapy initiation, leading to personalized treatment decisions and a reduced burden of hepatitis C-related complications.

Outcomes of hepatitis C treatment are similar in Canadian Indigenous people compared to non-Indigenous patients

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BACKGROUND: To achieve HCV elimination in Canada, it is essential to ensure that over-represented key populations can access care and treatments are effective. Indigenous people may less frequently access current HCV care pathways, and have been under-represented in clinical trials. Furthermore, there are scarce data on HCV treatment and care effectiveness in this population.

PURPOSE: We assessed real world effectiveness of direct-acting antivirals (DAAs) in Indigenous people.

METHOD: Prospective data in the Canadian Network Undertaking against Hepatitis C (CANUHC) database were analyzed. There were 322 self-identified Indigenous persons in the database, of whom SVR outcomes are available for 108. Paired non-Indigenous controls from each centre were randomly selected (n = 108). Age, sex, HCV genotype and viral load, elastography data, DAA type, and SVR outcomes were compared.

RESULT(S): Indigenous patients were significantly younger (47±13 vs 53±14, P <0.001) compared with controls. The indigenous group contained more females (53 of 108; 49%) than the control group (31/108 (29%), p <0.005). Genotype 1a was most common in both groups (52% in Indigenous and 48% in controls, P = 0.5), followed by genotype 3 (35% in Indigenous and 27% in controls, P = 0.2). Transient elastography scores were also similar: 10.5±9.6 kPa in Indigenous and 9.0±5.8 kPa in controls (p = 0.2). Sofosbuvir+velpatasvir (52% in both groups) and elbasvir+grazoprevir (25% in Indigenous and 26% in controls) were most commonly used. Other regimens included sofosbuvir+ledipasvir, sofosbuvir+daclatasvir and paritaprevir+ombitasvir+dasabuvir). The overall SVR rate was 96.3% in Indigenous and 99.1% in other populations (P = 0.18). The SVR rate for genotype 1a was 94.6% in Indigenous and 98.1% in controls; for genotype 3 was 97.4% in Indigenous and 98.1% in controls. There were 5 patients who did not achieve SVR; 2 were treated with sofosbuvir+ledipasvir, 1 with elbasvir+grazoprevir, 1 with sofosbuvir+velpatasvir and 1 with sofosbuvir+daclatasvir.

CONCLUSION(S): Indigenous patients with reported SVR were younger and more likely to be female. Importantly, DAA SVR rates were comparable to the non-indigenous control group. These real-world effectiveness data add to the limited global data on DAA effectiveness in Indigenous people, and suggests DAA-based HCV microelimination in Indigenous people is possible. Higher HCV treatment rates in the Indigenous female population requires further study.

Treatment differential in HCV treatment prescribers in British Columbia over time

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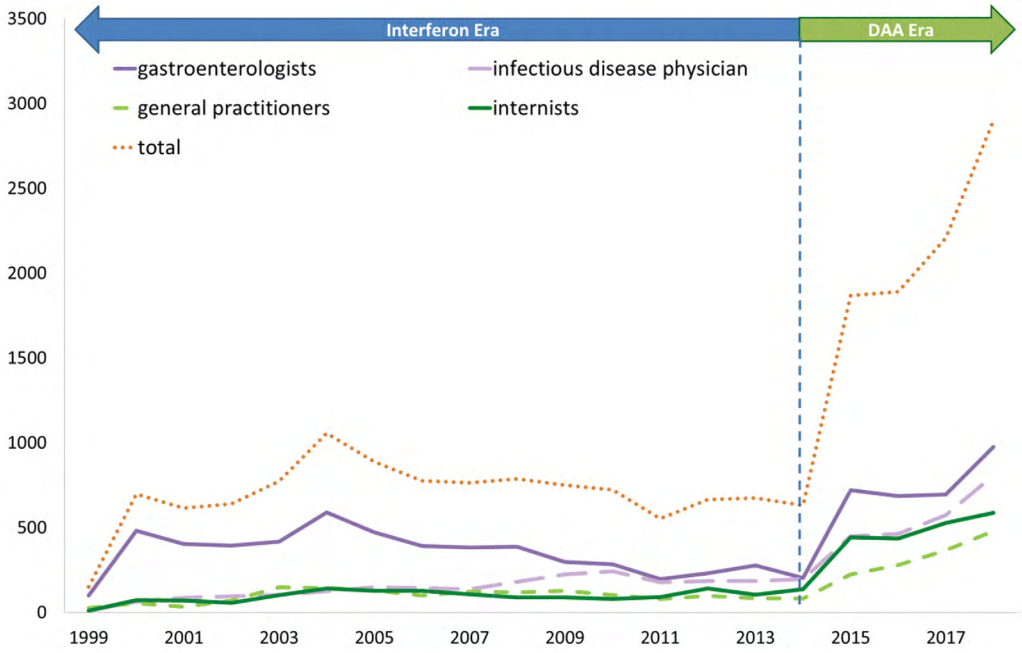
BACKGROUND: As of 2018, Approximately 53,441 people in British Columbia (BC) are infected with hepatitis C virus (HCV), which is a leading cause of liver disease. Direct acting antivirals (DAA) greatly simplify the treatment of HCV (through their ease of administration [oral dosing], improved cure-rates, reduced side-effects, and shorter treatment durations), and, in 2015, DAAs became publicly funded in BC. Before the advent of DAAs, HCV treatment was almost exclusively prescribed by gastroenterologists and infectious disease specialists (GIDS); however, generalists (general practitioners [GPs] or internal medicine physicians) are now able to prescribe DAAs.

PURPOSE: The scale up of generalist prescribers is proposed as an essential strategy to increase HCV treatment uptake. Monitoring HCV prescriber



types over time in BC may help reveal both gaps and successes in the healthcare system and identify areas to improve treatment access.

METHODS: The BC Hepatitis Testers Cohort (BC-HTC) includes all HCV cases in BC from 1990 to 2015, followed up to 2018. Physicians' specialties were obtained and summarized from PharmaNet dispensations, Medical Service Plan visits, and the Discharge Abstract Database. Patients (based on their first treatment regimen) were linked to physicians who initiated their HCV treatment. Physicians with multiple specialities were assigned the one with highest specialty (associated with subspecialization/fellowship) or the one most associated with HCV treatment.

RESULT(S): Between 2000–2018, 20,005 patients were dispensed HCV medications. The annual number of patients initiating treatment was relatively constant from 2000–2014, and increased dramatically from 630 patients in 2014 to 2,899 in 2018 (Figure 1). Compared to individuals receiving non-DAA treatments (n = 11,041), those receiving DAAs (n = 8,964) had higher proportions of generalist treatment (0.38 vs 0.28) and lower proportions of GIDS treatment (0.62 vs 0.72). There were differences in patient characteristics by prescriber specialty; more people who had ever injected drugs were prescribed DAA treatment by GPs than gastroenterologists (64% vs. 21%).

CONCLUSION(S): After introduction of DAAs, there was a marked increase in overall number of individuals receiving HCV treatment, as well as generalist initiated regimens. There are differences in distribution of clinical and social characteristics among patients treated for HCV, depending on the prescriber type. This suggests alignment and integration of services for people with multiple needs (i.e. addiction or mental health services) may be required to sustain increases in HCV treatment uptake. Further investigations are needed to improve service integration according to population group needs. To achieve HCV elimination in BC, further promotion of generalist-delivered DAA treatment will likely be required to enhance treatment access.

Characteristics of resistance-associated substitutions in "unusual" hepatitis C virus (HCV) subtypes

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BACKGROUND: HCV is highly variable; 8 genotypes and over 84 subtypes have been identified so far. Recently, "unusual" subtypes in patients from African and Asian origin have been associated with lower response rates to DAAs. This was ascribed to polymorphisms at relevant amino acid positions as compared to the most sensitive subtype in the same genotype.

PURPOSE: Using the international SHARED network, we aimed to assess the prevalence of post-treatment failure RASs and their patterns among unusual HCV subtypes, defined as GT1 non1a/b, GT2 non2a/b, GT3 non3a, GT-4 non4a/d, GT5, and GT6.

METHODS: We extracted data from the SHARED database of patients who did not achieve a sustained virological response on DAA therapy. Only patients who failed DAA strategies recommended by EASL guidelines were included. Genotype and subtypes were sequence-derived, and analyses grouped by HCV subtype. RASs were analysed at positions according to the 2018 EASL guidelines.

RESULT(S): We identified a 6% prevalence (74/1176) of unusual subtypes among patients who failed NS5A inhibitor-containing regimens, including: GT1g (n = 2), 1l (n = 5), GT2c (n = 8), 2q (n = 2), 2i/j (n = 1 each), GT3h (n = 7), 3b (n = 6), 3k (n = 2), GT4r (n = 13), 4v/4ns (n = 3 each), 4g/4o (n = 2 each), 4b/4f/4k/4n/4q/4t (n = 1 each), GT6q (n = 3), 6e/6h/6p/6r/6xe (n = 1 each). Patients were treated with SOF+LDV+/-RBV (n=18), SOF+DCV+/-RBA (n = 15), SOF+VEL+/-RBV (n = 13), GZR+EBR (n = 11), 2D/3D+/-RBV (n = 11, GLP+PIB (n = 5), or other regimens (n = 1). At failure, all patients harbored NS5A RASs regardless of their subtype, with a mean number of 3 NS5A RASs per sample. Interestingly, failures with GT6h/p/r/xe carried 5 to 6 NS5A polymorphisms possibly associated with reduced NS5A inhibitors susceptibility. All GT3b failing patients harbored the NS5A A30K+L31M+S62D/E combination. Additionally, in patients failing NS3 protease inhibitor-based therapy, combinations of NS3 RASs were detected in specific subtypes: R155Q/A156T/D168N/E and Y56H+D168V in two GT4g and one GT6q patients failing GZR/EBR, and A156F/D168V in a GT6q patient failing GLP+PIB. Two GT4r patients harbored S282T RASs in NS5B after failing a SOF-containing regimen.

CONCLUSION(S): Unusual subtypes may be over-represented among DAA failures. In-vitro characterization of RAS in these subtypes is needed.

Comparison of hepatitis C prenatal screening approaches between provinces: Seroprevalence and infection rates in universal vs risk-based screening

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BACKGROUND: Screening for hepatitis C virus (HCV) has focused on identifying those with risk factors for HCV acquisition. However, due to low diagnosis rates, consideration has been given to alternative approaches to screening such as birth cohort, and more recently prenatal screening in Australia and the US. At present, the Society of Obstetricians and Gynaecologists of Canada continues to recommend only risk-based screening for prenatal HCV testing. However, it has been demonstrated

in many countries that women do not disclose their risk factors, may be unaware of them, or had documented risk factors but were not tested. Furthermore, rates among women of childbearing age may be increasing as a result of the opioid crisis.

PURPOSE: Currently, no Canadian prenatal HCV seroprevalence data is available. However, in contrast to most Canadian provinces, Saskatchewan (SK) has been universally screening for anti-HCV antibodies among pregnant women and all such testing is centralized at the provincial laboratory, allowing for robust data collection to evaluate seroprevalence. By contrast, Ontario (ON) continues to utilize a risk-based approach. The objective of our study was to compare HCV positivity rate and viremia by age and year among pregnant women in SK and ON.

METHODS: Anonymous, linked, aggregate data was extracted from the Roy Romanow Provincial Laboratory in Saskatchewan from 2012–2018, and from Public Health Ontario Laboratories from 2010–2017. As a result of unique identification numbers, we were able to link persons who were anti-HCV positive to subsequent testing for HCV RNA in both provinces, and HCV core antigen in SK.

RESULT(S): Over the time periods listed, seroprevalence of HCV in SK among pregnant women was 1.85%. In ON, where risk-based screening is used, the overall anti-HCV positivity was 1.44%. The lowest prevalence of 0.94% occurred among those ages 15–20 in SK (n = 11,552) and 1% among those ages 31–35 in ON (n = 7,412); whereas the highest rates in SK were 2.0% among women ages 26–30 (n = 37,685), and 2.6% in ON ages 21–25 (n = 3,889). In order to differentiate exposure from infection, subsequent testing in SK utilizes HCV core antigen or HCV RNA, whereas only HCV RNA is used in ON. Among those who were antibody positive, subsequent testing occurred 89.9% of the time in SK, likely related to the introduction of HCV core antigen reflex testing; and confirmation of infection within the study period by HCV RNA or core antigen positivity was 49.0%. In comparison, subsequent testing uptake in ON was 56.1%, with a 56.8% RNA positivity rate.

CONCLUSION(S): The SK data represent the first universal prenatal HCV screening data from Canada and reveal a very high prevalence of HCV among pregnant women in SK. The observation that universal testing in SK yielded a higher positivity rate than focused risk-based screening in ON is striking, as universal testing usually identifies more positive individuals but at a much lower positivity rate. While these differences may partially reflect varying exposure risks between provinces, the data support consideration to adopt universal prenatal screening across Canada, as many women may be missed by using a risk-based approach. Knowing whether a woman is actively infected with HCV is essential to assess transmission and pediatric/maternal follow-up, with the potential for maternal cure prior to subsequent pregnancies.

Factors associated with on-demand HCV screening among Canadian provincial inmates

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BACKGROUND: Although 25% of people in Canadian prisons have been exposed to hepatitis C virus (HCV), a minority of provincial inmates undergo HCV screening via "on-demand" testing – the current standard of care in most Canadian provincial prisons. Understanding the factors associated with on-demand screening is essential in determining whether targeted efforts are necessary to screen those at highest risk of chronic HCV infection.

PURPOSE: We aimed to investigate factors associated with on-demand HCV screening among provincial inmates in a Quebec institution.

METHODS: From March to September 2019, a total of 330 male inmates (≥18 years) with sentences between 2–12 weeks were recruited from the largest provincial prison in Quebec (Établissement de Détention de Montréal). Participants completed a baseline questionnaire assessing sociodemographic and behavioural characteristics. Individuals who reported not being infected with HCV or not knowing their HCV status were able to request HCV screening during their incarceration. Univariate and multivariable logistic regression models

were used to identify factors associated with on-demand HCV screening. Variable selection was based on limited research exploring barriers and facilitators to HCV screening uptake among people in prison. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) are reported.

RESULT(S): Among the 329 participants with complete data, 151 (46%) reported not being infected with HCV and 131 (40%) not knowing their HCV status. Of these, 13 (9%) and 19 (15%) requested HCV screening, respectively. The majority of participants (median age 36) self-identified as heterosexual (97%), had less than a high school education (53%), and earned <$30,000 CDN/year (65%). Participants reported a median of 3.5 previous incarcerations; 22% reported having received a tattoo while incarcerated, whereas only 16% reported ever injecting drugs. Those requesting on-demand screening were more likely to have never been previously tested for HCV (aOR: 3.12; 95% CI: 1.33–7.63), view HCV screening as "very important" (aOR: 2.78; 95% CI: 1.27–6.38) and perceive themselves to be at "any risk" for HCV (aOR: 2.56; 95% CI: 1.02–7.39). However, inmates who reported concerns regarding HCV confidentiality were less likely to request screening (aOR: 0.22; 95% CI: 0.07–0.58).

CONCLUSION(S): A minority of participants requested on-demand HCV testing, regardless of testing history. Viewing HCV testing as important, perceiving oneself to be at risk, and never having been previously tested were associated with on-demand screening; HCV knowledge and perceived stigma were not. In this real-world population of incarcerated men (some having tested HCV-negative and others with unknown HCV status), targeted efforts to promote awareness about HCV risk factors and reduce confidentiality concerns could improve on-demand HCV screening in Canadian provincial prisons.

Real world single centre experience on the efficacy of stopping long term nucleos(t)ide analog therapy in patients with chronic hepatitis B (CHB)

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BACKGROUND: Nucleos(t)ide analogs (NA) suppress hepatitis B virus (HBV) replication but have minimal effect on the intrahepatic HBV cccDNA template, and rarely lead to HbsAg loss, requiring prolonged therapy. Although, expert guidelines recommend that HbeAg (+) patients may stop NA after achieving HbeAg seroconversion and consolidation therapy, many relapse with treatment cessation. In HbeAg (-) chronic hepatitis B (CHB) some suggest that NA's may be stopped in non-cirrhotic patients with undetectable HBV DNA on serial testing. Recent data show that quantitative (q)HbsAg levels <100 IU/mL may be a robust treatment endpoint.

PURPOSE: Our study aims to describe the baseline characteristics and outcomes of patient with CHB who stop NA therapy.

METHOD: In this retrospective observational cohort study we reviewed all NA treated patients who stopped long-term NA therapy at our centre. Some patients stopped NA based on physician recommendation and low-level qHBsAg, others due to medication non-adherence. Data after stopping therapy was collected prospectively as per standard of care (i.e., qHBsAg, ALT, HBV DNA).

RESULT(S): To date, 46/1200 NA-treated CHB patients have stopped NA (30% female, 71% East Asian, median age 55 (range 18–74), 25/46 treated with tenofovir disoproxil fumarate, 17/46 entecavir, and 4 lamivudine and/or adefovir combination). At baseline, 7/46 patient were HbeAg positive. At the time of NA discontinuation, all patients were HbeAg negative, 44/46 had undetectable HBV DNA, and median liver stiffness measurement by FibroScan® was 5.2kPa (range 4.1–11.1kPa). To date, 4/46 (qHBsAg at NA discontinuation 74, 5, 21, 2 IU/mL) restarted NA due to a virologic (median HBV DNA 4,296.5 IU/mL) and ALT flare (ALT 1467, 828, 139, 149 U/L). Median time to restarting antiviral therapy was 82 days after discontinuation. No patient experiencing a flare-up developed hepatic dysfunction, and all successfully responded to restarting potent NA therapy.

CONCLUSION(S): Stopping long-term NA is feasible in HbeAg negative CHB, however significant

hepatic flares can occur despite very low levels of quantitative HbsAg (<100 IU/mL), warranting close follow-up.

Reticulon-3 modulates the loading of replication competent hepatitis C virus molecules for release inside infectious exosomes

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BACKGROUND: Exosomes play an important role in mediating immunologic escape, treatment resistance and disease persistence of almost all hepatic viral infections. Central to this pathomechanistic process is the incorporation of specific host and viral molecules inside infectious exosomes. The precise molecular mechanisms directing the selective cargo sorting and loading inside infectious exosomes remains elusive.

PURPOSE: To decipher the mechanistic role of Reticulon 3 (RTN3) in the generation of infectious viral exosomes.

METHODS: We took advantage of the Huh7 cells – JFH1 HCV infection and HCV Full-Length (FL) replicon systems. Additionally, we made use of human liver and serum exosome samples from healthy and HCV infected patients. Our experimental analysis made use of molecular biology and immunology techniques including confocal microscopy, gene modulation, RNA-chromatin immunoprecipitation (RNA-ChIP) assay, electron microscopy, NanoSight, quantitative RT-qPCR and western blot analysis.

RESULT(S): We reveal that HCV infection of Huh7 cells in the context of JFH1 or HCV-FL replicon cells was associated with increased cellular expression of both long and short isoforms of RTN3 (RTN3L & RTN3S). Accordingly, increased expression and significant enrichment of RTN3L&S were observed in liver and serum exosome samples respectively from HCV infected individuals compared to healthy control subjects. Confocal microscopy and RNA-ChIP analysis of HCV infected hepatocytes revealed that RTN3S&L co-localized and interacted with dsHCV RNA and HCV NS3. Western blotting evaluations revealed that control and infectious exosomes contained TSG101 but no Calnexin, suggesting no microsomes contamination of our exosome preparations. Lentiviral CRISPR/Cas9-mediated knockdown (KD) of RTN3 and specific plasmid overexpression of wild type, C- and N-terminal deletion mutants of RTN3S&L in HCV-JFH1 infected Huh7 cells did not affect HCV NS3 protein and HCV RNA expressions suggesting that RTN3 did not impact HCV replication. Strikingly, RTN3 KD in hepatocytes (Huh7 and FL Replicon cells) significantly decreased, while RTN3 overexpression significantly increased the number of cell-released exosomes. Further, cellular overexpression of C-terminal deleted RTN3S mutant in HCV infected hepatocytes was associated with an increase in RTN3L protein expression. These observations suggest possible compensatory overexpression of RTN3L following overexpression of RTN3S c-terminal deletion mutant. Subsequently, co-culture experiments revealed that exosomes from HCV infected RTN3 KD hepatocytes were significantly less infectious. Sofosbuvir (NS5B polymerase inhibitor) treatment of JFH1 HCV-infected Huh7 and HCV FL-replicon cells significantly reduced HCV induced RTN3L&S expression and attenuated cell released of infectious exosomes.

CONCLUSION(S): This study revealed RTN3 as a novel regulator and a potential therapeutic target that can be exploited to prevent the cellular release of infectious exosomes carrying replication-competent HCV. The role of RTN3 in mediating the generation of infectious exosomes in other viral infections – such as HBV or its implications on extrahepatic HCV complications needs further investigations.

Birth cohort screening for hepatitis C during routine outpatient endoscopy

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BACKGROUND: The Canadian Liver Foundation recommends routine hepatitis C (HCV) screening for Canadians born between 1945–1975 with

recent suggestions from the Unites States to screen all individuals between the ages of 18–79 years regardless of risk factors. There are currently no established programs for HCV screening in Canada.

PURPOSE: The aim of this study was to determine the feasibility of birth cohort HCV screening during routine outpatient endoscopic procedures.

METHODS: Prospective cohort study of individuals born between 1945–1975 attending outpatient endoscopy procedures at Kingston Health Sciences Center from November 2017 – March 2019 without previous HCV antibody (HCV Ab) testing documented in the electronic medical record. Patients who consented to the study received the HCV OraSureã point-of-care test for the HCV Ab. If HCV Ab positive, serum for HCV RNA was sent at the time of the endoscopic procedure and patients were linked to HCV care with a hepatologist. The proportion of individuals eligible, who consented, who had positive HCV Ab, RNA, and SVR was evaluated.

RESULT(S): Over 174 endoscopy days, 2,179 patients meet birth cohort criteria for HCV screening. Of those, 1,079 (49.5%) were approached for study inclusion, 160 (15.0%) declined participation leaving 912 patients who consented to the study. The median age was 62 years (IQR 55–67), 51% were female, and 87% were of Caucasian race. Overall 6/912 (0.7%) of participants were HCV Ab positive and 5/912 (0.6%) were HCV RNA positive. All 5 were linked to care for consideration of direct acting antiviral therapy. Two have achieved sustained virologic response (SVR), however despite best efforts, two have not returned in follow-up for treatment start and one has deferred treatment due to a medication interaction.

CONCLUSION(S): Birth cohort screening for HCV in an outpatient endoscopy unit identified an HCV prevalence of 0.6%, similar to population estimates. In this screening model, linkage to care was 100% however this did not translate into SVR for all individuals. These results highlight the need for ongoing strategies to improve engagement in antiviral therapy of the HCV population once a diagnosis is made. Future budget impact analyses will help determine the feasibility of large-scale uptake of this model of HCV screening into routine clinical practice.

Mechanistic analysis of miR-122 promotion of HCV replication

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BACKGROUND: The genome of hepatitis C Virus (HCV) is a 9.6 kb positive sense RNA which contains a polyprotein coding region, a 5′UTR and a 3′UTR. Its replication requires host miR-122 (small-RNA) annealing to two sites on its 5′UTR. The mechanism by which miR-122 promotes HCV replication is thought to involve viral genome stabilization and translation promotion but is poorly understood. We recently found that annealing of small perfect match RNAs (spmRNAs) to HCV 5′UTR can also promote HCV replication as efficiently as miR-122, when siRNA-mediated target cleavage was abolished using Ago2 knockout cells (Ago2KO).

PURPOSE: To map the locations on the HCV genome to which spmRNA annealing can promote HCV replication and to determine the mechanism behind miR-122 and spmRNA dependent HCV replication.

METHODS: To identify regions where spmRNAs annealing can promote HCV replication, several 19bp spmRNAs (identical to siRNAs) targeting different sites on the HCV genome were tested for their ability to promote HCV replication. To gain insights into the mechanisms by which miR-122 and spmRNAs induce the viral life cycle, we monitored translation stimulation and genome stabilization by spmRNAs that do and do not promote HCV life cycle. To assess translation stimulation, we used a non-replicative mutant of HCV RNA and spmRNAs to measure protein production 4 hours post co-electroporation. To assess genome stabilization by miR-122 and the spmRNAs, we used northern blot assays to determine the half-life of non-replicative HCV RNA in presence of miR-122 or spmRNAs that do and that do not promote virus replication.

RESULT(S): From our replication assay, we found that spmRNAs annealing between nucleotides

1 and 44 in HCV 5′UTR, promoted replication, and spmRNAs annealing within IRES, NS5B and 3′UTR regions, including other predicted miR122 binding sites, did not. Replication promotion efficiency decreased as the spmRNA target site moved away from the center of this region and was abolished if the spmRNA target included nucleotide 45. This suggested that location specific annealing of small RNAs is required to promote virus replication. Translation assays showed correlation between translation stimulation and replication promotion by individual spmRNAs suggesting replication promotion and translation stimulate are linked functions. RNA structure predictions of HCV RNA in presence of spmRNAs that promote virus replication showed formation of canonical HCV IRES structure, required for virus translation. These data suggest that translation promotion by small RNAs is necessary to promote HCV lifecycle. We further sought to determine correlation between replication and genome stabilization by spmRNAs. We observed that spmRNAs stabilized HCV RNA whether they did or did not promote virus replication. This suggested that genome stabilization by spmRNAs is not sufficient for promotion of HCV replication.

CONCLUSION(S): We present a model in which position-specific annealing of small RNAs induces the formation of the viral IRES RNA structures and promotes virus translation and replication. In addition, position-independent small RNA annealing stabilizes the viral genome but alone is insufficient to promote the virus life cycle. Future studies will characterize how RNA structures are modulated by small RNA annealing to better understand the mechanism by which miR-122 promotes HCV life cycle.

Identification of patients with compensated cirrhosis who can safely use protease inhibitor-based therapy for HCV infection

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BACKGROUND: Direct-acting antivirals (DAAs) are now widely used as treatment for chronic HCV in patients with compensated and decompensated cirrhosis. Based on reported decompensation events during treatment, advisories about use of protease inhibitors (PI) have been issued. Simple identification of patients with a very low risk of decompensation during treatment who can safely use PI-based therapy would be very helpful.

PURPOSE: To identify patients with a very low risk of decompensation during treatment who can safely use PI-based therapy.

METHOD: Retrospective cohort study including all consecutively chronic hepatitis C (HCV) patients treated with DAAs in 4 international hepatology clinics. Baseline was defined as the initiation of treatment. Primary endpoint was liver decompensation (ascites, variceal bleed or encephalopathy), with a follow-up until SVR12. ROC analyses were used to define cut-offs for continuous variables.

RESULT(S): 432 patients were included, 318 with Child-Pugh A cirrhosis (CP-A) and 114 Child-Pugh B/C cirrhosis (CP-B/C). Median (IQR) age was 58 (53–63) years and 73 (17%) had genotype 3. 107 (34%) patients with CP-A were treated with Pis and 23 (20%) patients with CP-B/C. SVR was attained in 263 (83%) CP-A patients 86 (75%) CP-B/C patients. Decompensation occurred in 50 (12%) patients, 8 with CP-A and 42 with CP-B/C in a median time of 8 (3–15) weeks. Factors significantly associated with experiencing no decompensation in univariate logistic regression were non-genotype 3 (G3), higher albumin, lower bilirubin, higher ALT, higher platelet (plt) count, lower INR and lower MELD. Among patients without baseline

Table: Risk of decompensation among patients with compensated cirrhosis starting DAA therapy

	Alb<38	Alb>38	Total
Plt<130	6/85 (7.1%)	3/77 (3.9%)	9/162 (5.6%)
Plt>130	2/36 (5.6%)	0/68 (0%)	2/104 (1.9%)
Total	8/121 (6.6%)	3/145 (2.1%)	11/266 (4.1%)

decompensation (no ascites, encephalopathy and normal bilirubin) (n = 266), albumin >38 and platelet count >130 accurately predicted no risk of decompensation. Of patients with baseline albumin >38 and plt count >130, 0 of 68 experienced decompensation. With albumin >38 but plt <130, the risk of decompensation was 3 of 77 (4%) similar to those with albumin <38 and plt >130 (2 of 36 [5.6%]). Of patients with albumin <38 and plt <130, 6 of 85 (7.1%) experienced a decompensation event with treatment. These thresholds were robust in those who received Pis and those who do not (Table).

CONCLUSION(S): Patients with cirrhosis who have no evidence of decompensation at baseline and albumin >38 and plt count >130 can safely be treated with DAAs including PI-based therapy with minimal or no risk of decompensation.

Prenatal hepatitis C screening and diagnoses in British Columbia, 2008–2018

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BACKGROUND: Hepatitis C (HCV) is not part of routine prenatal screening in British Columbia (BC) Canada: pregnant people may be tested if they have risk factors or their prenatal care providers request HCV testing. In some jurisdictions universal prenatal screening for HCV is being implemented, however, there is paucity of data in BC on HCV screening patterns during pregnancy.

PURPOSE: We aimed to calculate frequency of prenatal HCV antibody testing and HCV diagnoses, as well as follow-up testing (RNA and/or genotype) among prenatally screened women in BC, from 2008–2018.

METHODS: We used BC Centre for Disease Control Public Health Laboratory (PHL) data linked with provincial surveillance data to estimate the number of women (female sex) aged 13–49 who received routine prenatal serological screening (HIV, hepatitis B, syphilis, and rubella) between 2008 and 2018. PHL performs >95% of all HCV screening tests in BC. HCV tests ordered on the same day as routine prenatal screens were considered prenatal HCV tests. Previously known HCV positive status was determined by HCV positive result prior to prenatal test. Seroconversion was a negative test at any time prior to a first positive test. Any follow-up RNA and/or genotype testing was assessed after prenatal anti-HCV screening.

RESULT(S): Prenatal HCV screening increased significantly from 2008 (Cochran-Armitage test for trend: $p < 0.001$), reaching nearly half of women receiving routine prenatal screening in 2018. Overall HCV prevalence among prenatally HCV screened women declined from 0.6% in 2008 to 0.36% in 2018. New HCV diagnoses due to prenatal HCV screening fluctuated over the ten year study period. Overall, prenatal HCV screening identified 337 new HCV diagnoses, 24.3% were seroconversions and 75.7% were first time reactive results. In 2018, most women newly diagnosed with a prenatal HCV screen received follow-up RNA and/or genotype tests; 100% (9/9) of those who seroconverted and 90.1% (30/33) of those with first time reactive results; this compared to 82.5% (572/693) of all new HCV diagnoses among all women in BC the same year. Of 1,524 women who had previously tested HCV positive before receiving a prenatal HCV screen between 2008 and 2018, 97% had any RNA and/or genotype testing (Figure).

CONCLUSION(S): Risk-based prenatal HCV testing identifies undiagnosed HCV infections, and most women identified appear to be receiving appropriate follow-up testing. Further research is needed to understand differences in risk-based vs. routine prenatal HCV screening, as well as HCV vulnerability, infection, and care among pregnant women in BC.

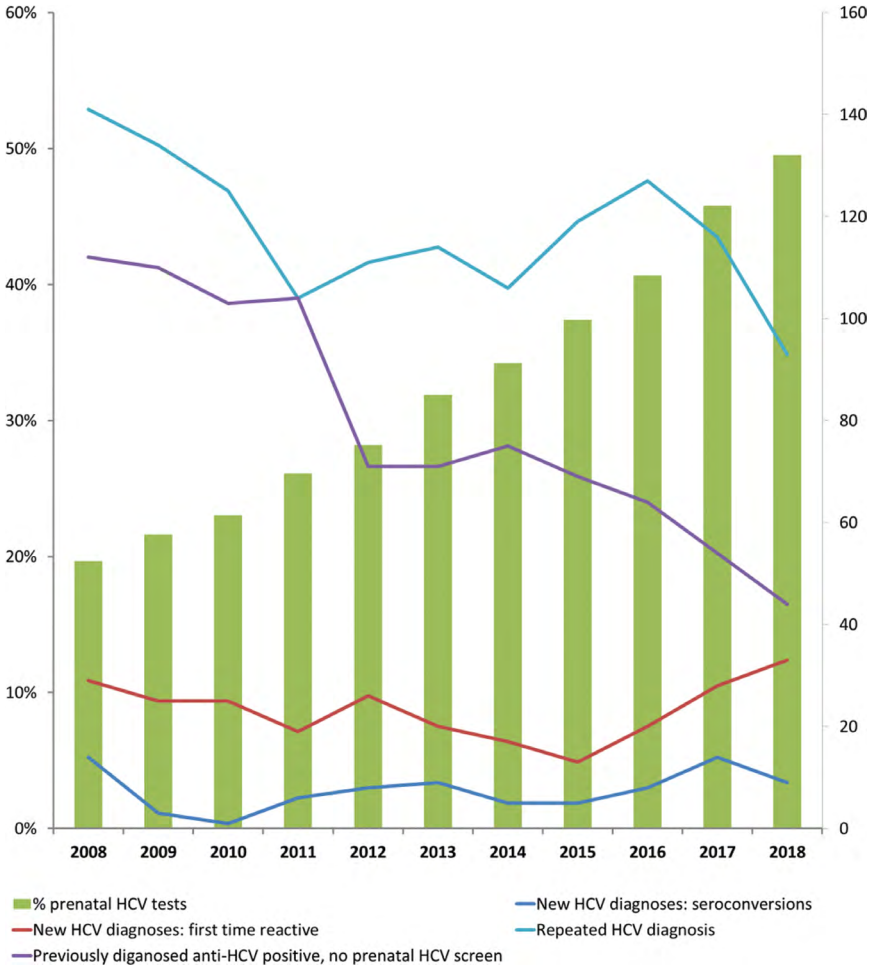

Figure: Proportion of all prenatal screens that included an anti-HCV test and number of women diagnosed anti-HCV positive as a result of a prenatal HCV screen, including new diagnoses (seroconversion or first time reactive) and previously known diagnoses (repeat testers) in BC, 2008–20018

Targeting hepatitis B virus cccDNA in vitro

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BACKGROUND: Over 257 million people worldwide are chronically infected with hepatitis B virus (HBV), the leading cause of hepatocellular carcinoma and accounting for over 880,000 deaths annually. Chronic HBV infection is established through the virus' highly stable covalently closed circular DNA (cccDNA) persisting in the nuclei of infected hepatocytes. The cccDNA serves as the template for transcription of all HBV mRNA transcripts. Currently approved treatments for HBV-infected individuals include nucleos(t)ide analogs, which target later steps in the viral replication cycle, and fail to clear the persistent source of infection, the cccDNA. Thus, ultimately curing HBV will require direct targeting of the minigenome and will require further detailed structural knowledge of the cccDNA to determine potential vulnerabilities.

PURPOSE: Previously, we identified a highly guanine rich sequence in a key promoter region in the HBV pre-core/core promoter (PreC/C), which forms a DNA secondary structure known as a G-quadruplex. This structure is comprised of planar arrangements of guanosines (G) that stack upon one another in a specific manner and functionally act as regulators of transcription.

We have designed proteins to bind the pre-core G4-quadruplex promoter region. We hypothesize that these proteins will be able to enter the nucleus of hepatocytes, bind the cccDNA and interfere with HBV pgRNA transcription.

METHOD: We designed multiple pre-core G-quadruplex-binding proteins (Gbp) and recombinantly purified them from *E.coli* Lemo21(DE3) cells, using affinity chromatography followed by anion exchange to remove endotoxins. Hirt extraction was used to isolate cccDNA from explant liver tissue and used in a pull-down assay with Gbp-bound nickel beads as the bait protein, followed by nested PCR for confirmation. Cellular localization studies were performed on HepG2 and NTCP-Huh7 cells using flurorescently-labelled G4bp. HBV inhibition studies were performed on transfected HepG2 cells and products of infection analyzed after 3 days with ELISA and qPCR.

RESULT(S): In HBV transfected HepG2 cells, the G4bp were able to diffuse across the cellular membrane and localize into the cytoplasm of the cell. ELISA results demonstrate a significant decrease in supernatant HbsAg production in the HepG2 cells treated with the modified G4bp compared to untreated cells. In the Huh7 cell line that expresses the NTCP receptor, the G4bp was able to localize into the nucleus of actively replicating cells.

CONCLUSION(S): Preliminary studies show that the G-quadruplex-binding proteins interact with cccDNA and localize in infected hepatocytes, potentially leading to novel therapies for HBV infection.

Exploiting cccDNA's structural features to find new HBV targets

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BACKGROUND: Approximately 250 million people worldwide are chronic carriers of hepatitis B virus (HBV), and are at increased risk of developing cirrhosis and hepatocellular carcinoma. The virus persists in the nucleus as covalently closed circular DNA (cccDNA), which 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. We have discovered and provide evidence for a unique structural motif in HBV's pre-core promoter region—a G4-quadruplex—a distinct, stacked, four-guanosine folding arrangement of DNA. Such quadruplexes are being found at key transcription and translation sites of numerous organisms and are thought to regulate these processes.

PURPOSE: To thoroughly characterize a unique structural feature in cccDNA in the pre-core promoter region, the G4-quadruplex, that will enable downstream design of inhibitors.

METHOD: Wild-type and single-nucleotide mutation oligomers of the HBV pre-core promoter region were purified and analysed using circular dichroism (CD), microscale thermophoresis (MST) and small-angle X-ray scattering (SAXS). Next, cccDNA was extracted from an HBV-infected liver explant. Using a known quadruplex-binding protein, DHX36, pull-down assays were performed on whole and fragments of cccDNA, as well as mutated fragments. Finally, functional studies of the wild-type and mutant HBV DNA were performed using a lipofectamine transfection model in HepG2 cells. Products were analysed for various markers of viral replication, including total DNA, RNA, protein, via ELISA, quantitative and nested PCRs, and Northern blot analyses.

RESULT(S): Through biophysical studies, we demonstrate that the wild-type oligomer forms a parallel quadruplex structure, while the single-nucleotide mutations do not. Employing the known quadruplex-binding protein, DHX36, we show that we can bind and pull down cccDNA from clinically-relevant liver-derived patient samples. Furthermore, we demonstrate the impacts on viral replication of the wild-type and mutant variants in cell culture.

CONCLUSION(S): This novel finding of a G4-quadruplex in the HBV pre-core promoter region,

supported by functional data, provides a unique opportunity to study a critical host-protein interaction site in HBV cccDNA transcription and ultimately the design of novel inhibitors.

NAFLD and alcohol affect long-term liver fibrosis regression post-HCV eradication

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BACKGROUND: Eradication of chronic hepatitis C infection results in fibrosis regression. There is evolving data for fibrosis regression post direct acting antiviral therapy. It is unclear which patient factors affect fibrosis regression.

PURPOSE: The aim was to evaluate predictive factors for fibrosis regression after HCV eradication.

METHOD: Retrospective review of HCV persons treated between 2015 and July 2019. We collected demographics, co-morbidities, baseline fibrosis using transient elastography (TE) (Fibroscan®), and FIB4, APRI at baseline. SVR 12 was documented and TE performed at 12 or 24-weeks post-treatment (SVR 12/24) and at 1-year (SVR-yr1). A significant decrease in fibrosis was defined as >30% decline in baseline TE kpa scores (TE-regression). We compared SVR 12/24 to SVR-yr1.

RESULT(S): We retrospectively studied 1199 patients who were followed for SVR 12/24, from which 694 had a SVR yr-1 TE. Median follow-up time was 35 (range 12–112) weeks post-therapy. From 326 patients with cirrhosis (kpa >12.5) at baseline, only 18 patients (5%) had a significant TE-regression at SVR 12/24 compared to baseline. Interestingly, 115 (35%) cirrhotic patients showed significant TE-regression to non-cirrhotic stages (kpa<12.5) at SVR yr-1 compare to SVR12/24.

High FIB4 >3.25 (OR: 3.58) and APRI >2 (OR: 2.55) at baseline were predictive of cirrhosis at SVR yr-1. A diagnosis of baseline NASH (OR: 4.26) and alcohol use (OR: 3.35) were also significant predictive risk factors for cirrhosis at SVR-yr-1. Baseline FIB4 >3.25 and APRI >2 had a positive predictive value (PPV) for cirrhosis at SVR-yr-1 of 85% and 82%, respectively. The AUC for prediction of cirrhosis at SVR yr-1 of FIB4 (AUC = 0.76; 95% CI, 0.72–0.85; P <0.05) was higher than APRI (AUC = 0.70; 95% CI, 0.68–0.77; P <0.05).

CONCLUSION(S): The baseline FIB4 and APRI are predictive of those who do not achieve significant TE improvements at SVR yr-1. Further, the baseline presence of NAFLD and Alcohol use, are predictive for lower fibrosis regression at SVR yr-1. These variables can potentially be used to risk stratify patients for long-term follow-up. Further study is needed to identify predictive variables to stratify those at highest risk of long-term negative outcomes.

Ethnic differences in HCV-related HCC (HCV-HCC) outcomes: Report from the real-world evidence by the Asia Pacific Rim liver consortium for HCC (REAL-HCC)

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BACKGROUND: HCV is one of the leading causes of HCC in globally.

PURPOSE: The impact of ethnicity on the clinical presentation and subsequent outcome of HCV-HCC is unknown.

METHOD: In a retrospective study, HCV-HCC patients enrolled at 4 U.S. centers and 5 Asia Pacific (AP) centers were analysed to identify ethnic differences in their presentation and outcome.

RESULT(S): Of the total 3339 patients identified with HCV-HCC, 1601 (48%) were Asian (330 US, 1271 AP), 1119 (34%) Caucasian, 272 (8%) Hispanic and 347 (10%) African American (AA). Asian patients were more likely to be female (41.8 % vs. 25.9% for non-Asians) and older (mean age 65.9 vs. 60.1) (p >0.0001 for both). The proportion of patients with decompensated cirrhosis (CTP Class B/C) was highest in Hispanic (64.4 % vs. 44.4% non-Hispanics, p <0.0001). Among cases of HCC

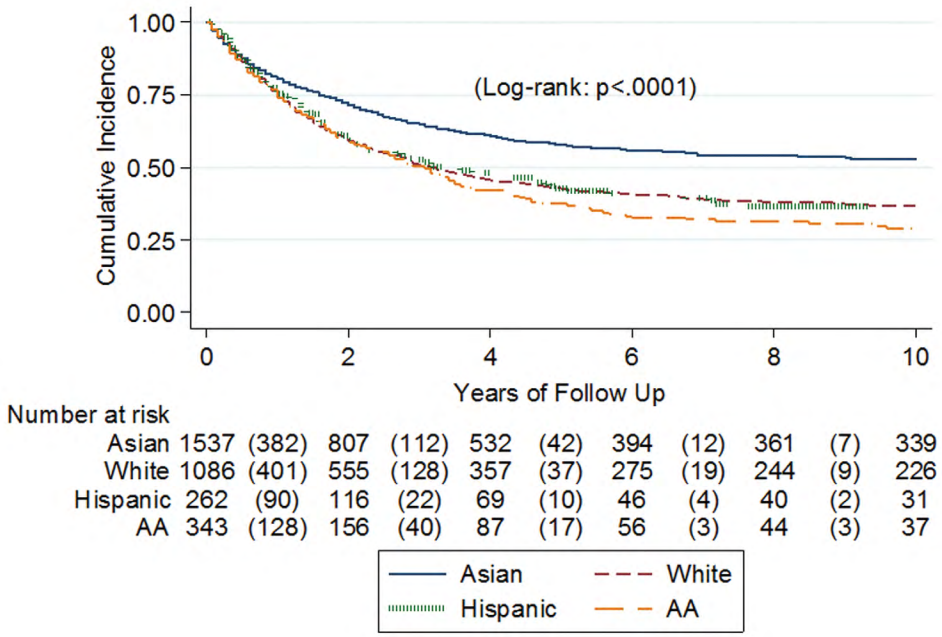

Figure: Kaplan-Meier survival estimates of HCV-HCC patients, by ethnicity

where screening history is documented, AA had much lower proportion of screen-detected HCC (42.5% vs 75% in non-AA, p <0.0001). Screening was documented for 66.7% of US Asian and highest at 84.9% for AP Asian. HCC was diagnosed at an earlier stage (BCLC stage 0/A/B) in 83.5% Asian (80.1% US, 84.5% AP), 75.3% Caucasians, 74.1% Hispanics, and 76.0% AA (p <0.0001). Rate of OLT listing was lowest at 16.6% for Asian (20.7% US, 1.3% AP) and 25% for AA compared with White 42.9% and Hispanic 42.9% (p <0.0001). Actual OLT rates were even lower for Asian at 4.1% overall (9.0% US, 2.7% AP) followed by AA 16.9%, Hispanic 21.5%, and highest in White 24.5% (p <0.0001). However, curative treatment rate overall (OLT, resection, RFA) were highest for AA 27.6%, followed by Asian 18.0%, White 17.3% and lowest for Hispanic 14.0%. On Kaplan-Meier survival estimates (see Figure), respective 5 and 10-year overall survival was lowest for African American (37.6% and 29.0%), followed by White (42.8% and 36.5%) and Hispanic (42.7% and 34.4%) and highest for Asian (57.8% and 53.2%) (p <0.0001), with AP Asian having higher survival than US Asian (p <0.0001).

CONCLUSION(S): In this large international collaborative study, ethnicity was an important determinant of HCV-HCC presentation, treatment, and long-term survival. African Americans with HCC have poor outcomes, likely reflecting both poor screening uptake and poor access to OLT. In contrast, despite lower OLT rates and overall curative treatment rate, Asian had the highest HCC screening rates and better long-term outcomes.

Ethnic disparities in the risk of hepatitis C virus-related diabetes in a large population-based cohort in Canada

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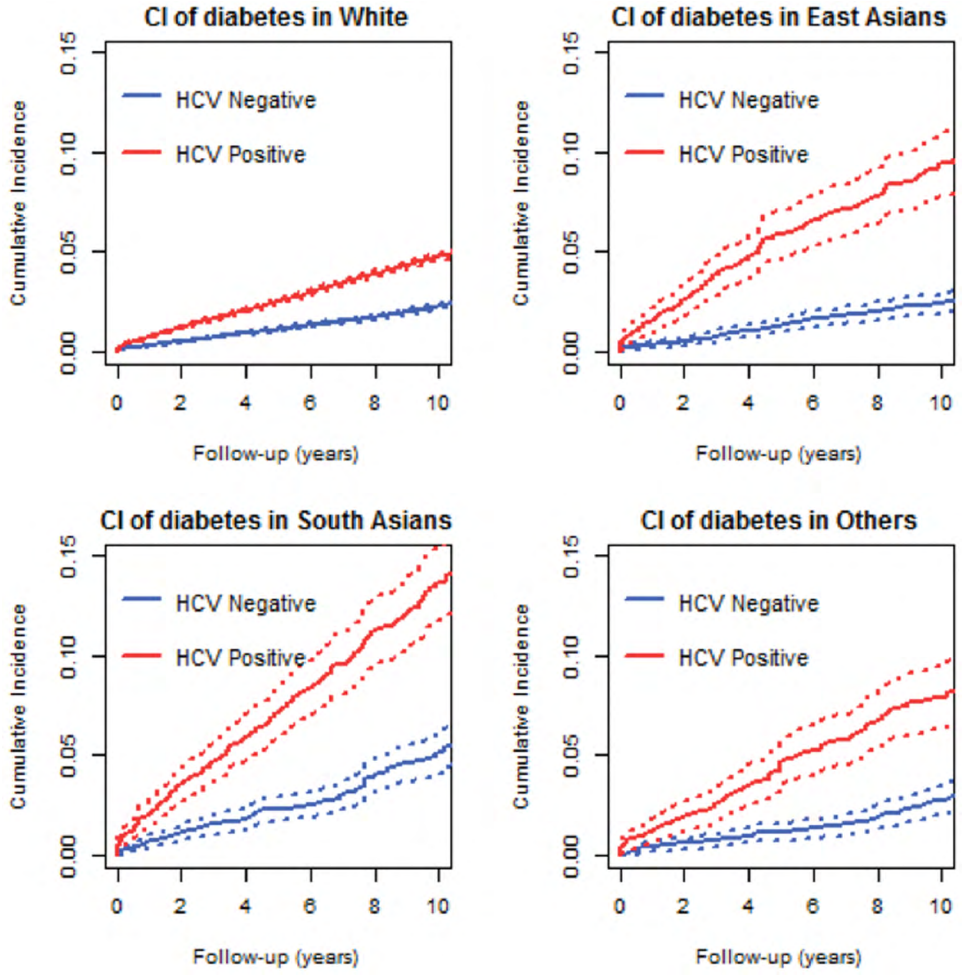
BACKGROUND: There is increasing evidence that persons living with hepatitis C virus (HCV) infection are at a higher risk of type 2 diabetes (T2D). Previous studies based in multi-ethnic settings have shown an ethnic disparity in diabetes, with an increased risk among non-White people. Thus, it can be hypothesized that the impact

of HCV infection on diabetes incidence differs across ethnic groups.

PURPOSE: The goal of this study was to assess the impact of HCV infection on incident T2D within a large ethnically-diverse population-based cohort in British Columbia. Additionally, we aimed to examine if the impact of HCV infection on T2D incidence varied by ethnicity.

METHODS: The incidence of T2D by HCV status was assessed in the British Columbia (BC) Hepatitis Testers Cohort, which includes ~1.7 million individuals tested or reported as a case of HCV in BC, linked with various health administrative data. Diabetes was defined using a validated algorithm modified with data on prescription drug and glucose strips dispensations. Individuals tested for HCV since 1990 were followed from the date of their first positive or last negative HCV RNA test to the earliest of 1) incident type 2 diabetes, 2) death or 3) end of study (12/31/2015). Propensity scores (PS) were estimated based on age at HCV diagnosis, duration of follow up, sex, material/social deprivation quintiles, HBV/HIV infection, mood and anxiety disorders, obesity, problematic alcohol use and injection drug use. HCV-positive and negative individuals were matched at a 1:1 ratio without replacement. We used Fine and Gray competing risk models, adjusting for competing risk of mortality and other potential confounders to estimate hazard ratios (HR) and 95% confidence intervals (CI) for incident diabetes, overall, and stratified by ethnicity in the PS-matched data.

RESULT(S): After PS matching, the study sample included 117,192 individuals. When adjusted for potential confounders and competing risk, HCV infection was significantly associated with incident T2D, with an adjusted HR of 2.32 (95% CI 2.20–2.46). Other characteristics significantly associated with an increased risk of T2D included older age at diagnosis, non-White ethnicities, material deprivation, obesity, having a mood and anxiety disorder,



problematic alcohol use and injection drug use. In stratified analyses, the aHR for White people with HCV was 2.00 (95% CI 1.88–2.12), for South Asian people, 2.60 (95% CI 2.11–3.20), and for East Asian people, 3.21 (95% CI 2.58–4.01). Other characteristics associated with T2D varied across ethnicities, with obesity being significantly associated with an increased risk of incident T2D in White people but not in South and East Asian people (Figure).

CONCLUSION(S): This analysis supports other studies that HCV infection is associated with a higher risk of developing diabetes. Furthermore, in BC, the impact of HCV infection on incident T2D differed across age and ethnic groups, with a higher risk among Asian people. The findings of this study highlight the need for continued care and screening for HCV-related chronic diseases such as diabetes in individuals living with HCV infection, especially among Asian population.

Natural history of cirrhotic people who use drugs (PWUD) following successful HCV therapy in the direct-acting antiviral (DAA) era

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BACKGROUND: Direct-acting antiviral (DAA) therapy regimens are highly effective for the treatment of HCV infection in all patient risk groups and at all levels of fibrosis, with cure associated with a significant reduction in the long-term consequences of liver disease. Among PWUD, real world data have confirmed the efficacy of DAAs in this population, but little is known about the natural history of liver disease among cirrhotic PWUD following cure of HCV infection (SVR12).

PURPOSE: We evaluated reversal of fibrosis and the development of hepatocellular carcinoma (HCC) in a group of cirrhotic PWUD maintained in long-term follow-up at our centre following achievement of SVR12.

METHODS: A retrospective chart review was performed on all HCV-infected cirrhotic PWUD (FibroScan measure >12.5 kPa prior to treatment) who remained in follow-up >6 months. All subjects were evaluated every 6 months, with monitoring of liver fibrosis and ascertainment of clinical status. For this analysis, changes in fibrosis level were documented as well as clinical outcome (death, development of HCC).

RESULT(S): The cohort (n = 36) was followed for a median 125 (range 28–297) weeks, with mean age 60 (45–73) years, 78% male, 25% HIV co-infected, 50% psychiatric co-morbidities, 31% treatment experienced at baseline (BL) and 81% active PWUD. Mean FibroScan scores at BL/SVR12/PT1 (weeks 79–130)/PT2 (weeks 131–297) were 21.9 (n = 36)/14.6 (n = 29)/11.5 (n = 20)/10.3 (n = 29) kPa, with only 5 patients remaining cirrhotic in last follow up. Thrombocytopenia (n = 15) normalized in 10 cases. In follow up, 3 patients developed HCC (3.1/100 person-years), one case in the second year and two in the third year of follow-up, all remaining cirrhotic at the time of diagnosis. There were 2 deaths, both from HCC. There were no opioid overdose fatalities and no cases of reinfection.

CONCLUSION(S): Among cirrhotic PWUD cured of HCV infection, significant and progressive improvement in liver fibrosis occurs over time, which may be associated with a more favorable long-term clinical outcome. The absence of overdose and reinfection events in this population maintained in care at our centre is encouraging. Given the risk of HCC, ongoing surveillance is mandated. Further data are needed to evaluate whether such follow up (in PWUD and other populations) must be maintained in patients in whom significant improvement in fibrosis is documented.

Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir as a hepatitis C virus infection salvage treatment

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BACKGROUND: First-line direct acting antiviral agents (DAAs) are highly effective (>95%), yet some hepatitis C (HCV) patients do not achieve sustained virologic response (SVR). In patients previously treated with DAAs, sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) has shown high SVR rates in clinical trials.

PURPOSE: We assessed the effectiveness of SOF/VEL/VOX in treating treatment-experienced patients with HCV genotype 1 (GT1) to genotype 6 (GT6) infection in a large population-based Canadian cohort.

METHOD: This analysis included individuals in the British Columbia (BC) Hepatitis Testers Cohort who had virological failure after prior DAA therapy, initiated SOF/VEL/VOX for retreatment of GT1-GT6 on or prior to June 30, 2019, and had at least one HCV RNA test after treatment initiation. SVR was assessed from treatment start until Oct 9, 2019. The primary outcome was SVR at 12 weeks following end of HCV treatment based on modified intention-to-treat, where individuals with a negative HCV RNA test after treatment end but no SVR assessment were excluded.

RESULT(S): Overall, 191 people treated with SOF/VEL/VOX (n = 153) or SOF/VEL/VOX+ribavirin (RBV; n = 38) were included in the analysis. The majority of were infected with GT1 (n = 104, 54.5%) or GT3 (n = 62, 32.5%), followed by GT2 (n = 17, 8.9%). Most individuals were male (82.2%) and aged ≥50 years (92.1%). The largest proportion of patients received SOF/ledipasvir (SOF/LDV; 37.2%), followed by SOF/VEL (14.1%) and SOF+RBV (13.6%) and as their last treatment. The overall SVR rate with SOF/VEL/VOX salvage treatment was 95.3% (182/191). SVR for GT1, GT2 and GT3 was 96.2%, 100%, and 91.9%, respectively. SVR was lower (but not statistically significant) for those with cirrhosis vs. no cirrhosis – overall (88.0% vs 96.4%) and across previous treatment regimens: SOF/VEL (75.0% vs 91.3%), SOF/LDV (85.7% vs 96.5%), SOF-containing (87.0% vs. 96.2%) and NS5A+SOF (84.2% vs. 95.1%).

CONCLUSION(S): In this real-world cohort of patients with virological failure after prior DAA therapy, retreatment with SOF/VEL/VOX resulted in SVR rates of more than 90% across all genotypes; however, SVR was lower for those with underlying cirrhosis. Comparisons were limited by small sample sizes.

Current opioid agonist therapy is associated with hepatitis C virus treatment uptake among people who inject drugs in a population-based data linkage study

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BACKGROUND: Hepatitis C virus (HCV) treatment uptake among people who inject drugs (PWID) lags behind treatment uptake among people without injection drug use (IDU); yet, most new HCV infections are among PWID. Previous studies suggest that Opioid Agonist Therapy (OAT) may reduce HCV incidence and reinfection among PWID; however, it is not known if OAT also increases treatment uptake among PWID. Understanding the interaction between OAT and HCV treatment uptake among PWID can inform public health policy to improve HCV prevention, care and treatment programming in this 'hardly reached' population.

PURPOSE: To evaluate retention on OAT among people diagnosed with HCV, and to determine the associate between OAT and increased HCV treatment uptake among PWID.

METHODS: The British Columbia (BC) Hepatitis Testers Cohort was used for this analysis, which includes all individuals tested for or diagnosed with HCV in BC linked to all prescription drugs, medical visits, hospitalizations and mortality data until December 31st 2018. People diagnosed with HCV (RNA positive) identified as PWID (using

previously validated algorithm- recent PWID; IDU <3 years, past PWID; IDU >3 years ago), or who ever received OAT ('never PWID'), were selected. A time-varying covariate for OAT was created, allowing a gap of up to 5 days between subsequent OAT dispensation records before participants were counted as being off OAT. To assess the impact of current OAT on HCV treatment uptake, multivariable Cox Proportional Hazards regression modelling was used. Models were stratified by history of IDU (recent, past or never PWID) and were fit adjusting for age, sex, race, urbanicity, material and social deprivation, HIV coinfection, cirrhosis, alcohol misuse, major mental illness, and opioid or stimulant use disorder/misuse. Participants were censored after death or HCV treatment initiation, whichever came first.

RESULT(S): Overall, 39% (7,323/18,913) of PWID diagnosed with chronic HCV had never received OAT, 31% (5,954/18,913) had past but not current OAT, and 30% (5,636/18,913) were currently on OAT as of December 31st 2018. Among those currently on OAT, 45% (2,518/5,636) had received HCV treatment, compared to 34% (4,572/13,277) of those not on OAT. Among HCV-positive PWID currently on OAT for >24 months, 54% (1282/2360) had received HCV treatment. After adjustment for other covariates, ongoing OAT was associated with higher HCV treatment uptake over time among all three groups (recent PWID; adjusted hazards ratio [aHR] 2.2 [95% CI, 1.96, 2.52], past PWID; aHR, 1.5 [95% CI 1.39, 1.59], and never PWID; aHR, of 1.3 [95% CI 1.17, 1.42]).

CONCLUSION(S): In this cohort of people with chronic HCV infection and history of drug use, ongoing OAT was associated with a higher rate of HCV treatment initiation. However, many people with HCV currently receiving OAT have yet to receive HCV treatment. Therefore, additional strategies to enhance integration between substance use care and HCV treatment are needed to improve HCV treatment uptake among PWID.

Syndemic of viral co-infections and incident end-stage renal disease

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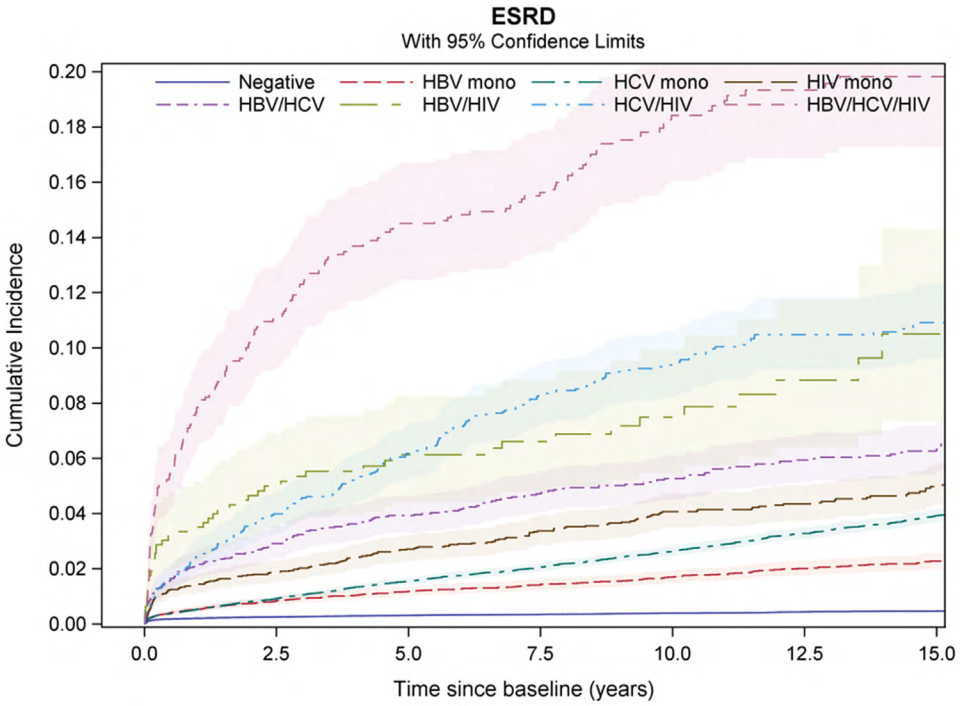
BACKGROUND: Despite advances in prevention, care and treatment, bloodborne infections (BBIs) including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) remain significant sources of morbidity and mortality. Globally, 257 million people are living with HBV, 71 million with HCV, and 37.9 million with HIV. Each of these BBIs are associated with various non-communicable chronic diseases (NCDs), such as chronic liver disease, chronic kidney disease (CKD) and end-stage renal disease (ESRD). Not only these chronic BBIs increase the risk of NCDs, the NCDs can, in turn, amplify the impact of infections. Additionally, syndemic viral infections are associated with increased risk of CKD and end-stage renal disease (ESRD). However, population-level estimates of the impact of syndemic co-infections are lacking.

PURPOSE: This study aimed to assess the effect of HBV, HCV and HIV co-infections on incident ESRD in a large population-based cohort.

METHODS: The British Columbia (BC) Hepatitis Testers Cohort includes ~1.7 million individuals tested for HCV or HIV, or reported as a case of HBV, HCV, or HIV in BC, and is linked with various administrative healthcare data. ESRD was defined through ICD-9/10 codes. Individuals tested for all three infections since 1990 were followed from the date of their last test until the earliest of 1) incident ESRD, 2) death or 3) end of study (12/31/2015). Fine and Gray competing risk models adjusting for mortality and potential confounders including age, sex, ethnicity, alcohol and injection substance use, social/material deprivation, and history of diabetes and hypertension were used to estimate sub-distributional hazard ratios (HRs) and 95% confidence intervals (Cis) for incident ESRD. Further stratified analysis was performed accounting for diabetes.

RESULT(S): Of 524,186 individuals tested, we observed 3,762 incident ESRD events (0.7%) and 24,714 deaths (4.7%) during a median follow-up



of 4.1 years. The highest ESRD incidence rate (per 1,000 person-years) was observed in persons with triple HBV/HCV/HIV infection (26.7) followed by HCV/HIV (10.2), HBV/HIV (10.0), HBV/HCV co-infection (5.8), and HIV (3.8), HCV (3.0) and HBV mono-infection (1.8), (Figure). In multivariable analysis, relative to those with no chronic infections, those with triple infection had the highest relative hazard for ESRD (HR 34, 95% CI: 29, 41). When stratified by diabetes status triple infection still had the highest relative hazard for ESRD (HRs 16, 95% CI: 5–28, and 38, 95% CI: 31–46) for both persons with diabetes and those without, respectively.

CONCLUSION(S): Persons living with HIV/HBV/HCV triple infection were at highest risk of ESRD. Management of these syndemic conditions, particularly through HBV, HCV and/or HIV treatment could reduce the risk of ESRD among people with co-infections.

Genotype misclassification and its impact on treatment choices, outcomes and drug resistance

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BACKGROUND: Genotype (GT) determination remains useful for hepatitis C virus (HCV) management. Discordant GT/subtype determined by commercial genotyping assays have been reported.

PURPOSE: To retrospectively examine the impact of GT misclassification on HCV treatment and outcomes.

METHOD: 1765 HCV sequences (57% failures) and the associated clinical and treatment data were collected from 15 countries through SHARED. The sequence-based GT/subtypes were compared with those reported by the clinics. Patients with discordant GT/subtypes were examined for the regimens administered, treatment response, and drug resistance.

RESULT(S): Sequence-based genotyping using ICTV references accurately determines GT/subtype in HCV. The concordances with published isolates were 100%, 100%, 100% in GT and 99.3, 99.2, 98.8% in subtype for the NS3, NS5A, and NS5B, respectively.

Discordances between clinically- and sequence-based GT/subtypes were observed in 304/1765 (17%) pts: 7% at the GT level, and 10% at the subtype level. All indeterminate isolates were assigned using the sequence-based genotyping.

GT1b and GT3 isolates made up most of the GT discordant cases with a discordant rate at 13% (57/430) and 9% (50/568), respectively. For the discordant GT1b, 52/57 (91%) were classified as GT3 by sequence-based genotyping, and 46/57 (81%) misdiagnosed pts were treated with inappropriate regimens. Drug resistance mutations, Y93H, A30K/S, and L62S within NS5A, were detected in 58%, 27%, and 17%, respectively, of these pts following therapy.

For the 50 discordant GT3, 38 (76%) turned out to be GT1b, and 11 (22%) GT1a. There was no significant impact on regimen choice, as regimens indicated for GT3 were also effective in the other GTs.

Genotyping is significantly associated with treatment response: 111/121 (92%) of the GT discordant patients failed therapy, whereas 891/1245 (72%) of the GT concordant patients failed ($P < 0.0001$).

CONCLUSION(S): GT misclassification may lead to inappropriate regimen choices and treatment failure. Sequencing can be used to study GT/subtypes, drug resistance, and transmission.

Association between prescription opioids and hepatitis C virus seroconversion among people who use injection drugs in British Columbia

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BACKGROUND: Prescription opioids (POs) have been implicated in rising hepatitis C virus (HCV) incidence in some jurisdictions.

PURPOSE: We evaluated the relationship between Pos and HCV seroconversion among people who use injection drugs (PWID) in British Columbia (BC)

METHOD: The BC Hepatitis Testers Cohort includes all individuals tested for HCV in BC (1992–2015) linked to administrative databases and a province-wide prescription drug database (PharmaNet). We limited the cohort to PWID using a validated algorithm based on hospitalization and physician diagnostic codes. PharmaNet was used to identify individuals as opioid-naïve or opioid-experienced, and to classify episodes of PO use for non-cancer pain as acute, episodic or chronic. Among repeat HCV testers (individuals with an HCV-negative test followed by at least one additional test), Cox proportional hazards models were used to measure the association between exposure to Pos and HCV seroconversion (approximated as the midpoint between an HCV-positive test and previous HCV-negative test). PO exposure was treated as a time-varying, hierarchical variable (eg. Individuals with acute exposure could transition to episodic/chronic; individuals with chronic PO exposure remained as such for duration of study).

RESULT(S): Between 2000 and 2015, there were a total of 4,204 HCV seroconversions among 46,658 PWID. Opioid-naïve/acute exposure made up the majority (56.7%) of the 350,510 person-years of follow-up, followed by episodic (29.7%) and

chronic (13.6%). Crude HCV incidence per 100 person-years was 1.0 for individuals with opioid-naïve/acute PO exposure, and 1.5 and 1.4 for those with episodic or chronic exposure, respectively. In multivariable analysis, the association with HCV was higher for chronic exposure (vs. opioid-naïve/acute; aHR = 2.5, 95% CI = 2.3–2.8) than episodic exposure (vs. opioid-naïve/acute; aHR = 1.9, 95% CI = 1.8–2.0). Other characteristics associated with a higher risk of HCV seroconversion included higher social deprivation quintile (most deprived vs. least deprived; aHR = 2.8, 95% CI = 2.5–3.2), HIV (aHR = 1.5, 95% CI = 1.3–1.8), opioid misuse (aHR = 2.1, 95% CI = 2.0–2.2) and stimulant misuse (aHR = 1.6, 95% CI = 1.5–1.7). Female sex (vs. male sex; aHR = 0.8, 95% CI = 0.8–0.9) and other ethnicity (vs. Caucasian; aHR = 0.6, 95% CI = 0.5–0.7) were associated with a lower HCV risk. In an additional model where episodic/chronic PO exposure was further stratified by type of PO medication used, the association with HCV risk was higher for codeine-only exposure (vs. opioid-naïve/acute; aHR = 2.4, 95% CI = 2.2–2.6) than oxycodone, hydromorphone, fentanyl, or morphine exposure (vs. opioid-naïve/acute; aHR = 1.9, 95% CI = 1.8–2.1).

CONCLUSION(S): In this cohort study, long-term use of POs was associated with a higher risk of HCV seroconversion. The codeine-only finding requires further investigation.

Evidence for a striking failure in diagnosis and linkage to care for hepatitis C–infected patients in Alberta, Canada

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BACKGROUND: Available and effective direct acting antiviral therapies have made eliminating chronic hepatitis C (CHC) an achievable target. Although many efforts are currently underway to identify and treat CHC patients, few population-based studies have examined these practices.

PURPOSE: Therefore, we evaluated CHC diagnosis practices in Alberta, Canada. Specifically, we determined whether patients who had been tested and identified with a positive HCV antibody (HCV Ab) screening test were subsequently HCV RNA tested to determine viremia and facilitate linkage to care.

METHOD: We used multiple provincial administrative databases including Physician Billings, Ambulatory Care Database, and Provincial Laboratory Database to identify CHC patients with a positive HCV Ab test in Alberta, Canada from 2012 through 2017. Alberta Health Services (AHS) is a single payer universal health care system providing diagnostic and medical management to 97.7% of Albertans (4.1 million people). First, we identified HCV Ab +ve patients from the Provincial Laboratory database, then linked this cohort to patients who had HCV RNA testing (as well as other chronic liver disease tests). We used logistic regression models to identify independent predictors for not having HCV RNA testing, adjusting for patient demographics, urban living, comorbidities, laboratories investigations, and aboriginal status.

RESULT(S): We identified 19,534 HCV Ab +ve individuals during our study period. Interestingly, 82.6% (n = 16,131) had repeated HCV Ab testing after an index positive test (median = 2: IQR, 2–4). Only 62.2% (n = 12,143) of our cohort had subsequent HCV RNA testing. Among those with HCV RNA testing, viremia was detected in 63.3% (n = 7,680). Only 34.9% (n = 2,683) had repeat HCV RNA testing after treatment to confirm viral elimination, while 65.1% (4,997) had persistent viremia or did not receive HCV RNA testing after treatment. Genotype testing was only performed in 67.3% of patients with positive HCV RNA. Only 42.5% (n = 8,295) had HbsAg testing. Patients who did not get HCV RNA testing were younger (median age: 48 vs. 51; P <0.01), less likely to have multiple comorbidities (>2 comorbidities: 58.9% vs. 66.4%; P <0.01), likely to be aboriginal (13.4% vs. 11.3%; P <0.01), and more likely to live outside urban centers (33.1 vs. 27.7%; P <0.01). Furthermore, patients with no HCV RNA testing more commonly had normal ALT (34 vs. 42 IU; P <0.01) and AST (36 VS. 43 IU; P <0.01) compared to their peers. In our adjusted models, aboriginal status was independently associated with lower HCV RNA testing (adjusted OR 1.18; 95% CI: 1.04–1.34), while age³ 50, having multiple comorbidities and living in Urban areas were independently associated with having HCV RNA testing.

CONCLUSION(S): In this large Canadian population-based study, we show that crucial education of CHC testing and evaluation is urgently needed for health care providers. Improving CHC diagnostic practices to identify patients at risk will improve health care utilization and enhance HCV elimination strategies in Canada.

Prescribing trends of direct acting antivirals (DAAs) for the treatment of hepatitis C in Ontario

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BACKGROUND: The ease and effectiveness of direct acting oral antivirals (DAAs) treatments provide opportunity to expand treatment for chronic hepatitis C (HCV). Reimbursement mechanisms for DAAs have changed on two occasions since these drugs were added to Ontario' publicly funded drug formulary. Whether these changes have appreciably modified prescribing patterns and increased access to DAAs is unknown.

PURPOSE: The purpose of this study was to summarize the utilization of DAAs in Ontario between 2012 and 2018, and describe changes in prescribing physician specialties. A secondary objective was to describe the characteristics of people who received treatment through public reimbursement in 2018.

METHODS: We conducted a repeated cross-sectional study for DAAs reimbursed by the public drug program in Ontario from January 1, 2012 to December 31, 2018. We measured the quarterly number of users, overall and by prescriber specialty. Characteristics of those receiving DAA treatments in 2018 were examined overall and by prescriber specialty.

RESULT(S): A total of 27,116 individuals received a publicly-funded DAA prescription between Q1-2012 and Q4-2018. Nearly two-thirds (n = 17,813; 65.7%) of all DAAs were prescribed by gastroenterologists, hepatologists or infectious disease specialists. Only 9.6% of DAA recipients were treated by general practitioners. Utilization of DAAs had three major phases of increased uptake: (1) the introduction of DAAs to Ontario's public drug formulary as a prior authorization benefit in Q1-2015; (2) expanded listing of DAAs as limited use products on the formulary in Q1-2017; and (3) the introduction of newer DAAs in Q2-2018. In 2018, 2,538 unique individuals received publicly funded DAAs. The majority were over age 50 (59.8%), male (63.8%) and living in urban (88.8%) neighborhoods of lower socioeconomic status (41.7% in lowest income quintile neighborhoods). There were important differences among patients who received treatment from gastroenterologists/hepatologists (GH).For example, patients who received treatment from a general practitioner (GP) or infectious disease specialist (IDS) were more likely to have a mental health diagnoses (GP: 77.7%; IDS: 71.2% v GH: 41.6%) and be receiving opioid agonist therapy (GP: 54.5%; IDS: 51.6% v GH: 12.4%).

CONCLUSION(S): HCV elimination guidelines call for an expansion of the range of who delivers HCV treatment. Changes in the listing criteria of DAAs in Ontario's public drug program has led to increased uptake of these agents. However, there does not appear to be increased prescribing of DAAs among primary care prescribers who could minimize barriers to accessing therapy. Further understanding of the differences in characteristics of who received treatment by provider type and the remaining barriers to broader DAA prescribing, is needed.

CD8 T cell dysfunction and cancer development in a murine model of liver fibrosis

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BACKGROUND: Advanced liver fibrosis in chronic hepatitis C virus (HCV) infection is associated

with a high risk of hepatocellular carcinoma and extra-hepatic cancers. Many immune cells are impaired in liver disease, including CD8 T cells which are important for anti-viral and anti-tumor responses. We previously reported CD8 T cell hyperfunction in cirrhotic HCV-infected individuals that persisted after anti-viral therapy.

PURPOSE: The underlying mechanisms and impact on *in vivo* immune responses are unknown. To evaluate the link between CD8 T cell dysfunction and liver fibrosis, we will use a murine toxin-induced model of liver fibrosis.

METHODS: Mice (C57BL/6) were injected with carbon tetrachloride (CCl_4, twice weekly) for 12–16 weeks. Liver fibrosis severity was evaluated over time. CD8 T cell functions were assessed by flow cytometry. In addition, *in vivo* responses to an ectopic cancer challenge (MC38, s.c.) and subsequent anti-PD1 + anti-CTLA-4 immunotherapy were measured.

RESULT(S): We report robust generation of liver fibrosis in CCl_4-treated mice marked by severe, diffuse fibrosis, inflammation, and focal necrosis after 12-weeks and advanced liver fibrosis (cirrhosis) after 16-weeks of CCl_4 injections. After stimulation of PBMC, the proportions of granzyme B^+ and IFN-γ^+ CD8 T cells from fibrotic mice were significantly higher than controls. The expression of PD-1 was also increased. Tumor size and growth were significantly greater in fibrotic mice, and continued CCl_4 administration exacerbated this difference. In addition, the response to immunotherapy was significantly delayed in fibrotic mice.

CONCLUSION(S): We show for the first time that CD8T cells are hyperfunctional in a murine model of liver fibrosis, emulating that observed in HCV infection with cirrhosis. Removal of liver insult demonstrates a long-lasting effect on T cells. This hyperfunction occurred at the expense of CD8 T cell control of tumor growth and reduced immunotherapeutic effects, demonstrating the profound impact of liver damage on circulating CD8 T cells. This model will facilitate investigations to determine the mechanism of this immune dysfunction in order to identify targets to restore immune function that willminimize morbidity and mortality due to clinical outcomes like cancer in advanced liver fibrosis.

Early peg interferon-related ALT flares of high magnitude lead to HbsAg decline and loss. A study of 639 chronic hepatitis B patients

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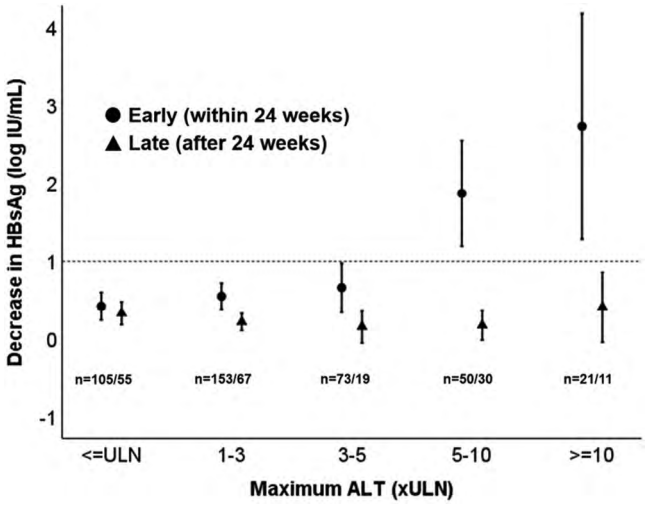
BACKGROUND: Serum alanine aminotransferase (ALT) flares play an important role in assessing nucleos(t)ide analogues (NA) discontinuation and during treatment with novel compounds aiming for functional cure (HbsAg loss). Flares can be a double-edged sword in chronic hepatitis B (CHB), as they may result in accelerated serological response but could also lead to liver failure.

PURPOSE: A post hoc analysis of four international randomized trials (HBV-99-01, PARC, ARES, PEGON) involving pegylated interferon (PEG-IFN-α-2a or α-2b)-based therapy was conducted to characterize ALT flares in CHB patients.

METHOD: Patients received PEG-IFN monotherapy (n = 260), de novo PEG-IFN+NA combination therapy (n = 128), PEG-IFN add-on to NA pretreatment (n = 123), or NA monotherapy (n = 128). A flare was defined as an episode of ALT elevation ≥5xULN after start of therapy, with those occurring within the first 24 weeks considered 'early', and after 24 weeks, 'late'. Patients with NA withdrawal flares were excluded. Logistic regressions were performed to describe the association between flares and serum HbsAg levels.

RESULT(S): During a median follow-up of 72 weeks, 111/639(17%) patients experienced at least one flare. The median timing of the first flare was 12 weeks (IQR 4–60) and the median magnitude was 6.6xULN (IQR 5.5–8.6). The flare group was older (36 vs 33 yrs), mostly Caucasian (79% vs 55%), largely genotype A/D (40%/50% vs 22%/38%), with higher baseline ALT (3.5 vs 1.5xULN), HBV DNA (7.8 vs 5.0 logIU/mL), and HbsAg levels (4.3 vs 3.9 logIU/mL), all p≤0.01.



Almost all flares (99%) were found in patients who received PEG-IFN-based therapy. Flares were observed in 38/251(15%) patients with PEG-IFN added on NA vs 72/260(28%) with PEG-IFN monotherapy (p <0.01). Among patients who received combination therapy, more flares were observed in the de novo PEG-IFN+NA therapy group compared to PEG-IFN add-on (36/128(28%) vs 2/123(2%), p <0.01). In total, 131 patients achieved ≥1log decrease in HbsAg. In univariable analysis, early flare was significantly associated with ≥1log decline in HbsAg (odds ratio (OR) (95% CI): 3.8 (2.3–6.2), p <0.01), as were male sex and increasing magnitude and number of flares. In multivariable analysis, compared to having no flare, early flares were independently associated with ≥1log decline in HbsAg (OR: 4.0 (2.2–7.3), p <0.01). Early ALT elevations ≥5xULN had a significant effect on serum HbsAg decline (figure; p <0.01). Of the 22 patients who achieved HbsAg loss, 16(73%) had at least one flare, which all occurred early during treatment (p <0.01). Neither decompensation nor death was observed with flares.

CONCLUSION(S): Early on-treatment flares were significantly associated with a greater decrease in serum HbsAg and with HbsAg loss compared to late flares or no flares.

Population-level hepatitis C cascade of care among men who have sex with men in British Columbia, Canada

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BACKGROUND: Gay, bisexual and other men who have sex with men (MSM) are at higher risk of hepatitis C virus (HCV) acquisition. Although monitoring progress of MSM across the care cascade is critical to achieving HCV elimination goals, there is lack of data from the population based systems for monitoring progress among MSM.

PURPOSE: We constructed the cascade of care among people diagnosed with HCV infection living in British Columbia (BC), Canada in 2018, stratified by MSM status, to compare progress in care and treatment in this population.

METHOD: The BC Hepatitis Testers Cohort (BC-HTC) was used for this analysis. The BC-HTC includes all individuals tested for HCV in BC since 1990, with their data linked to all prescription drugs, medical visits, hospitalizations and mortality data. We defined six cascade of care stages: 1) anti-HCV positive (diagnosed); 2) RNA tested; 3) RNA positive, 4) genotyped; 5) initiated treatment; and 6) achieved a post-treatment sustained virologic response (SVR). We compared progression through the care cascade by MSM status. MSM identification was based on self-report as well as validated algorithm which imputed missing information with 95% specificity.

RESULT(S): Of 33,647 males diagnosed with HCV and alive in 2018, 3,940 were MSM and 29,707 were non-MSM. Slightly more MSM (3,314, 84%) received confirmatory HCV RNA testing compared non-MSM (24,264, 82%). Among those with a positive RNA test, there was no difference in progression to genotyping between the MSM and non-MSM groups (2,231, 90% vs 16,514, 90%). However, slightly more MSM initiated treatment than non-MSM (1,406, 63% vs 9,964, 60%). There was a substantial increase in treatment uptake between 2012 and 2018 among both groups (MSM: 37% to 63%; Non-MSM: 36% to 60%). Among those who were RNA positive, treatment uptake was slightly

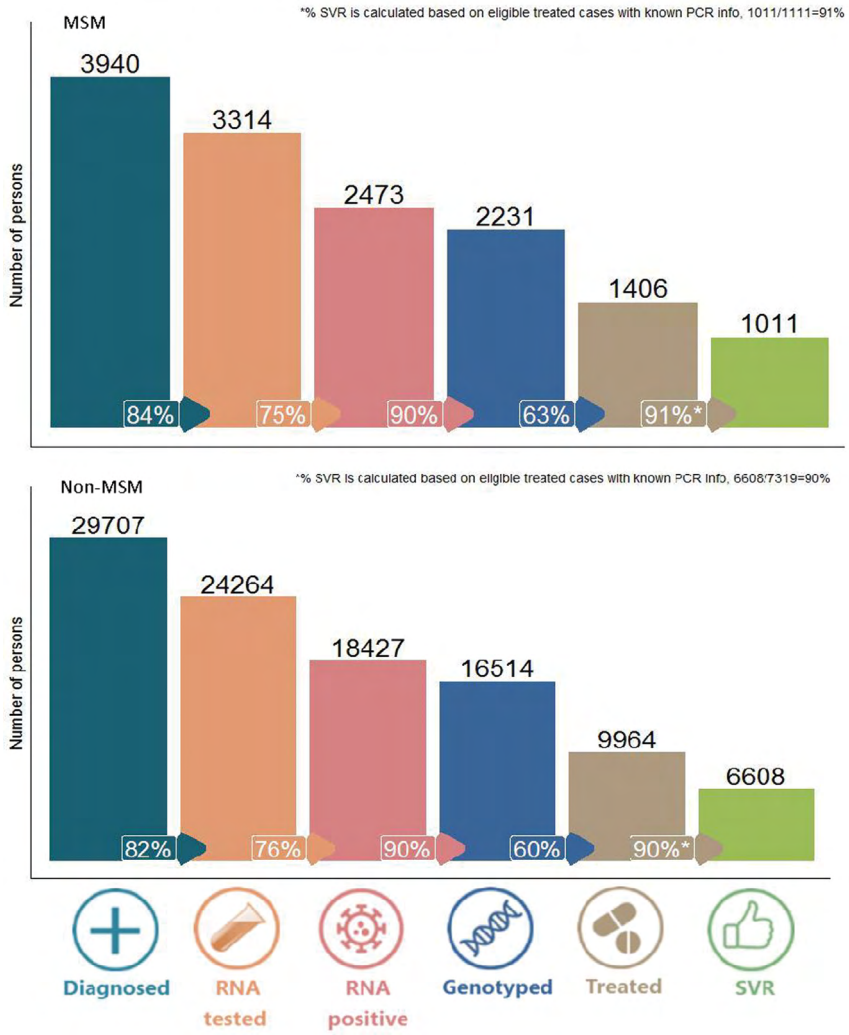

Figure: HCV care cascade among MSM and non-MSM groups in British Columbia in 2018

higher among MSM than non-MSM (1,406/ 2,473, 57% vs. 9,964/ 18,427, 54%). Among those who received treatment and were assessed for SVR, a similar proportion achieved SVR (MSM: 1,011/1,111, 91% vs non-MSM: 6,608/7,319, 90%) (Figure).

CONCLUSION(S): There has been substantial progression across the care cascade stages after introduction of DAAs. MSM had slightly better progression than non-MSM across the testing, care and treatment cascade.

Live animal imaging of oncolytic virus infection in non-cancer cells; how this might affect therapeutic outcome

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BACKGROUND: Oncolytic virus therapy (OVT) is an emerging treatment, both on the bench and in clinical trials, for various cancer types, including hepatocellular carcinoma (HCC). Viruses that are tropic to cancer cells are used to lyse tumour cells and subsequently generate an anti-tumour immune response culminating in tumour clearance. OVT is an attractive therapy as it can have reduced off target tissue damage and side effects compared to current treatment regimens. Additionally, immune system stimulation by OVT can provide an abscopal effect, assisting is reduction and control of metastatic disease. However, the precise mechanisms by which OVT activates the immune system is not completely determined.

PURPOSE: Our lab is interested in elucidating the mechanisms of immune activation in response to systemic OVT therapy with the belief that a better understanding of how immune cell populations are activated by OVT will yield new treatment strategies, better therapeutic results and improved patient outcomes.

METHOD: Live animal imaging (intravital microscopy; IVM) is used to visualize interactions between the host immune system, viral particles and infected cells following OVT. Vesicular Stomatitis Virus with a deletion in the M protein for enhanced safety (VSVdM51) and encoding green fluorescent protein (GFP) is used to visualize infected cells, while fluorescently conjugated antibodies label immune cells in the tumour microenvironment. Live anesthetized mice bearing tumours can be visualized under the microscope for several hours in order to collect information on how immune cells are responding to the VSVdM51 infection.

RESULT(S): Upon imaging multiple tumour bearing mice, we have observed few cancer cells to be directly infected by virus. On the contrary, tumour associated perivascular cells are consistently infected. Although we were aware that hepatic stellate cells (HSCs) were known to be susceptible to VSV infection, it was surprising that the attenuated virus demonstrated a preference for infection perivascular cells over cancer cells. Importantly, despite this lack of cancer cell infection, these tumour models remained responsive to this very therapy.

CONCLUSION(S): This novel observation indicates that the anti-tumour immune response, possibly initiated by perivascular stromal cells, is likely the main driver of therapeutic efficacy of OVT and not direct tumour lysis functions of the virus. These finding provide further validation for the need to better understand viral dynamics within the overall tumour microenvironment in an effort to fully understand the host response to systemic OVT treatment.

Differential hepatitis B virus (HBV) and hepatitis D virus (HDV) specific T cell response in HDV RNA positive and negative patients

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BACKGROUND: Although the adaptive immune responses to hepatitis D virus (HDV) are weakly detectable, recent data suggest the involvement of innate immunity in the progression of HDV infection (Grawbowski et al., 2011, Giersch et al., 2015). Hepatitis B virus (HBV)/HDV co-infection increases the risk of severe liver disease compared to HBV mono-infection (Wedemeyer & Manns, 2010). The role of intrahepatic CD206+ (M2) macrophages in viral end stage liver disease has been reported in humanized mice (Bility et al., 2016, Tan-Garcia et al., 2017).

PURPOSE: We hypothesize that an overall innate immune activation in HBV/HDV co-infection plays a role in liver disease progression. Our aim is to analyze cytokines and monocytes in association with HBV and HDV specific T cell responses in HBV/HDV co-infection.

METHOD: 30 HBV/HDV-co-infected-patients (median age 51y, 11F, 14 Asian/5 Caucasian/12 African) and 15 HBV- mono-infected-patients (8F, median HBV-DNA 39IU/mL, median age 39 y, median ALT 33U/L) were enrolled. To date, proliferation of CD3+CD4+ cells in response to HDV antigen HDAg, HBV surface antigen (HbsAg) and HBV core antigen (HbcAg) using flow cytometry based CFSE assays, immunophenotyping of monocytes using LPS stimulated PBMC and serum cytokines in a 13-plex Luminex were analyzed in 11 HDV-RNA+ (median HBV-DNA 10IU/mL, 5/11 IFN + NA, 3/11 NA monotherapy, 3 untreated, median ALT 77U/L); 5 HDV-RNA- (median HBV-DNA 13IU/mL, 3/5 prior IFN + NA, 1 NA, 1 untreated, median ALT 31 U/L) vs. 8 HBV untreated mono-infected cases (median HBV DNA 42IU/mL, median ALT 30U/L).

RESULT(S): PBMC stimulation with HDAg, HbcAg and HbsAg showed weaker CD3+CD4+T – cell proliferation in HDV-RNA+ vs. HDV-RNA- and HBV-mono-infected patients ($p < 0.05$, Krushkal-Wallis-test). We found that in HBV/HDV co-infected patients most tested cytokines/chemokines were comparable, but IL-10 levels were higher in the HDV-RNA+ vs. other groups and IL-1β showed increase in all HDV cases vs. HBV-mono-infected-patients ($p < 0.05$). A correlation between ALT and TNFα levels was noted only in the HDV-RNA+

patients (spearman's r = 0.76, p = 0.008). Increased proportion of CD11b+CD80+TNFα+ cells were found in HBV/HDV-RNA+ group vs. other groups (p < 0.05).

CONCLUSION(S): We observed weak HBV and HDV specific responses in both IFN untreated and treated HDV- RNA+ patients in association with increased TNFα producing monocytes that deserve further mechanistic evaluation.

Differences in surveillance for HCC in HIV infected patients with and without HCV/HBV coinfection: Insights from LIVEHIV cohort

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BACKGROUND: HIV-infected patients are at high risk for end-stage liver disease. Hepatocellular carcinoma (HCC) is one of the deadliest complications resulting from compensated advanced chronic liver disease (cACLD) and chronic hepatitis B. Guidelines advocate for regular surveillance for HCC with ultrasound with or without alpha-fetoprotein in HIV infected patients with cACLD or hepatitis B coinfection.

PURPOSE: The aim of our study was to assess the adherence rate to surveillance for HCC, as well as reasons for lack of adherence, in HIV infected patients with and without HCV or HBV coinfection, recruited from a large real-life, prospective cohort (LIVEr disease in HIV, LIVEHIV) established at McGill University Health Centre in Montreal.

METHODS: Patients in the LIVEHIV cohort receive annual screen for liver fibrosis by transient elastography. We included HIV infected patients eligible for HCC surveillance, according to current guidelines; specifically, inclusion criteria were: i) presence of cACLD defined as liver stiffness measurement (LSM) ≥ 10kPa in patients with HIV monoinfection and HIV/HCV coinfection; or HIV/HBV coinfection regardless of LSM; ii) follow-up time of at least 12 months. Patients with decompensated liver cirrhosis were excluded from this analysis. Adherence to surveillance was defined as: at least yearly examination for ultrasound and twice a year determination for alpha-fetoprotein.

RESULT(S): Out of 850 patients enrolled in the LIVEHIV Cohort, 154 patients were included (mean age 52, 77% males, mean duration of HIV infection 18 years, 52% with undetectable HIV viral load, mean CD4 cell count 645). Among them, 22% were HIV monoinfected with cACLD, 37% were HIV/HCV coinfected with cACLD, and 41% were HIV/HBV coinfected. Mean follow-up time for study population was 15 months (IQR 16–63). Characteristics of adherence to HCC surveillance are shown in the Table. Adherence rate by ultrasound was similar among HIV monoinfected, HIV/HCV and HIV/HBV coinfected patients. Conversely, adherence rate to HCC surveillance by alpha-fetoprotein was significantly lower in HIV monoinfected patients compared to HIV/HCV and HIV/HBV coinfected patients (p = 0.005). Overall, among the reasons for lack of adherence to HCC surveillance, lack of patient compliance was more frequent in HCV or HBV coinfected patients (p = 0.03) and was mostly associated with alcohol or drug abuse, psychiatric conditions and long distances to cover to reach the hospital. In 42% of HIV/HCV coinfected patients the surveillance for HCC was discontinued because of the reduction in liver fibrosis measured by LSM during the follow-up, mostly associated with HCV antiviral treatment (p < 0.001). Undermonitoring by physician was significantly more frequent in HIV monoinfected (62%) and in HIV/HBV coinfected patients (63%) compared to HIV/HCV coinfected ones (18%) (p < 0.001). During the follow-up, incidence of HCC in the study population was 1.3% (Table).

CONCLUSION(S): Adherence to HCC screening was suboptimal in HIV-infected patients from the LIVEHIV Cohort, regardless of the HCV or HBV coinfection status. Possible lack of awareness of liver-related complications in HIV monoinfected and HIV/HBV coinfected patients, as well as potential patient-related factors in HIV/HCV coinfected may explain these findings. Effort should be focused in improving physician awareness and to facilitate the access to care in disadvantaged patients.

Table: Surveillance for HCC in HIV infected patients, according to HBV and HCV coinfection status (n = 153)

	HIV monoinfected (n = 34)	HIV/HCV coinfected (n = 57)	HIV/HBV coinfected (n = 63)
Adherence to HCC surveillance by imaging, n (%)	13 (38)	24 (42)	28 (44)
Adherence to HCC surveillance by alpha-fetoprotein, n (%)	10 (29)	34 (59)*	33 (52)*
Reasons for lack of adherence to HCC surveillance, n (%)	**n = 21**	**n = 33**	**n = 35**
Lack of patient compliance	1 (5)	9 (27)*	12 (34)*
Transfer	0 (0)	3 (9)	1 (3)
Death	0 (0)	2 (6)	1 (3)
Undermonitoring by physician	13 (62)**	6 (18)	22 (63)**
Reduction of LSM during follow-up	7 (33)**	14 (42)**	0 (0)

**p value <0.05; **p value <0.001 in the univariate analysis.*

Long-term follow-up of people who use drugs cured of hepatitis C infection: re-infection and re-treatment

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BACKGROUND: To achieve elimination of hepatitis C virus (HCV) infection as a public health concern by 2030, a broad range of populations will have to be engaged in care. These populations include vulnerable inner-city residents, many of whom are people who use drugs (PWUD). The use of direct-acting antiviral (DAA) therapies leads to a cure in >90% cases, but there is some concern, especially in PWUD, about the rate of re-infection that may occur and the availability of reimbursement for subsequent re-treatment.

PURPOSE: The aim of this analysis was to evaluate the rate of recurrent viremia and the process of re-treatment in a population engaged in care and enriched for active drug users.

METHODS: We performed a retrospective analysis of patients at our center who received DAAs (+/- ribavirin, RBV) and achieved a sustained virologic response (SVR). They were subsequently maintained in long-term multidisciplinary care to address medical, psychologic, social, and addiction-related needs. HCV RNA was repeated every six months or more frequently if clinically indicated. The occurrence of recurrent viremia was documented and a plan of intervention was designed to provide a second course of HCV therapy.

RESULT(S): A total of 403 patients achieved SVR using DAAs at our centre and were available for evaluation. Of these, 10 had documented re-infection (10/403 = 2.48% re-infection rate), a rate of 1.98 cases/100 person years. Comparing the patients who became re-infected vs. those maintaining SVR, the mean age at treatment start (51.5 vs. 52.6 years) was similar, but the patients who became re-infected were more often male (100% vs. 72.0%), drug users (100% vs. 82.7%), HIV co-infected (20% vs 13.5%), and cirrhotic (40% vs. 19.1%). For the 10 re-infected patients, re-treatment is ongoing or completed in 6 cases, with re-treatment regimens including 1 sofosbuvir/velpatasvir (SOF/VEL), 1 SOF/VEL/voxilaprevir, 3 glecaprevir/pibrentasvir (GLE/PIB), and 1 GLE/PIB/RBV. The other 4 patients are scheduled to initiate re-treatment shortly. No cases of failure of re-treatment regimens have been documented at our centre to date.

CONCLUSION(S): HCV re-infection rates remain low in our inner-city population with a predominance of PWUD successfully treated with DAA-based regimens. There have been no obstacles to public funding for re-treatment and a universal acceptance of affected patients to receive it.

Transaminase flares during HbsAg reduction to <1 IU/mL are correlated with the establishment of virologic control and functional cure of HBV following NAP-based combination therapy

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BACKGROUND: Nucleic acid polymers (NAPs) inhibit the assembly and secretion of HBV subviral particles and interact with small and large forms of the hepatitis delta antigen. Asymptomatic transaminase flares are highly prevalent during combination therapy with NAPs and pegIFN in HBV and HBV/ HDV co-infection.

PURPOSE: An analysis of all 52 participants in the REP 301 and REP 401 studies was conducted to examine the correlation between HbsAg clearance, transaminase flares and therapeutic outcome for HBV (rebound, virologic control or functional cure) reported for these studies.

METHOD: All 52 participants from the REP 301 (NCT02233075, who have completed extended follow-up in the REP 301-LTF study, NCT02876419) and REP 401 (NCT02565719) were included. Variables analyzed included on therapy HbsAg and anti-HBs response, maxima and area under the curve (AUC) for ALT, AST and GGT, baseline characteristics, and therapeutic outcomes (based on 48-week follow-up in the REP 401 study and 2-year follow-up in the REP 301-LTF study). Virologic control of HBV is defined as HBV DNA ≤ 2000 IU/mL with normal ALT ≥ 24 weeks off therapy. Functional cure of HBV is defined as HBV DNA target not detected, HbsAg <LLOQ and normal ALT ≥ 24 weeks off therapy.

RESULT(S): Outcomes were balanced between rebound, virologic control and functional cure ($p = 0.750$) and independent of baseline characteristics ($p \geq 0.274$). Transaminase flares occurred in 96% of participants, were otherwise asymptomatic with unaltered liver function throughout (normal bilirubin, INR and albumin) and normalized during follow-up in 81% of participants.

The incidence ($p = 0.733$) and magnitude ($p \geq 0.189$) of flares were similar between outcomes and independent from baseline characteristics or anti-HBs titers during therapy. Transaminase maxima or AUC during therapy were significantly correlated with HbsAg reductions >3 $\log_{10}$ from baseline ($p < 0.05$)

Transaminase elevations (maxima and AUC) during different thresholds of HbsAg clearance (<1000, <100, <10 and <1 IU/mL) were analyzed and were significantly greater in the virologic control and functional cure groups ($p < 0.05$) at all thresholds. However, the prevalence of flares in virologic control and rebound outcome groups declined at lower HbsAg thresholds and the presence of flares while HbsAg was <1 IU/mL was significantly more selective for virologic control and functional cure ($p < 0.001$).

CONCLUSION(S): Transaminase flares during NAP therapy occur regardless of outcome and are well tolerated, with intensity correlated with HbsAg decline >3 $\log_{10}$ from baseline. Increased strength of transaminase flare activity, and its occurrence during HbsAg declines to <1 IU/mL may be important for the establishment of virologic control and functional cure of HBV.

Hepatitis C virus reinfection after successful treatment with direct acting antiviral therapy in British Columbia

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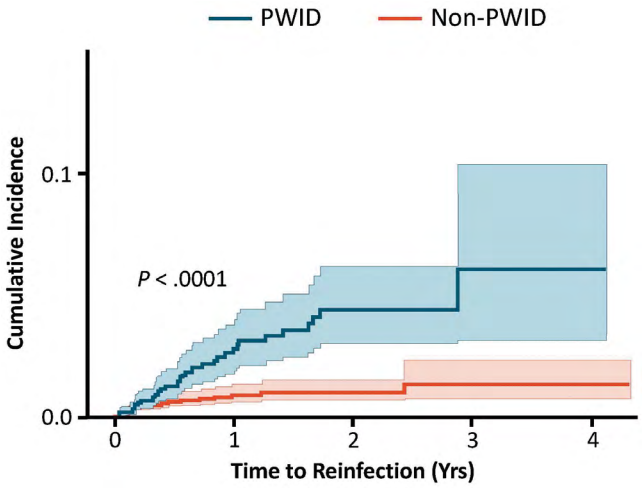
BACKGROUND: People who inject drugs (PWID) can be effectively treated with direct-acting antiviral therapies (DAA), however, HCV reinfection remains a concern.

PURPOSE: We estimated HCV reinfection rates among DAA-treated individuals in a population-based cohort study in British Columbia (BC), Canada.

METHODS: HCV-infected individuals the BC Hepatitis Testers Cohort treated with DAAs who achieved sustained virologic response (SVR) and had ≥1 subsequent HCV RNA measurement from SVR until April 9, 2019 were followed. Reinfection was defined as a positive RNA measurement after SVR. PWIDs were identified using a validated algorithm. Crude reinfection rates per 100 person-years (Pys) were calculated and Cox proportional



hazards modelling was performed to identify factors associated with reinfection.

RESULT(S): Among 5,702 individuals who received DAA treatment, the majority were male (n = 3,704, 65%), born <1965 (n = 5,298, 93%), and about a quarter were PWID (1,613, 28.3%). Among PWID, 42% received opioid-agonist therapy (OAT) after HCV treatment. We identified 62 reinfections during 4,834.70 Pys of follow-up post SVR, yielding a reinfection rate of 1.28/100 Pys. Reinfection rates were higher among PWID (n = 36, 2.36/100 Pys) than non-PWIDs (n = 26, 0.79/100 Pys). In a multivariable model for PWID, birth after 1975 (adjusted hazards ratio (AHR): 4.69, 95% CI: 2.07–10.62) and male sex (AHR: 4.1, 95% CI: 1.6–10.5) were associated with re-infection. Antipsychotic treatment was associated with lower re-infection risk (AHR: 0.55, 95% CI: 0.27–1.12). No reinfections were detected among PWID who received uninterrupted OAT, while the re-infection rate was 3.42/100 PY among those with interruptions.

CONCLUSION(S): Population-level reinfection rates after DAA therapy are higher among PWID – especially younger males. Uninterrupted OAT and antipsychotic treatment was protective against reinfection.

Glecaprevir/pibrentasvir for the treatment of hepatitis C virus infection among active drug users: The GRAND PLAN study

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BACKGROUND: In order to achieve the WHO objective to eliminate HCV infection as a public health concern by 2030, specific strategies to identify active drug users who are infected and to engage them in care will be required. The availability of shorter course treatment regimens may allow for more efficient use of available resources and better adherence to the entire course of medications.

PURPOSE: Our aim is to describe a program for the identification of vulnerable inner-city residents living with HCV infection and their engagement in a multidisciplinary program for the administration of antiviral therapy with glecaprevir/pibrentasvir (G/P).

METHODS: Using a community-based recruitment program (weekly outreach clinics on the Downtown Eastside of Vancouver), we identified individuals with a prior diagnosis of chronic HCV who were disengaged from care. Other individuals presented to our center by self-referral, referral from a corrections facility, or direct recruitment by existing participants in our program. All subjects were offered a broad-based intervention to address medical, social, psychiatric and addiction-related needs. Cirrhotic patients were excluded. HCV therapy was delivered in this context, with G/P dispensed on a daily, weekly or monthly basis (8 week course of treatment) to support adherence as required. The endpoint of this analysis is the achievement of a cure of HCV infection, defined as an undetectable HCV RNA 12 or more weeks after the end of treatment (SVR12).

RESULT(S): To date, 55 patients have been enrolled (mean age 47 years, 78% male, 49%/27%/47% fentanyl/cocaine/amphetamine use and 40% with an active psychiatric comorbidity, with 60% on opioid agonist therapy and 64% unstably housed at treatment start). Twenty-six patients have completed therapy, with no premature treatment discontinuations. Post-treatment, all patients (26/26) remain in follow-up, with 6 having reached the SVR12 time point and all 6 achieving SVR (SVR12 rate 100% for eligible patients). There have been no deaths in this population at high risk of opioid overdose. Treatment outcome in all patients will be available by March 2020.

CONCLUSION(S): When delivered within the context of a multidisciplinary program of care, HCV therapy with G/P for 8 weeks is highly effective in a vulnerable and marginalized population with a high prevalence of HCV infection. Approaches such as this will be an important part of HCV elimination over the next decade.

Overdose events among active drug users successfully treated for HCV: The impact of homelessness

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BACKGROUND: Since 2015, the opioid crisis has led to over 5,000 overdose deaths in British Columbia, Canada. Previous studies have demonstrated increases in risky drug use behaviour among individuals with unstable housing, a finding that may be mitigated by engagement in care, which may occur in the provision of HCV treatment to this priority population. We sought to evaluate the interaction of homeless and overdose events in a group of drug users having received HCV therapy in the context of a multidisciplinary system of care.

PURPOSE: To examine the interaction of homelessness on overdose events in the context of HCV treatment in a multidisciplinary setting.

METHODS: We conducted a retrospective analysis of active drug users engaged in HCV treatment at our centre from 01/15–10/19, as a function of their housing status. All patients were enrolled in multidisciplinary care addressing their medical, social, psychological, and addiction needs. The primary endpoints of this analysis are correlates and occurrence of medically significant overdose events, including mortality.

RESULT(S): We compared 211 (74%) well-housed and 75 (26%) homeless active drug users engaged in HCV care at our centre. Of these, 25 remain on HCV therapy and 243/261 (93%) others achieved a cure of their infection and remain in care. Mean age among well-housed active drug users was 53 years, 25% female, 55%/30%/39% opioid/amphetamine/cocaine use, 53% on opioid substitution therapy (OST), 50% psychiatric comorbidities. Among homeless active drug users, mean age was 52 years, 13% female, 76%/48%/45% opioid/amphetamine/ cocaine use, 56% on OST, 64% psychiatric comorbidities. Among well-housed active drug users, 18 individuals experienced medically significant overdose events and there were 7 deaths (12% event rate). Among homeless active drug users, 13 individuals experienced medically significant overdose events and there were 3 deaths (21% event rate).

CONCLUSION(S): Among HCV-infected active drug users engaging in care at our centre, one quarter were homeless, who were more often male, more active poly-substance users and with a higher prevalence of psychiatric co-morbidities. Overdose events (including mortality) were twice as frequent in this population. Although engagement in care served to reduce the occurrence of opioid-related events by over 50% compared to the overall population of active drug users in the community, homelessness remains associated with a higher risk of events even in the setting of provision of HCV care in a multidisciplinary setting. This setting will provide the ideal setting to evaluate additional interventions to reduce opioid-related events, particularly in the homeless population.

Prevalence and genotype of occult hepatitis B infection in a human immunodeficiency virus (HIV) positive patient cohort in Gondar, Ethiopia

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BACKGROUND: Globally, ~3.7 million people are co-infected with the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV). In endemic regions such as Ethiopia, HBV is not routinely tested in HIV positive patients. HBV co-infected patients are often treated with anti-HIV polymerase/ reverse transcriptase inhibitors that are active against HBV (i.e., lamivudine or 3TC).

Our previous study found that 5.5% of HIV positive patients from Gondar, Ethiopia had chronic (HbsAg positive) HBV infection. To date, there is limited knowledge on the prevalence of occult hepatitis B (OHB) in HIV positive patients in Ethiopia. OHB is characterized by low levels of HBV DNA despite undetectable serum HBV surface antigen (HbsAg). In immunosuppressed individuals, OHB is at risk of HBV reactivation, including HIV positive persons with low CD4+ T cell counts.

PURPOSE: To determine the prevalence of 1) OHB, 2) HBV genotype, and 3) mutations associated with nucleos(t)ide analog (NA) resistance, diagnostic escape mutants and liver disease progression in a cohort of HBV/HIV co-infected patients from Gondar, Ethiopia.

METHOD: From March to July 2016, 308 HIV-1 positive patients were recruited from the University of Gondar Teaching Hospital. Sociodemographic data (i.e., age, sex, risk factors for HIV or HBV) and clinical data (i.e., antiretroviral treatment, CD4+ T cell count, and risk of liver disease) were collected through chart review and patient questionnaire. Plasma was tested for HbsAg and anti-HBc antibody at the Alberta Provincial Laboratory using commercial assay (Abbott Architect). In anti-HBc positive samples, total DNA was isolated using phenol-chloroform. HBV DNA was amplified by nested PCR with primers specific to HBV surface and pre-core/core regions, followed by Sanger sequencing. HBV genome analysis was performed using MEGA 7.0.

RESULT(S): In 308 HIV-1 positive patients (62.7% female, median age of 38.4, IQR 18–68), 208 (67.5%) had lifestyle risk factors for HBV/HIV acquisition (i.e., blood transfusion, drug use, and unsafe injection). 290 (94.2%) were on antiretroviral therapy (ART) with combinations of Zidovudine (AZT)-Lamivudine (3TC)-Nevirapine (NVP). The median CD4+ T cell count was 405 cells/μL (IQR 75–734). There were no patients with cirrhosis or HCC. 115 patients were anti-HBc positive, of which 22 (19%) were HBV DNA positive. The HBV genotype results showed 86% D, 10% E, and 4% A. HBV precore/core mutations association with liver disease progression, NA resistance, and HBV surface gene variants were not detected in any cases.

CONCLUSION(S): In this cross-sectional study, OHB was detected in 19% of anti-HBc positive HBV/HIV co-infected patients with predominant HBV genotype D. The collected data further contributes to the limited knowledge on the epidemiology of OHB in Northwest Ethiopia.

Trends in hepatocellular carcinoma survival among individuals infected with HBV and/or HCV in British Columbia, Canada (2001–2016)

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BACKGROUND: Hepatocellular carcinoma (HCC) survival rates are generally poor but improvements may be possible if detected earlier.

PURPOSE: Our objective was to assess trends in and predictors of HCC survival in British Columbia (BC).

METHOD: We used data from the BC Hepatitis Testers Cohort, which includes all HBV/HCV cases (1990–2015) in the province linked to administrative data sources. We retrieved HCC data from the BC Cancer Registry (1923–2016) which captures ~95% of malignant cancers in BC and deaths from Vital Statistics (1985–2018). Co-morbidities were flagged using physician billings and hospitalizations (1990–2015). Survival after HCC diagnosis was assessed using Kaplan Meier analyses stratified by calendar year of diagnosis. Individuals were censored 2-years after HCC diagnosis or end of study (Dec 31, 2018). Cox proportional hazards models were used to identify characteristics associated with all-cause mortality.

RESULT(S): A total of 2,420 HCC cases were diagnosed from 2001–2016 among individuals with history of HBV and/or HCV infection. The annual number of new HCC cases doubled from ~100/year to ~200/year over the study period. Overall, 59.6% were HCV-positive, 32.6% were HBV-positive and 7.9% were co-infected. Most were male (80.3%) and Caucasian (66.9%), and the median (IQR) age at HCC diagnosis was 61 years (55–68). Overall, median survival time was 426 days and 2-year survival rate was 39.8%. By calendar year

of HCC diagnosis, the 2-year survival rate was 33.5% in 2001–2004, 38.9% in 2005–2008, 41.7% in 2009–2012 and 41.3% in 2013-2016. In adjusted analyses, a lower risk of mortality was observed in the more recent time periods (vs. 2001–2004): 2009–2012 (HR = 0.69, 95% CI = 0.59–0.81) and 2013–2016 (HR = 0.66, 95% CI = 0.57–0.78). Other factors associated with mortality were cirrhosis (aHR = 1.25, 95% CI = 1.10–1.41), greater Elixhauser co-morbidity index score (≥4 vs. 0, aHR = 1.53, 95% CI = 1.30–1.81) and higher social deprivation quartile (most deprived vs. least deprived, aHR = 1.37, 95% CI = 1.15–1.63). East Asian ethnicity was associated with lower mortality (vs. Caucasian, aHR = 0.76, 95% CI = 0.64–0.90).

CONCLUSION(S): Similar to other studies, HCC diagnoses are increasing and survival rates are low. Improvements in 2-year survival rates were observed over time but have stabilized in more recent years. Further research is needed to identify missed opportunities for prevention and earlier identification.

A population-level latent class analysis of people living with hepatitis C virus for effective program planning and health care resource distribution

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BACKGROUND: Since the advent of direct acting antivirals (DAAs), hepatitis C virus (HCV) treatment uptake has dramatically increased. As of 2018, 53,441 people were diagnosed HCV antibody positive in British Columbia (BC), yet only 54.4% of those diagnosed HCV RNA positive have been treated. HCV affects diverse populations, such as people who inject drugs (PWID), 'baby boomers', and immigrants from endemic countries, however these populations often overlap. Therefore, understanding combinations of shared characteristics among subpopulations may allow for more holistic and targeted program planning of HCV services.

PURPOSE: To classify people diagnosed with HCV based on sociodemographic and clinical characteristics using latent class analysis, to better match programming and services to patient populations.

METHODS: The BC Hepatitis Testers Cohort includes all HCV cases in BC from 1990 to 2015 followed up to 2018 and linked with data on medical visits, hospitalizations, cancers, prescription drugs, and deaths. Latent Class Analysis (LCA) was used to group HCV diagnosed people according to shared characteristics previously shown to be related to HCV treatment uptake (age, gender, ethnicity, sexual identity, urbanicity, social/material deprivation, history of injecting drug use or opioid agonist therapy, alcohol use, mental illness, co-infections, and liver disease). Among people treated, their HCV prescribers were identified. Models were fitted using 1–10 classes, with the best fitting model chosen based on fit statistics, epidemiological meaningfulness, and maximisation of posterior probability for class assignment. Latent classes were named based on defining characteristics (Figure 1).

RESULT(S): Among people treated with DAAs, the specialties of prescribers between classes differed. The best fitting model had 6 classes with the following characteristics:

1. Younger PWID: n = 11,123, 46% born>1974, 69% recent PWID, 24.0% treated, top prescriber = general practitioners–36.4%
2. Most MSM: n = 9,751, 39% MSM, 100% urban, 92% most socially-deprived, 27.7% treated, top prescriber = gastroenterologists–32.7%
3. Other—healthier people: n = 8,285, 24% rural, 0% liver disease, 22.1% treated; top prescriber = gastroenterologists–35.6%
4. People born <1964: n = 24,244, 95% born <1964, 19% liver disease, 32.7% treated, top prescriber = gastroenterologists–44.1%
5. People of Asian backgrounds: n = 4,744, 27% born <1945, 92% East and South Asian, 34.2% treated, top prescriber = gastroenterologists–61.9%

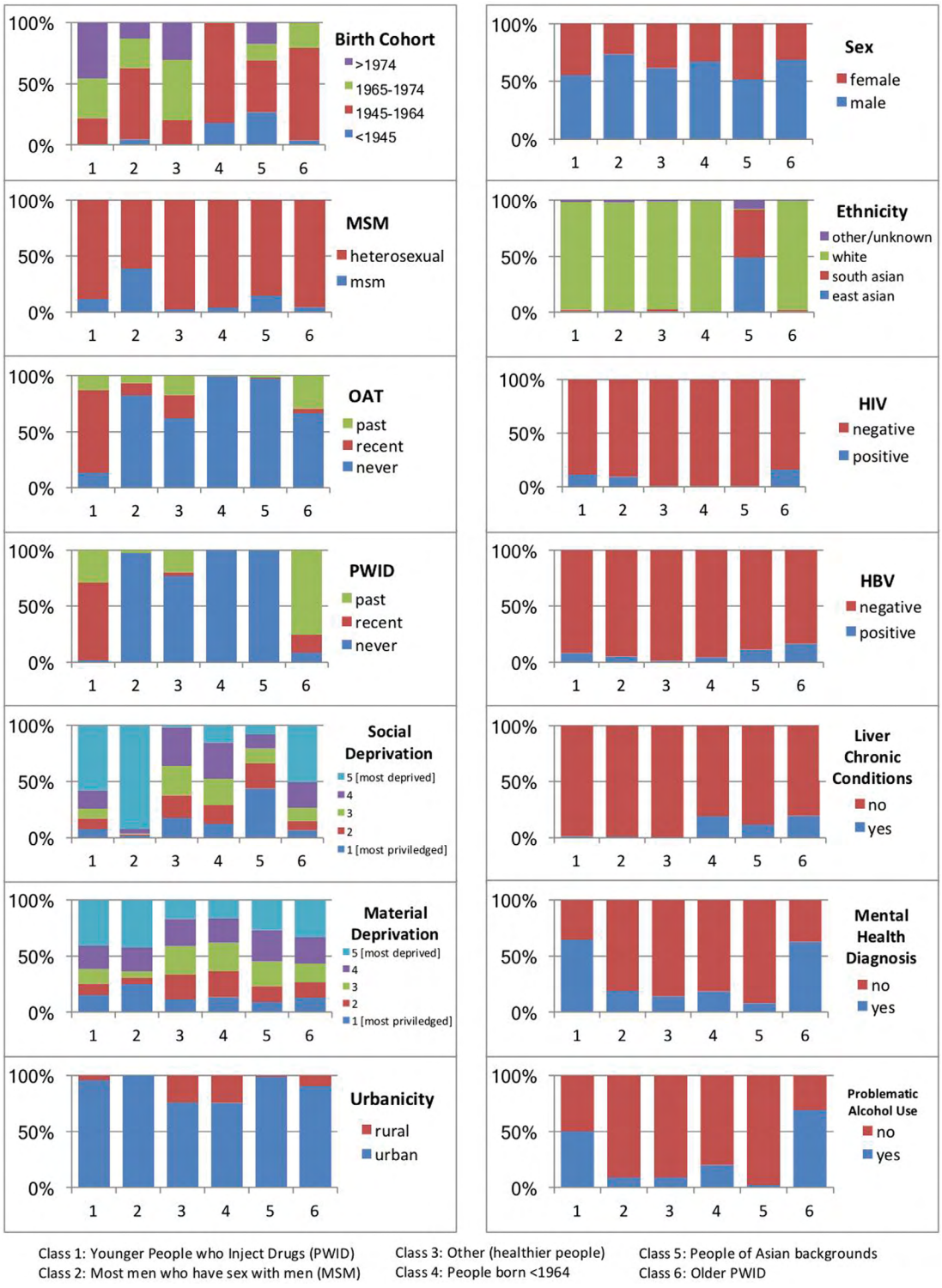

Figure 1: Characteristics of latent classes (on x-axis) of people living with hepatitis C in British Columbia

6. Older PWID: n = 15,518, 76% born 1945–1964, 16% HIV+, 76% past PWID, 21.0% treated; top prescriber = infectious disease–29.3%

CONCLUSION(S): LCA identified 6 classes with distinct characteristics, which could be utilized to align various services based on their background and needs. Differences in HCV treatment uptake among the classes suggest that the co-occurrence of multiple factors may influence the likelihood of HCV treatment uptake. Further investigation of health service utilization patterns related to multivariable patient profiles may inform optimal layout of prevention and care services. This analysis

could also help inform approaches to addressing structural or system barriers that impede care-cascade engagement for particular subpopulations.

Sofosbuvir/velpatasvir (S/V) for the treatment of chronic HCV in active drug users: The CHIME study

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BACKGROUND: To meet the WHO HCV elimination goals by 2030, members of priority populations, such as people who use drugs (PWUD), must be identified and engaged in care. With the availability of single tablet, once-daily short-course regimens, PWUD have a higher likelihood of regimen adherence and achievement of sustained virologic response (SVR).

PURPOSE: We describe the identification and engagement of HCV-positive PWUD into a program of multidisciplinary care and outcomes of S/V-based HCV therapy.

METHODS: We identified individuals with chronic HCV through community-based outreach programs in Metro Vancouver and Kelowna, British Columbia or by direct recruitment from other program participants. Subjects were active PWUD and/or prescribed opioid agonist therapy (OAT). Individuals were engaged in care in a multidisciplinary program to address medical, social, psychiatric, and addiction-related needs. Within the context of these interventions, 12 weeks of S/V was dispensed on a daily, weekly, or monthly basis depending on the needs of the patient. The primary endpoint is achievement of HCV cure as defined by SVR twelve weeks post-treatment (SVR12).

RESULT(S): To date, the study has enrolled 36 subjects (mean age 48.4 years, 78% male, 39% psychiatric co-morbidities). All subjects who were approached to participate and were eligible to receive government-funded S/V agreed to enroll. Most enrollees used street drugs within six months of enrollment. Urine drug screens at the screening visit showed 58%/44%/69% fentanyl/cocaine/amphetamine use, OAT at screening was 69%, and psychiatric medication use at treatment start was 41%, none of which required dose adjustment or modification in the context of HCV therapy. Seventeen have completed therapy and there were no premature treatment discontinuations. Of these 17 at post-treatment, 9 are awaiting the SVR timepoint, 1 was a virologic failure (no viremia detected at end of treatment, but viremic at post-treatment week 4), and 7 have achieved SVR12, for an SVR rate to date of 87.5% (7/8). There have been no known deaths due to opioid overdoses within this population.

CONCLUSION(S): Single tablet S/V delivered for 12 weeks within the context of a multidisciplinary program of care is highly effective in PWUD, including 11 patients on medications for psychiatric co-morbidities at HCV treatment start. Multidisciplinary engagement for the treatment of chronic HCV in vulnerable populations will be a critical part of meeting HCV elimination goals over the next decade.

Clinical evaluation of cholesterolic metabolism on the background of biliary insufficiency in patients with chronic hepatitis C

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BACKGROUND: Hepatitis C virus (HCV) subverts host cholesterol metabolism for key processes in its lifecycle. How this interference results in the frequently observed, genotype-dependent clinical sequelae of hypocholesterolemia, hepatic steatosis, and insulin resistance (IR) remains incompletely understood. Hypocholesterolemia typically resolves after sustained viral response (SVR), implicating viral interference in host lipid metabolism.

PURPOSE: To analyze cholesterol metabolism in patients with chronic hepatitis C with a low replicative level of viral bodies and biliary insufficiency with chronic hepatitis C.

METHOD: The study involved 45 patients with chronic hepatitis; the diagnosis was serologically verified using ELISA, and PCR method. The amount of HCV RNA did not exceed 1 × 106/ mL of copies. The average age was 38 ± 7. The duration of the disease since the diagnosis of hepatitis was more than 6 years. Diagnosis of biliary insufficiency was carried out method of stepwise chromatic duodenal sounding.

RESULT(S): The study showed that in patients with chronic hepatitis C, violations of the biochemical composition of bile were detected, namely: in the cystic and hepatic portions of bile, the concentration of cholic acid was significantly reduced and the cholesterol-cholesterol coefficient is reduced. When calculating the total production rate of the components released into the duodenum an hour after the introduction of the stimulus was also found a significant decrease in the production of cholic acid, cholate-cholesterol and phospholipid-cholesterol coefficients. When studying lipid metabolism in patients with diagnosed biliary insufficiency, an increase was detected in a biochemical blood test cholesterol level, and amounted to 8.2 ± 2.2 mmol/L ($p > 0.5$). Blood cholesterol has been elevated in 31 patients (48% of cases).

CONCLUSION(S): In patients with long-term chronic hepatitis C, cholesterol metabolism is impaired at all stages of its metabolism, and hypercholesterolemia is diagnosed in 64%.

Who are the real transformational leaders? From peer educators to peer navigators

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BACKGROUND: Dopamine is a Montréal-based community organization located in the Hochelaga-Maisonneuve neighbourhood, with the mission to help, support, and work alongside people who use drugs.

It has been ten years since Dopamine initiated the Dopalliés project, with the goal of mobilizing participants to adopt and promote more secure behaviours through educative workshops aiming to prevent the transmission of HIV/AIDS, hepatitis C and other STIBBs. Each year approximately fifty participants of the Dopalliés project become progressively equipped with prevention knowledge and act as peer educators in their own community.

PURPOSE: This change in our educative approach has had a direct impact in the community: participants finally wanted to start treatment. However, they remained confronted by structural barriers: a health care system that is not adapted to their life situation.Consequently, Dopamine developed a new service in partnership with CAPAHC (Centre Associatif Polyvalent d'Aide Hépatite C) and the Lotus project was born. The project provides personalized accompaniment services in partnership with the Quartier Latin clinic. A team of dedicated health professionals work to adapt and modify services so that a minimum of ten participants each year can access and adhere to treatment and avoid reinfection. Despite the willingness of health professionals to adapt to this specific population, participants still faced cultural barriers: when an institution must accommodate diverse adult needs, it has the reflex to infantilize and to offer privileges that can then be revoked. Ultimately, the institution loses confidence in the patient because they are unable to adapt to its formal functions.

METHOD: Subsequently, the organization has continued its reflections in order to further adapt health care services to better suit the needs of people who use drugs. In order to complement the services offered by the Lotus project in collaboration with its partners, Dopamine created a medical clinic at the drop-in centre called Dopamed.

RESULT(S): This new clinic aims to engage service users of Dopamine who are already implicated in various projects offered by the organization. In this new structure, two peers are responsible for the reception of patients and the functioning of the clinic. They are the first visionaries and decision makers of the structure and culture of the Dopamed clinic. Decisions are made collectively between team members including peers, doctors, nurses, and the intervention team.

CONCLUSION(S): People who have had positive experiences with Dopamine's services and projects are able to use their experiential knowledge to become peer navigators. They are able to turn their

fear of being stigmatized into a desire to take care of themselves! They are the true transformational leaders of social and medical change.

Transcriptomic analyses of the immune response during HCV re-infection

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BACKGROUND: Development of efficient vaccines against chronic viral infections like HCV is hampered by our limited understanding of the cellular and molecular pathways that form a potent protective memory immune response that is effective in "real-life" settings. Transcriptome analysis of primary and memory responses in murine models of viral infection demonstrated that different gene clusters distinguish effector and memory T cells, with memory T cells becoming imprinted with transcriptional programs that reduce exhaustion and facilitate rapid proliferation and long-term survival. We have recently performed transcriptomic analysis of the peripheral immune response during acute primary hepatitis C virus (HCV) infection where we observed rapid activation of pathways associated with innate immune activation, interferon signalling, and reduced B cell signatures. Whether, these same signatures are induced or maintained during a memory immune response is unknown.

PURPOSE: The goal of this proposal is to compare the transcriptomic and functional signatures of immune response to primary HCV infection versus reinfection and their contribution to long term protective immunity.

METHODS: We analyzed longitudinally the transcriptomic changes in the peripheral blood of six subjects who successfully resolved two successive episodes of HCV infection and three who resolved their primary infection but developed persistent viremia upon reinfection. Whole PBMC samples collected at baseline (Pre-infection), early acute (~ 4 weeks), late acute (~ 12 weeks) and follow-up phase (~48 weeks) of each reinfection episode were used to perform bulk RNA-seq.

RESULT(S): Pathways differentially regulated during each episode were determined using Gene Set Enrichment Analysis (FDR <0.05). In contrast to our previously published data on primary infection, we did not observe upregulation of pathways associated with innate leukocytes in either resolvers or chronics at the early acute time point. Pathways associated with B cells, memory and follicular helper CD4 T cells (Tfh) were upregulated in early acute in both groups. Furthermore, we observed an enriched plasma cells signature only in resolvers at early acute and at late acute that remained HCV RNA positive. This plasma cell signature was delayed in chronics and observed only at the late acute time point. Comparison with recently published HCV vaccine (ChAd3-Nsmut prime and MVA-Nsmut boost) data in healthy donors revealed similar T cell signatures as observed in re-infection samples. However, B cell signatures were absent in vaccine samples, as expected from this T cell-based vaccine.

CONCLUSION(S): At the transcriptomic level, there is an early up-regulation of the plasma-cells module in resolvers, while this signature is delayed in chronics. Preliminary analysis suggests that humoral immunity may be an important additive to T cell-based vaccines. Functional validation of these observations is ongoing and will be presented at the meeting.

Association between hepatitis B virus infection and risk of non-alcoholic fatty liver disease: A meta-analytic synthesis of observational studies

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BACKGROUND: Hepatitis B virus (HBV) infection has experienced an epidemiological shift in recent decades and significantly associated with risk of non-alcoholic fatty liver disease (NAFLD). Apart from potential progress of NAFLD to cirrhosis and hepatocellular carcinoma, NAFLD is an evolving risk factor in type 2 diabetes mellitus, cardiovascular diseases, and all-cause mortality.

PURPOSE: Available limited data regarding risk factors are still inconclusive to find out association

between HBV infection and risk of NAFLD. Therefore, current meta-analysis of observational studies designed to find out association between HBV infection and risk of NAFLD.

METHOD: A systematic literature search in Embase and Medline was conducted to identify relevant observational studies reporting HBV infection and risk of NAFLD. Odd ratio (OR) with 95% confidence interval (CI) were calculated to evaluate the association between HBV infection and risk of NAFLD. Subgroup analysis was also performed to find out association between HBV infection and risk factors responsible for the NAFLD. Meta-analysis was performed by R software using random effect model depending on heterogeneity (I^2). The data analyzed in the studies were collected from 2002 to 2019. New Castle Ottawa (NOS) scale was used to access the quality of included studies.

RESULT(S): A total of 1,464 studies (Medline = 437, Embase = 1,027) were screened through the initial search. Out of 1,464 studies, only 6 studies (cohort studies = 2, case-control study = 1, cross sectional studies = 3) involving a total of 8,428 HBV infected and 113,832 uninfected patients met inclusion criteria and considered for the qualitative and quantitative synthesis (meta-analysis). Mean age and body mass index (BMI) of the included patients were >38 years and >23 kg/m^2 respectively.

Pooled results from the meta-analysis of included studies reported no association between HBV infection and risk of NAFLD (OR: 1.19; 95% CI: 0.71–1.91; $I^2 = 96\%$; $P = 0.48$) when compared to uninfected control patients. However, from subgroup analysis of HBV infected patients it was found that diabetes mellitus (OR: 2.34; 95% CI: 1.80–3.04; $I^2 = 0\%$; $P < 0.00001$), reduced high density lipoprotein (HDL) (OR: 2.60; 95% CI: 1.76–3.83; $I^2 = 0\%$; $P < 0.00001$) and obesity (OR: 5.99; 95% CI: 3.01–11.93; $I^2 = 86\%$; $P < 0.00001$) were significantly associated with increased risk of NAFLD when compared to uninfected control patients. The NOS results showed that the average score was 7.7 (range 4–9) for the included studies.

CONCLUSION(S): From the current results, it was found that HBV infected patients are not associated with risk of NAFLD, however metabolic factors such as diabetes, reduced HDL and obesity play an important role for risk of NAFLD in HBV infected patients. Due to limited available studies and substantial heterogeneity, further long term randomized controlled trials and observational studies are required to confirm the present findings.

MicroRNA-122 promotion of Hepatitis C Virus translation is important early in the HCV infection cycle to initiate an HCV infection

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BACKGROUND: Hepatitis C virus (HCV) is a serious global health problem, infecting almost 3% of the world's population. Infection with HCV leads to chronic liver infections in an estimated 70% of infected individuals, and can lead to the development of various cancers, liver cirrhosis, and other complications late in chronicity. A liver-specific microRNA, miR-122, that binds to the 5′ UTR of the HCV genome plays an important role in HCV life cycle by positively modulating the viral RNA replication.

PURPOSE: Work from our lab demonstrates that, unlike the wild-type HCV genome, some full length RNAs with mutations in the 5′ UTR and bicistronic HCV replicons containing an additional IRES can replicate at low rates in miR-122-deficient cells. Although there are reports of miR-122-independent replication of HCV, no mechanism for independent replication has been proposed. In this study, we hypothesize that an altered translation regulation of viral genome at an early stage of infection affects viral propagation and, in-turn, promotes miR-122-independent replication.

METHODS: To prove our hypothesis we have studied transient translation of HCV replicating independent of miR-122, along with *in silico* analysis of HCV RNA using RNAfold software. We have also used fluorescent activated cell sorting (FACS) and microscopy techniques to study cells supporting miR-122 independent replication of HCV.

RESULT(S): We observed that the presence of the internal ribosomal entry site (IRES) from encephalomyocarditis virus (EMCV) and mutations in the

5′UTR that enhance HCV genome translation efficiency also promoted miR-122-independent replication. These findings support a role for enhanced translation in promoting miR-122-independent HCV replication. *In silico* structural analysis of miR-122 bound 5′UTR of HCV shows that the bound 5′UTR RNA forms an open structure similar to the canonical HCV IRES in contrast to the unbound which forms a closed non-canonical structure. The mutants which can replicate independent of miR-122 also forms the open structure similar to miR-122 bound 5′UTR of HCV. Thus, we speculate that the predicted structural change might be conferring enhanced translation efficiency by promoting the formation of the HCV IRES structure. Analysis of cells supporting miR-122-independent and dependent HCV replication by microscopy and flow cytometry revealed cells supporting miR-122-independent replication expressed HCV proteins at levels similar to that seen during miR-122-dependent replication, but that the numbers of cells supporting HCV is small.

CONCLUSION(S): These results suggest that establishment of replication in a high proportion of cells requires miR-122, but for genomes capable of miR-122-independent HCV replication, the life cycle is efficient after establishment. Further, in time course studies we also show that miR-122 supplementation or antagonization has little influence on HCV replication after an infection has been established. Hence, we suggest miR-122 plays an important role at the initial stage of infection by promoting viral translation, but it appears to have a relatively small influence on the maintenance of an infection within a cell.

Improved linkage to care by targeting HCV RNA(+) persons in the BC-HCV network

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BACKGROUND: There is no national HCV screening program in Canada. Many persons with chronic HCV are not linked to care (LTC). In British Columbia (BC) 60% of HCV persons have been tested but are untreated. A major challenge in the cascade of care is the linkage of persons who are HCV RNA (+) but lost to follow-up (LTFU).

PURPOSE: The aim was to evaluate the linkage to care by directly and indirectly contacting those persons who are HCV RNA (+) and previously seen but untreated as yet.

METHOD: A retrospective review for HCV RNA (+) persons in various clinics of the BC HCV Network was performed, to define which persons are cured or infected. Thereafter, the HCV RNA (+) persons would be contacted via a letter to their Family Physician (FP) and if ineffective, direct patient contact would be attempted.

RESULT(S): 1900 HCV infected persons' charts were reviewed from 2008 to 2019. Mean age was 59.2±12.3 years, 1060 (55%) were males, and 494 (26%) had cirrhosis. Before Jan 2017, when the program started, 779 (41%) persons with some contact to the network were cured. From Jan 2017 to April 2019 (DAA era), new and re-referrals of 1121 (59%) patients were included AND LTC, from which 585 patients (65%) were successfully LTC and cured. However, 536 patients (30%) remained infected and LTFU.

Of these 536 LTFU patients, we found that 172 (32%) patients were treated outside the network, 47 (9%) died, and 13 (3%) spontaneously cleared RNA. In the remaining 304 LTFU patients, in first attempt to re-LTC, letters were sent to their FP. Responses indicated that 15(5%) patients had died, 28 (9%) were treated outside the network; thus, we were able to re-link to care 49 (16%).

In remaining 203 persons with no response from FP, in second attempt to re-link to care, we contacted patients directly. We found out 65(32%) patients were treated outside network and 5 (2.4%) had died. We were able to re-link to care 9 patients (5%).

Overall, on average, 65% of patients were LTC and cured each year and 35% remained untreated. Encouragingly, out of 304 LTFU patients 58 (20%) were re-linked to care by letter to FP or direct contacts, and 124 (40%) remain LTFU.

CONCLUSION(S): Linkage to care can be improved by targeting those HCV RNA (+) persons previously seen but untreated by reconnecting them through their primary care providers or direct patient contact. Identifying HCV RNA (+) persons

and linkage to care can be an effective modality towards HCV elimination.

The impact of small RNA binding on hepatitis C virus replication via structural changes within the 5' untranslated region

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BACKGROUND: Hepatitis C virus (HCV) is a blood-borne viral infection affecting millions of people worldwide. The virus is a positive sense, single-stranded RNA virus of approximately 9.6kb in length, consisting of a single ORF which encodes for a polyprotein, flanked on either side by highly structured 5′ and 3′ untranslated regions (UTRs). A unique aspect of HCV is its reliance on a liver-specific microRNA, miR-122, to promote its replication. MicroRNAs (miRNAs) are typically involved in regulation of protein expression by binding to the 3′UTR of an mRNA transcript, leading to suppression of translation and subsequently degradation. By contrast, in the case of HCV, miR-122 binds to two sites within the 5′UTR and promotes viral replication. The exact mechanism of this RNA-RNA interaction has yet to be elucidated, but we hypothesize that small RNA binding promotes HCV replication by inducing RNA structural changes within the 5′UTR. These RNA structural changes could result in different outcomes, such as exposing or hiding protein binding sites, or allowing more efficient translation of the virus polyprotein.

PURPOSE: Our goal is to determine if the RNA-RNA interactions induce structural changes and identify pro-viral RNA structures. Computational predictions of the HCV 5′UTR secondary structure indicate that in the absence of small RNA binding the RNA folds into a "closed," non-canonical conformation, whereas when bound to a small RNA it adopts an "open" conformation identical to the canonical internal ribosome entry site (IRES) conformation presented in the literature.

METHODS: We will determine the 5′UTR RNA structure in collaboration with the Patel lab at the University of Lethbridge by using small angle X-ray scattering (SAXS). This involves the generation and purification of high-quality, mono-dispersed RNA solutions through in vitro transcription and size exclusion chromatography. The purified RNA is then subjected to high-energy, monochromatic X-rays and the scattering pattern produced by the molecule is measured. The scattering pattern is then processed and analyzed, and a low-resolution 3D envelope is produced through ab initio modeling.

RESULT(S): SAXS analysis has been done for both HCV 5′UTR RNA alone, as well as in the presence of miR-122 or alternative small perfect match RNAs (spmRNAs) that we have shown to also promote viral replication. The SAXS data we obtained indicate that the RNA structure of the HCV 5′UTR alone differs somewhat from that of the 5′UTR bound to small RNAs. Furthermore, we have identified several mutants that are capable of replicating independently of miR-122. The structures of these mutants were significantly different when compared to that of the wild type RNA alone, with multiple protrusions and altered conformations being observed.

CONCLUSION(S): While the structures we have obtained thus far are valuable, the low-resolution nature of SAXS makes it difficult to draw concrete conclusions, especially considering the conformational changes we expect may be relatively small. To solve this issue, 3D modeling of the RNA using the computationally predicted secondary structure will be done, and this model will then be fitted into the SAXS envelope. The higher resolution of an appropriate model would allow us to model the predicted RNA structural changes and determine if they correlate with our other data. Overall, we believe our SAXS data will provide us with valuable information on the structure of the HCV 5′UTR, and how it is affected by small RNA binding.

Can neurological weakness be the first presentation of chronic hepatitis in immunosuppressed population? Case report and literature review

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BACKGROUND: Until recently, hepatitis E virus was considered a cause of acute hepatitis that is self-limiting in most cases although fulminant hepatitis can occur. There is an emerging evidence that it can progress to chronic hepatitis and even cirrhosis. Extrahepatic manifestations have been reported

PURPOSE:

1. To describe an interesting case of hepatitis E infection whose initial presentation was neurological weakness that preceded the liver disease & improved after diagnosis & successful treatment of hepatitis E
2. To review the literature on the current epidemiology, various presentations, histological findings in addition to current available therapy.

METHOD: Patient information was extracted from electronic health records. In addition, we conducted a literature review using PubMed database.

RESULT(S): We are reporting a case of 48-year-old female who was diagnosed with cystic fibrosis since birth for which she required lung transplantation. Four years following the transplant, she developed radioculomyelopathy with an episode of transient mild elevation in liver enzymes. Extensive workup only revealed unquantifiable CMV viremia that was treated but her weakness never recovered. A few years later during a routine follow up, liver enzymes were found to be persistently elevated in a hepatocellular pattern excluding CF as a cause of elevation. Investigations including medications review, basic viral serology, autoimmune profile and metabolic screen as well as imaging came back negative apart from a positive ANA. Ultimately, liver biopsy had been performed and it was consistent with findings suggestive of autoimmune hepatitis with presence of bridging fibrosis (stage 3/4). Treatment with steroids was initiated and it resulted in modest decrease in the enzymes. Further investigation revealed positive serology for Hep E IgM, IgG and elevated viral load. Reducing her immunosuppression was not an option as she was on the lowest acceptable dose for patient post lung transplant. Based on the available data, off-labeled Ribavirin was given for a total of 12 weeks with continuous monitoring of enzymes which returned to normal after 3 weeks of treatment and negative Hep E PCR by the end of treatment and surprisingly, a significant improvement in her lower limb weakness.

Hepatitis E infection is a common cause of acute hepatitis worldwide especially in Asia. It is thought to be mainly affecting pregnant women and patients with chronic liver disease. However, there is increasing number of cases of Hep E chronic hepatitis and even cirrhosis detected in immunosuppressed population. It is reportedly associated with a range of systemic extrahepatic manifestations. Histologically, findings are non-specific unless special immunohistochemistry staining is available. Current available treatments include reduction in immunosuppression drugs, Ribavirin and some observational studies reported successful use of Sofosbuvir.

CONCLUSION(S): Hepatitis E infection should be always & routinely suspected in immunosuppressed patients especially solid organ transplant recipients who present with hepatic or unexplained extrahepatic features. Successful treatment is possible but further research is needed to determine the prognosis.

SESSION #2: GENERAL HEPATOLOGY

Differences in clonal evolution of recurrent hepatocellular carcinoma depending on the immune environment

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BACKGROUND: Hepatocellular carcinoma (HCC) is a highly heterogeneous cancer arising in the setting of chronic liver disease. Transplantation for

HCC is uniquely offered as a cure for cancer, and recurrent HCC tends to be aggressive.

PURPOSE: In order to delineate the molecular profiles and understand how immunosuppression shapes recurrent HCC, we examined the clonal evolution of recurrent HCC post-transplant (immunosuppressed setting) in comparison to recurrent HCC post-hepatectomy (immunocompetent setting).

METHOD: We examined the methylome and whole exome sequencing (WES) in archived FFPE samples from: 1) recurrent HCC after LT compared to the dominant tumour on liver explant (immunosuppressed, all patients on tacrolimus only, 22 samples in total), and 2) recurrent HCC after hepatectomy compared to tumour at hepatectomy (immunocompetent, 10 samples in total).

RESULT(S): Our data suggest that highly heterogeneous epigenetic evolution defines variation between primary and recurrent tumours that arise in the immunosuppressed environment of transplant. When we performed methylation modelling at baseline, before divergent treatment with and without immunosuppressive regimes, we found no significant differences (median delta-beta >0.3, FDR <0.05), but at recurrence, 9860 methylation variable positions (MVPs) were observed at the same thresholds (Figure 1). Visualizing the distribution of these MVPs showed that gene body and intergenic region associated changes were most common, followed closely by promoter changes. The differentially methylated genes between recurrences in the immunosuppressed and immunocompetent settings were involved in the cell cycle (Table 1). We also applied MethylCIBERSORT, an immune deconvolution method to robustly estimate the composition of the stroma, to our methylation-profiled samples. We discovered that the vast majority of tumors were immune-hot at both baseline and recurrence. Therefore, the abundance of immune cells did not differ between the two states, regardless of suppression status.

CONCLUSION(S): In summary, we have for the first time performed integrative genomic/epigenomic profiling of recurrent HCCs post-liver transplant in comparison to recurrent HCCs post-hepatectomy. This work demonstrates highly heterogeneous epigenetic evolution when selective immune pressure is removed (immunosuppressed setting) as opposed to the immunocompetent setting. The significantly higher presence of cell cycle-related genes could inform identification of chemopreventive agents, allowing our patients to fulfill the opportunity of their transplant.

Table 1: Differently ethylated genes in recurrent HCC between immunocompetent and immunosupressed are involved in cell cycle

Pathway Name	q-value (FDR: BH-method)
Cell Cycle	2.93E-07
M Phase	2.41E-04
G1/S Transition	7.46E-03
Mitotic Anaphase	8.12E-03
G2/M Checkpoints	8.12E-03
S Phase	8.59E-03
Mitotic Metaphase and Anaphase	8.99E-03
M/G1 Transition	9.13E-03

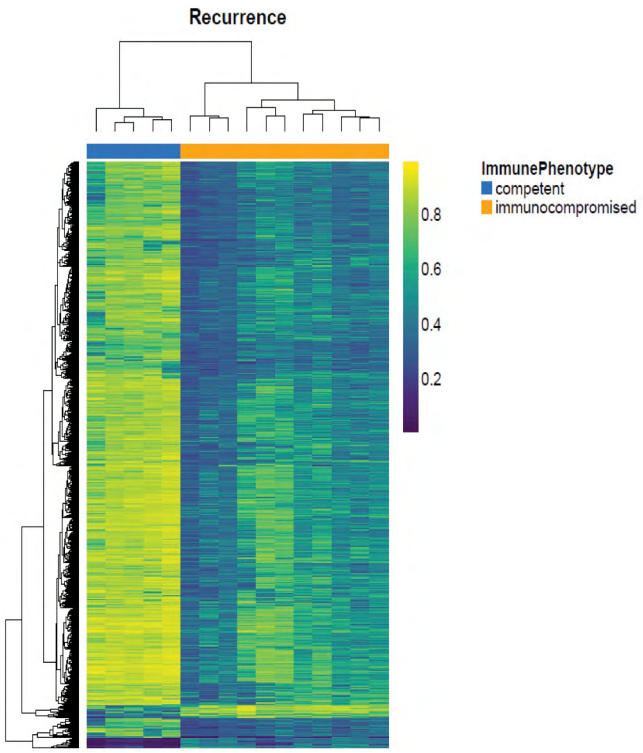

Figure 1: Methylation profile identified 9860 Methylation variable positions (MVPs) in recurrent HCC arisen in immuosuppressed setting compared to immunocompetent

Women likely to benefit from having a potential living liver donor compared to men

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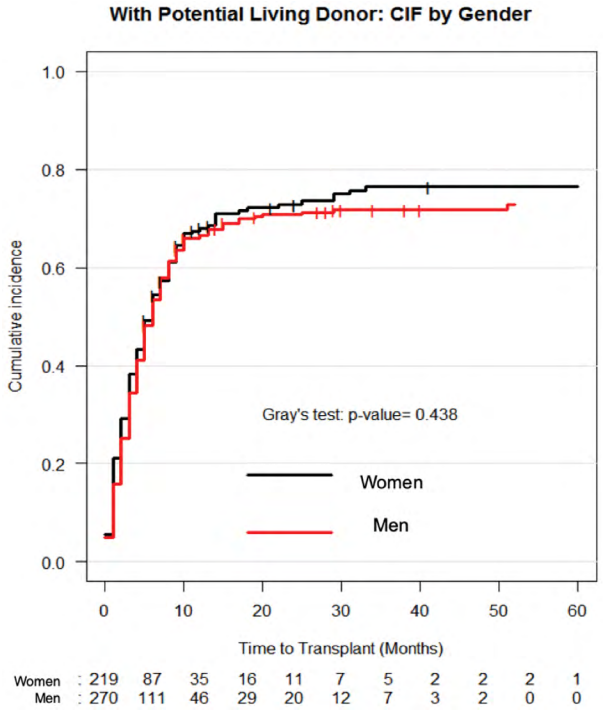
BACKGROUND: It is well recognized that there is a disparity in liver transplantation (LT) rates between men and women. Several factors account for this disparity, including smaller body size and lower muscle mass leading to lower serum creatinine in women.

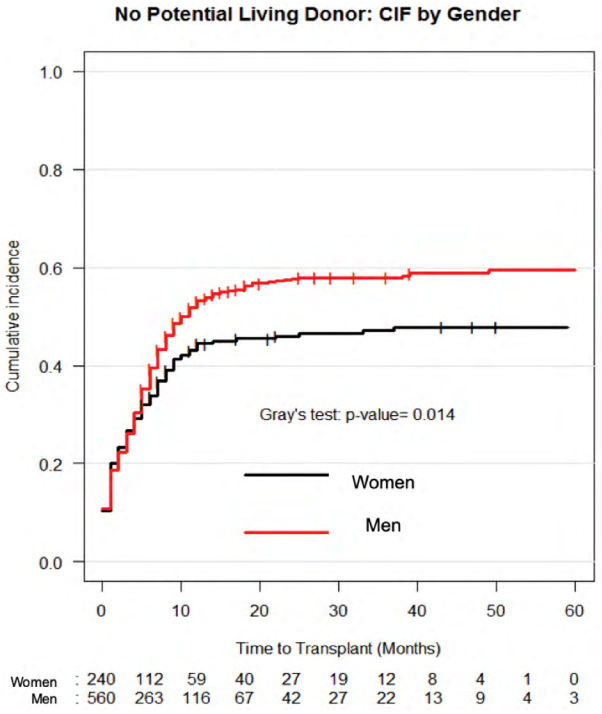
PURPOSE: We sought to determine whether the presence of a Potential Living Donor (PLD) helps women gain better access to LT.

METHOD: We performed a retrospective analysis of data on adult patients above the age of 18 listed for LT from November 2012 till December 31, 2018. Patients were followed till the time of dropout from the waiting list and LT. Subgroup analysis was done based on gender and type of LT. Patients with acute liver failure and those requiring exception points for listing were excluded. Variables that would potentially influence listing and LT were identified based on a priori clinical relevance. A PLD referred to an individual who had stepped forward for living donation and had completed the initial assessment as well as imaging assessment.

RESULT(S): 783 of 1289 listed patients (573 deceased donor LT, 210 living donor LT) underwent LT during the study period. In the group with no PLD at assessment: a) 46.13% failed to attract LT and NaMELD score did not differ between men and women at the time of listing or drop out, b) in patients eventually receiving deceased donor LT, women had both a higher NaMELD at listing ($p = 0.0004$) and at LT ($p < 0.0001$) compared to men. In the group with PLD, NaMELD score did not differ between gender at time of listing, LT or drop-out. Fine and Gray model suggested that in the no PLD group, the cumulative incidence curve for time to LT was higher in men than women ($p = 0.014$) (Figure 1), whereas there was no gender difference detected in the PLD group ($p = 0.44$). Cox PH model revealed a trend of higher overall survival in men than in women ($p = 0.08$) in the no PLD group and no difference was found in the PLD group ($p = 0.93$). Also, among women with no PLD, taller women were associated with higher chances of LT (HR 1.04, 95% CI 1.01–1.07, $p = 0.01$) (Figure).

CONCLUSION(S): With no PLD during assessment, women were at potential risk of lower survival and





were significantly disadvantaged at receiving LT compared to men. Women receiving LT were much sicker than their male counterparts both at time of listing and at time of LT, and were taller than other women who failed to receive LT. When PLD were identified at time of assessment, access to LT and overall survival improved for women and their results became comparable with men.

Durable response in the markers of cholestasis through 5 years of open-label extension study of obeticholic acid in primary biliary cholangitis

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BACKGROUND: Obeticholic acid (OCA) is a selective and potent farnesoid X receptor agonist indicated for treatment of primary biliary cholangitis (PBC). POISE was a placebo-controlled, phase 3 study of the efficacy and safety of OCA in PBC, and included a 12-month double-blind phase with a 5-year open-label extension (OLE).

PURPOSE: The OLE was to assess the long-term safety of OCA and the durability of OCA effects on serum markers of cholestasis.

METHOD: Key inclusion criteria included PBC diagnosis, alkaline phosphatase (ALP) ≥1.67× upper limit of normal (ULN) and/or total bilirubin >ULN to <2× ULN, and on a stable dose of—or intolerant of—ursodeoxycholic acid. During the double-blind phase, 216 patients were randomized to daily placebo, OCA 5–10 mg (titrated after 6 months based on response and tolerability), or OCA 10 mg. 193/198 patients completing the double-blind phase enrolled in the OLE and received OCA. The POISE composite primary endpoint was the percentage of patients with ALP <1.67× ULN, with a reduction of ≥15% from baseline, and total bilirubin ≤ULN at 12 months. This analysis pooled double-blind placebo (OCA baseline was OLE day 0) and double-blind OCA patients to evaluate the efficacy and safety of up to 72 months of OCA treatment.

Table: Serum markers of cholestasis from baseline through 72 months of OCA treatment

		Change from baseline	
Mean (SD)	Baseline (N = 193)	12 months (N = 185)	72 months (N = 52)
Alkaline phosphatase (U/L)	317 (120)	−105 (88)*	−118 (128)*
Total bilirubin (µmol/L)	11.5 (7.0)	−0.9 (4.1)†	−0.1 (4.5)
Aspartate aminotransferase (U/L)	51.2 (33.5)	−12.8 (24.7)*	−14.1 (18.2)*
Alanine aminotransferase (U/L)	56.7 (37.0)	−21.5 (24.4)*	−28.2 (29.4)*
Gamma-glutamyl transferase (U/L)	275.2 (306.0)	−157.7 (205.1)*	−156.1 (200.1)*
Liver stiffness (kPa)†	11.4 (9.4)	0.5 (5.6)	1.2 (10.1)

**p <0.0001; †p = 0.004; †Baseline N = 79, 12 months N = 32; kPa, kilopascal.*
p-values for the within-treatment comparisons were obtained using a paired t test.

RESULT(S): 146 patients (76%) completed the protocol as specified following administrative shutdown of the study. 158 patients (82%) completed 4 years of OCA treatment and 116 (60%) patients completed 5 years of OCA treatment; 52 patients who had received OCA in the double-blind phase completed 6 years on treatment. The percentage of patients meeting the primary endpoint was 46% at 12 months and 50% at 48, 60, and 72 months. Significant and durable reductions were observed for ALP, alanine aminotransferase, aspartate

aminotransferase, and gamma-glutamyl transferase throughout the study (Table). Mean total bilirubin remained stable through 72 months of OCA treatment. Throughout the study there was no significant worsening in hepatic stiffness as measured by transient elastography in a subset of patients. During the OLE, 8 patients (4%) discontinued treatment due to pruritus. Adverse events were consistent with the established safety profile of OCA in PBC, with no new safety observations during long term treatment out to 6 years.

CONCLUSION(S): OCA treatment resulted in sustained improvement in liver biochemistry during up to 6 years of follow-up.

Preventive effect of celecoxib in sorafenib-related hand-foot syndrome in hepatocellular carcinoma patients, a single-center, open-label, randomized, controlled clinical phase III trial

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BACKGROUND: Skin toxicity, especially hand-foot syndrome (HFS), is one of the most common sorafenib-induced adverse events (AEs) in hepatocellular carcinoma (HCC) patients, leading to treatment interruption and failure.

PURPOSE: We investigated whether celecoxib can alleviate HFS, improve patients' quality of life and increase survival when administered in conjunction with active therapy

METHOD: Our randomized, open-label study prospectively enrolled 116 advanced HCC patients receiving sorafenib as targeted therapy from July 2015 to July 2016. All patients were randomly assigned (1:1) via a computer-generated sequence to receive sorafenib with or without celecoxib. Sorafenib-related AEs were recorded, Survival was compared between the two groups

RESULT(S): Compared to the Sorafenib group, the SoraCele group had lower incidence rates of ≥ grade 2 and grade 3 HFS (63.8% vs 29.3%, $P < 0.001$; 19.0% vs 3.4%, $P = 0.008$, respectively), hair loss, rash and abdominal pain. Kaplan-Meier analysis revealed a lower risk of ≥ grade 2 HFS (HR, 0.384; $P = 0.002$) and a lower dose reduction/interruption rate (46.6% to 15.5%, $P < 0.001$) in the SoraCele group. Cox proportional hazards regression analysis demonstrated that celecoxib was the only independent predictive factor of developing ≥ grade 2 HFS (HR, 0.414; $P = 0.004$). Longer progression-free survival (PFS) was also observed in the SoraCele group ($P = 0.039$), although overall survival was not prolonged ($P = 0.305$).

CONCLUSION(S): Sorafenib+celecoxib administration alleviated sorafenib-related skin toxicity. Longer PFS was achieved in clinical practice, although overall survival was not prolonged (ClinicalTrials.gov: NCT02961998).

Noninvasive tests (NITs) may more accurately quantify fibrosis than liver histology in patients with advanced fibrosis due to NASH

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BACKGROUND: Staging of hepatic fibrosis by liver biopsy is the reference standard, but has limitations that may be overcome by noninvasive tests (NITs). NITs accurately predict fibrosis stage as well as the risk of liver-related complications in patients with NASH.

PURPOSE: To compare improvement in fibrosis as measured by histology and NITs in patients with advanced fibrosis due to NASH.

METHOD: Adults with advanced fibrosis (F3-F4) due to NASH (NAS ≥3) were enrolled in two phase 3, placebo-controlled trials of selonsertib (STELLAR-3 and -4). These trials were stopped at 48 weeks (W48) due to lack of histologic efficacy. Baseline (BL) and W48 biopsies were staged centrally according to the NASH CRN classification. Histologic Response (H-R) was defined as ≥1-stage improvement in fibrosis without worsening of NASH. BL predictors of histologic response (H-R) were evaluated, and changes from BL to W48 in clinical and laboratory parameters were compared according to H-R, ELF response (ELF-R; defined as ≥0.5-unit reduction), and Transient Elastography (TE) response (TE-R; ≥25% relative reduction)

RESULT(S): 1,527 patients (802 F3, 725 F4) with histology, ELF, and TE data at BL and W48 were included. At BL, median (IQR) ELF was 10.0 (9.4, 10.6) and 10.6 (10.0, 11.3), and liver stiffness (LS) by TE was 12.8 kPa (9.7, 17.3) and 21.1 kPa (14.3, 28.8) in patients with F3 and F4, respectively. Patients with H-R had lower BL hepatic collagen, α-SMA expression, serum NITs (ELF, FIB-4, NFS, FibroTest), LS by TE, AST, GGT, CK-18, bile acids (in F4), and greater hepatic fat and serum albumin (in F4) compared to non-responders (all $p < 0.05$). At week 48, only hepatic collagen and α-SMA expression were significantly reduced in patients with H-R compared with histologic non-responders (H-NR) (Table). In contrast, patients with ELF-R or TE-R had consistent improvements across a range of parameters (Table) including liver biochemistry, weight, NITs, LS,

Table.

		H-R	H-NR	p-value	ELF-R	ELF-NR	p-value	TE-R	TE-NR	P-value
		N = 90	N = 657		N = 122	N = 643		N = 143	N = 380	
	Collagen, %	−48.7	−12.6	<0.0001	−28.1	−20.0	0.5830	−25.0	−22.2	0.6447
	ALT, U/L	−17.8	−8.3	0.0508	−34.4	−5.2	<0.0001	−16.9	−3.1	<0.0001
F3	GGT, U/L	−4.2	−4.6	0.4512	−27.7	0.0	<0.0001	−20.5	1.8	<0.0001
	Weight, kg	−0.4	−0.8	0.4820	−2.2	−0.4	<0.0001	−2.0	−0.5	0.0003
	ELF	−0.2	1.3	0.0365	−8.4	2.1	<0.0001	−1.60	1.8	<0.0001
	LS by TE	−5.8	−4.9	0.4232	−30.0	−1.5	<0.0001	−38.7	5.1	<0.0001
		N = 117	N = 667		N = 134	N = 678		N = 150	N = 391	
	Collagen, %	−47.3	−10.6	<0.0001	−18.1	−21.7	0.8360	−18.9	−24.2	0.6264
	ALT, U/L	−5.1	−6.5	0.8849	−18.9	−4.3	<0.0001	−14.6	−4.3	0.0003
F4	GGT, U/L	−11.3	−7.8	0.1783	−22.6	−4.4	<0.0001	−17.6	−3.7	<0.0001
	Weight, kg	−0.3	−0.9	0.6826	−2.3	−0.4	<0.0001	−1.5	−0.3	0.0035
	ELF	−0.2	1.3	0.1494	−7.1	2.3	<0.0001	−0.5	2.0	0.0003
	LS by TE	−7.9	−0.5	0.0255	−18.4	1.0	0.0009	−38.7	12.0	<0.0001

Data are median relative (%) change from BL to W48. P-values by Wilcoxon rank sum test.

hepatic fat, serum bile acids, glycemic indices, CK18, and CRP.

CONCLUSION(S): In patients with advanced fibrosis due to NASH, improvements in ELF and TE are associated with each other and with other clinical parameters, but not histologic improvement. On the contrary, histologic improvements were not associated with changes in non-histologic parameters. These discordant observations are likely attributable to sampling error of liver biopsy and emphasize the need for additional studies that validate clinical trial endpoints

Health-related quality of life—A rapid independent predictor of hospitalizations and mortality in cirrhosis

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BACKGROUND: Patients with cirrhosis experience a worsened quality of life; this may be quantified by the use of health-related quality of life (HRQoL) constructs, such as the chronic liver disease questionnaire (CLDQ) and EuroQoL Group–visual analogue scale (EQ-VAS). As opposed to other disease states, it remains unclear in cirrhosis whether HRQoL may be predictive of outcomes of hospitalization and mortality.

PURPOSE: In this multi-centre prospective study, we aimed to evaluate HRQoL as a predictor of unplanned hospital admission/early mortality, identify HRQoL domains most affected in cirrhosis, and identify predictors of low HRQoL in patients with cirrhosis.

METHOD: Multivariable logistic regression was used to determine independent association of HRQoL with primary outcome, and identify predictors of low HRQoL. HRQoL was also compared with population norms.

RESULT(S): In this cohort of 402 patients with cirrhosis, mean MELD was 12.5 (4.9). Over 50% of the cohort had low HRQoL, considerably lower than population norms. HRQoL (measured by either CLDQ or EQ-VAS) was independently associated with the primary outcome of short-term unplanned hospitalization/mortality. Every 1-point increase in the CLDQ and every 10-point increase in the EQ-VAS reduced the risk of reaching this outcome by 30% and 13%, respectively. Patients with cirrhosis had lower HRQoL scores than population norms across all domains of the CLDQ, with fatigue being the most disparate. Younger age, female sex, current smoker, lower serum albumin, frailty and ascites were independently associated with low CLDQ.

CONCLUSION(S): Patients with cirrhosis experience poor HRQoL. HRQoL is independently associated with increased mortality/unplanned hospitalizations in patients with cirrhosis, and could be an easy-to-use prognostic screen that patients could complete in the waiting room prior to their appointment.

IL-16 as a new marker for the diagnosis of AIH/PBC overlap syndrome

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BACKGROUND: AIH/PBC overlap syndrome is notoriously difficult to diagnose, therefore, the identification of a biomarker specific to AIH/PBC overlap syndrome could prove very useful to rapidly diagnose these patients. CD4+ T cells are an important lymphocyte subset present in the liver inflammatory infiltrates of patient with autoimmune hepatitis (AIH) and AIH/PBC overlap syndrome. CD4+ T cells can provide T-cell help to B cells for the secretion of IgG and autoantibodies and lead to the activation of cytotoxic CD8+ T cells. IL-16 is a proinflammatory cytokine that functions as a chemoattractant of CD4+ T cells.

PURPOSE: The aim of this study was to assess the involvement of IL-16 in patients with AIH and AIH/PBC overlap syndrome and its possible usefulness as a disease-specific marker.

METHOD: We used our newly created *AIH Research Biobank*, composed of biological samples and clinical data from patient with features of AIH to establish an immunological profile of patients with AIH (n = 65), AIH/PBC overlap syndrome (n = 26), PBC (n = 45) and PSC (n = 11).

RESULT(S): Patients with an AIH/PBC showed significantly higher plasma levels of IL-16 compared to AIH, PBC or PSC patients (296.1±42.6 pg/mL vs 193.6±10.9 pg/mL, 66.8±8.4 pg/mL and 73.11±16.85 pg/mL respectively, $p < 0.0001$). 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 mild to moderate fibrosis (F1 to F2) (348±75 pg/mL) compared to patient with higher stages of fibrosis (136±18.6 pg/mL, $p = 0.0029$). PBMCs from patients with overlap syndrome expressed more IL-16 than those from AIH patients and healthy controls (2695±823AU vs 2233±586AU and 22.40±2.943AU, $p < 0.0001$). Expression of IL-2 by PBMC was not significantly different between AIH and AIH/PBC patients (29±4.3AU compared to 38±21.69AU, $p = 0.6873$). AIH/PBC patients have more $CD3^+$ T lymphocytes that express IL-16 than AIH patients ($p < 0.001$) and $CD8^+$ T cells from AIH/PBC patients express significantly more IL-16 than $CD8^+$ T cells from AIH patients ($p < 0.01$). AIH/PBC patients have higher levels of circulating $CXCR3^+$ $CD4^+$ activated T cells ($p < 0.0001$) andAIH/PBC patients have increased levels of intrahepatic CD4+ T cells ($p < 0.001$).

CONCLUSION(S): IL-16 is specifically increased in patients with overlapping features of AIH and PBC. These results suggest that plasma levels of IL-16 could be a useful biomarker for the diagnosis of AIH/PBC overlap syndrome. These data also suggest that the IL-16/ CD4+ T cell axis is active in AIH/PBC overlap patients and could contribute to its pathogenesis. Further research is needed to understand the contribution of IL-16 in the pathogenic process at play in these patients and to validate the use of IL-16 plasma levels for the diagnosis of AIH/PBC overlap syndrome.

Hypofibrinolysis as a contributing mechanism of cirrhotic portal vein thrombosis as evidenced by rotational thromboelastometry (ROTEM)

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BACKGROUND: Portal vein thrombosis (PVT) is a well-recognized complication of liver cirrhosis. The etiology is thought to be related to a combination of venous stasis from portal hypertension and altered hemostasis from reduced hepatic synthesis of both pro- and anti-coagulant proteins. Previous studies have demonstrated that elevated Factor VIII levels (pro-coagulant) and reductions in protein C (anticoagulant driver) have been described as possible mechanisms of the development of cirrhotic PVT. In contrast, other standard laboratory parameters such as INR, fibrinogen, and platelet count have failed to demonstrate any insight into the mechanism of PVT. Rotational thromboelastometry (ROTEM) is a viscoelastic method for investigating the interaction between coagulation factors, platelets, fibrinogen, and fibrinolysis of whole blood. There is a paucity of data examining the ROTEM assay profile of cirrhotic patients with PVT compared to those without. We hypothesize that those with PVT will have ROTEM assay profile suggestive of a pro-thrombotic state.

PURPOSE: To examine the ROTEM assay profile (i.e. EXTEM Clotting Time [CT], EXTEM Amplitude 10 [A10], FIBTEM, and Maximum Lysis [ML] 60) of cirrhotic patients with PVT compared to those without PVT.

METHOD: Retrospective study of all patients who received an orthotopic liver transplant at Vancouver General Hospital between Nov 2016–Oct 2019. ROTEM values were obtained prior to surgical incision for each patient's liver transplant. Exclusions: Non-cirrhotic patients, antiplatelet or vitamin K antagonists within 5 days of transplant, direct oral anticoagulant within 48 hours, low molecular weight heparin within 24 hours of transplant, heparin before 6 hours of transplant, and those who received frozen plasma immediately before transplant. Chi-square and two tail t-tests (where appropriate) were used to determine statistical significance with $p > 0.05$.

Table 1: ROTEM assay profile of cirrhotic patients with PVT vs. non-PVT

	PVT (n = 12)	Non-PVT (n = 174)	p-value
EXTEM CT	87.2	83.6	0.88
EXTEM A10	38.8	38.9	0.98
FIBTEM	10.7	11.1	0.83
ML60	2.9	5.8	0.023

RESULT(S): 214 patients were identified with 28 patients excluded based on above criteria. Of the 186 patients remaining, there was no statistically significant difference between gender, mean age, MELD, INR, bilirubin, albumin, platelets, presence of hepatocellular carcinoma, ascites, hepatic encephalopathy, variceal bleeding, and chronic kidney disease. Cirrhotic patients with PVT had statistically lower ML60 compared to those without PVT. There were no other statistically significant differences in other ROTEM assays (Table 1).

CONCLUSION(S): To our knowledge, this is the first reported study using ROTEM to demonstrate a reduction in the degree of fibrinolysis (ML60) amongst cirrhotic patients with PVT compared to those without. This suggests that hypofibrinolysis may play a mechanistic role in the development of PVT in patients with cirrhosis. Interestingly, there was no difference in other parameters suggesting that coagulation factors, platelets, and fibrinogen function may not play a significant role in its pathogenesis. Further larger prospective studies are warranted to examine the association between ROTEM assay profiles and the development of PVT in cirrhotic patients.

"FIB-4 First" strategy in a NAFLD assessment pathway for HIV mono-infected patients

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is the main cause of liver disease in people living with HIV (PLWH). Even if transient elastography (TE) is a feasible and effective option to assess promptly both NAFLD and fibrosis, it is not largely accessible. Fibrosis-4 (FIB-4) index at the threshold of 1.3 is used to exclude fibrosis in patients at risk for NAFLD from the general population. FIB-4 could be used to triage PLWH in need for further evaluation for NAFLD and associated liver fibrosis.

PURPOSE: The aims of this study were: i) to estimate the proportion of TE examinations which would be spared using a FIB-4 first strategy in PLWH; ii) to determine prevalence and associated cofactors of discordance (false negativity) between TE and FIB-4 in patients classified as low risk for fibrosis by FIB-4.

METHOD: We included PLWH from three prospective cohorts (LIVEHIV in Montreal, LHIVPa in Palermo, MHMC in Modena). Exclusion criteria were: presence of significant alcohol intake, HBV or HCV coinfection, or other liver disease. All patients underwent TE with controlled attenuation parameter (CAP). FIB-4 index was computed within three months from TE measurement. NAFLD was defined as CAP ≥248 dB/m. Significant liver fibrosis and cirrhosis were defined as liver stiffness measurement ≥7.1 and ≥13 kPa, respectively. Unreliable TE examination was defined as IQR value >30% and/or less than 10 valid measures. A FIB-4 threshold of 1.3 was used to categorize patients as low or high-risk for liver fibrosis. Multivariable logistic regression analysis was used to identify cofactors associated with discordance between TE and FIB-4 for low-risk category.

RESULT(S): 1607 HIV mono-infected patients were included. Prevalence of NAFLD and liver fibrosis was 37% and 15%, respectively. 585 (36%) patients were categorized at high risk for liver fibrosis by FIB-4: 212 (36%) had NAFLD and 127 (22%) had significant liver fibrosis by TE (of whom 69 patients had NAFLD and 44 patients had cirrhosis). Patients stratified as low risk were 1022 (64%): 108 (11%) had significant liver fibrosis by TE (of whom 78 patients had NAFLD and 13 patients had cirrhosis) (see Figure). After adjusting for sex (adjusted Odds Ratio [aOR] 1.1, 95% CI: 0.66–1.82), CD4 nadir (aOR 1.21, 95% CI 0.77–1.89), undetectable viral load (aOR 1.27, 95% CI 0.69–2.32), time to HIV diagnosis (aOR 1.01, 95% CI 0.98–1.03) and diabetes (aOR 0.77, 95% CI 0.46–1.28), BMI ≥25 kg/m^2 (aOR 3.82,

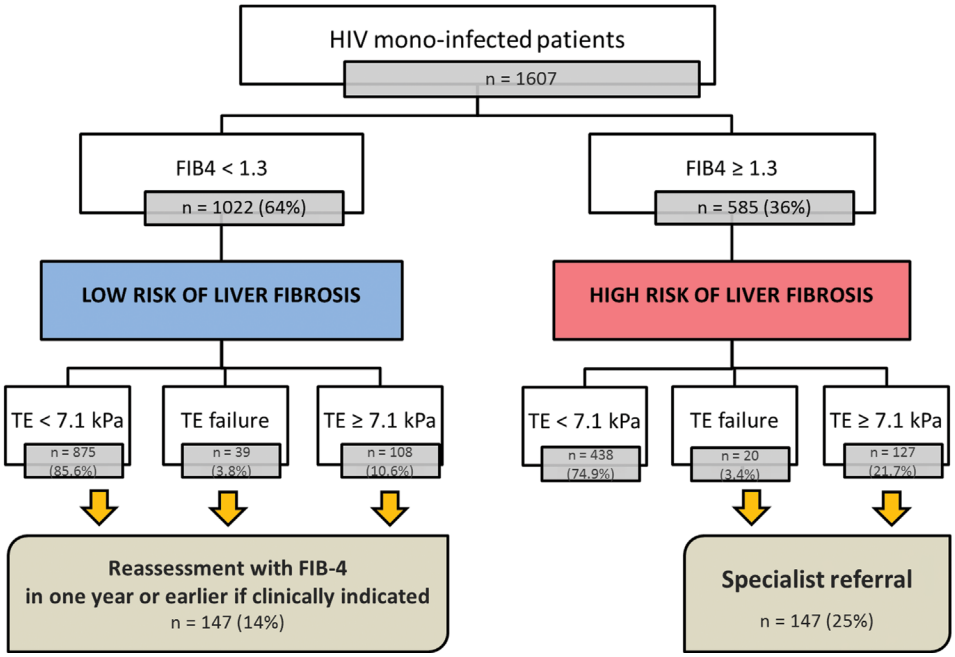

Figure : Impact of implementation of a "FIB-4 First" strategy to triage HIV mono-infected patients entering a NAFLD assessment pathway

95% CI: 2.40–6.07, p <0.05) and low HDL cholesterol (aOR 1.80, 95% CI: 1.15–2.83, p <0.05) were independently associated with discordance between TE and FIB-4 in patients with FIB-4 <1.3.

CONCLUSION(S): A FIB-4 first risk-stratification model could save more than 50% of TE examinations, helping resource optimization in HIV clinics. Patients stratified as low risk by FIB-4 should be considered for referral for TE examination in case of metabolic risk factors for NAFLD, in particular overweight and low HDL cholesterol.

Combined regimen immune checkpoint inhibitor-associated hepatitis: Experience from a North American multicenter cohort

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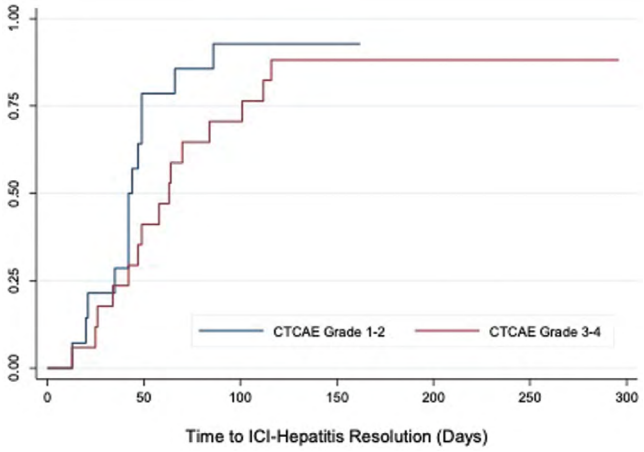
BACKGROUND: The onset of immune-related adverse events (irAEs) is a well-described complication of immune checkpoint inhibitor (ICI) therapy. While the use of combination ICIs for the treatment of advanced melanoma has been associated with improved patient outcomes, it also increases the risk of irAEs.

PURPOSE: This study aimed to evaluate the incidence, clinical course and treatment of hepatic irAEs associated with combination ipilimumab and nivolumab therapy.

METHOD: We identified a retrospective case series of consecutive patients receiving combination ipilimumab and nivolumab for treatment of stage III or IV melanoma between 2013 and 2017 at two tertiary care cancer centers in Alberta, Canada. ICI-related hepatitis was defined by the Common Terminology Criteria for Adverse Events (CTCAE) reporting. We identified the proportion of patients developing ICI-related hepatitis, stratified by hepatitis grade and hepatitis treatment. We identified the length of duration to hepatitis resolution, treatment with corticosteroids or ICI discontinuation, and death.

RESULT(S): A total of 63 consecutive patients diagnosed with Stage III or IV melanoma who were treated with combination ipilimumab (3mg/kg) and nivolumab (1mg/kg) with a target of four treatment cycles were identified. 31 patients (49%) developed ICI-related hepatitis following combination treatment, at an average time to onset of hepatitis 34 days after the first cycle. Of those who developed hepatitis, 14 patients (45%) had CTCAE grade



1/2 hepatitis compared to 17 patients (55%) with CTCAE grade 3/4 hepatitis. 90% (28/31) of patients had resolution of hepatitis. Three patients (10%) died prior to hepatitis resolution. Time to hepatitis resolution is summarized in Figure 1 and was not significantly different by CTCAE grade (p = 0.17). The average duration of ICI-related hepatitis was 52 days. A total of 20 patients (68%) were treated with corticosteroids and 15 patients (48%) had their ICI treatment held solely for hepatitis. A total of 17 patients (55%) received ICI monotherapy following their combined regimen and of those 17 patients, 7 received monotherapy despite early cessation of combined ICI treatment. Of the 31 patients who developed hepatitis, 11 died within the study period, none from hepatitis-related complications.

CONCLUSION(S): Approximately half of the patients treated with combination ipilimumab and nivolumab developed ICI-related hepatitis that required treatment with corticosteroids, ICI treatment cessation, or both. However, most patients experienced resolution of ICI-related hepatitis with these measures, independent of CTCAE grade. Additional studies to identify predictive factors for ICI-related hepatitis development and treatment response are required.

Hemojuvelin deficiency predisposes mice to hepatocellular carcinoma

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BACKGROUND: Hemojuvelin (HJV) is a bone morphogenetic protein co-receptor that enhances signaling to the iron regulatory hormone hepcidin in hepatocytes. Genetic inactivation of HJV leads to juvenile hemochromatosis, a disease caused by severe hepcidin deficiency and characterized by excessive iron accumulation in the liver, pancreas and heart. Hepatic iron overload poses a risk factor for liver cirrhosis and hepatocellular cancer (HCC). HJV-/- mice recapitulate systemic iron overload. They do not manifest spontaneous liver pathology at young age but are sensitized to more advanced liver injury in response to CCl_4 intoxication or long-term feeding with high iron-diet.

PURPOSE: The goal of this study was to evaluate the responses of HJV-/- mice to diethylnitrosamine (DEN), a chemical that promotes HCC.

METHOD: 1-week old HJV-/- and isogenic wild type (WT) control female pups were injected with DEN or saline (n = 8–11 in each group). The animals were sacrificed after 6 months and analyzed for liver pathology.

RESULT(S): As expected, livers of all saline-treated animals did not exhibit any histopathological abnormalities. Similar results were obtained with DEN-treated WT mice, presumably because females are relatively resistant to DEN-induced hepatocarcinogenesis, while the time of DEN exposure was suboptimal. By contrast, 10 out of 11 HJV-/- mice developed dysplastic foci in the liver or grade 1 HCC. Livers from all animals were analyzed by mass spectrometry. Principal component analysis of differentially expressed proteins revealed a distinct separation of saline-treated WT control from HJV-/- mice; the latter cluster around DEN-treated WT and HJV-/- mice. This shows that HJV deficiency triggers similar effects on liver proteomic profile as the hepatocarcinogen DEN. In line with this, in a group of aged (18-months old; n = 32) male HJV-/- and WT mice, 60% of the former and only 30% of the latter developed spontaneous HCC.

CONCLUSION(S): We conclude that HJV deficiency triggers a reprograming in liver gene expression

and predisposes mice to HCC. Experiments are underway to elucidate whether this is due to iron overload, lack of HJV per se or both.

Simple non-invasive prediction of advanced fibrosis in NAFLD – a stepwise approach and external validation study to reduce indeterminates and biopsy

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BACKGROUND: Advanced hepatic fibrosis in patients with NAFLD is associated with increased liver-related outcomes. Simple non-invasive tests (NIT) designed to rule-in or rule-out advanced fibrosis in NAFLD are limited by 'indeterminate' (IND) results, necessitating liver biopsy.

PURPOSE: Our aim was to determine whether sequential or parallel combinations of serum-based NIT and vibration-controlled transient elastography (VCTE) can accurately predict advanced NAFLD fibrosis (AF), reduce IND and misclassifications (MIS), and thus decrease need for liver biopsy.

METHOD: Biopsy-proven NAFLD patients were retrospectively identified between 2010–2018 from two Canadian tertiary centers, to represent derivation and independent external validation cohorts for sequential algorithms. Cohorts were combined for parallel analysis. FIB-4, APRI, NFS, BARD, AST/ALT scores were calculated based on blood work performed within 6 months of biopsy. VCTE was available in n = 172, and liver stiffness measurement (LSM) ≤7.2 kPa was considered as F0-2. AF was defined as F3-4 fibrosis stages. Areas under the ROC curve (AUC) and weighted Obuchowski measures (OB) were determined for binary outcomes.

RESULT(S): 541 cases of NAFLD were identified (407 derivation, 134 validation). Characteristics of derivation/validation cohorts included: males 54%/59%; mean age 48.5/52.5 y; mean BMI 32.3/33.6; diabetes 30%/34%; AF prevalence 48%/ 43%. For single serum NITs, AUC for AF were 0.70–0.83, and 0.68–0.81 for derivation and validation cohorts, with IND rates of 25%–39%, and 34%–45%. Concordance between FIB-4 and NFS for both cohorts was 71%–73%. Sequential combinations of NIT reduced IND while maintaining diagnostic accuracy (Table 1). For the overall cohort, parallel FIB-4 + NFS had similar accuracy (AUC = 0.81) but was limited by a 38% IND rate. In our overall cohort, liver biopsy for AF was avoided in 27%–30% of patients using sequential algorithms, representing an additional 6%–9% biopsies avoided compared to using FIB4/NFS/VCTE alone.

CONCLUSION(S): In this study with an external validation cohort, sequential combinations of NIT predict advanced fibrosis in NAFLD with good accuracy, while reducing IND. Use of sequential algorithms reduce need for liver biopsy for Advanced Fibrosis compared to individual NIT. Parallel combined algorithms are limited by high rates of IND. In our tertiary cohorts, sequential FIB-4 + NFS performed with similar accuracy to VCTE-containing algorithms, and if validated in low prevalence cohorts, highlights potential use in resource-limited clinical settings as a means of risk stratification for advanced NAFLD fibrosis.

Table 1.

	Derivation					Validation				
Sequential NIT	Sens	Spec	AUC (OB)	IND	MIS	Sens	Spec	AUC (OB)	IND	MIS
FIB-4	0.66	0.94	0.83 (0.74)	27%	17%	0.88	0.61	0.81 (0.74)	34%	26%
NFS	0.64	0.90	0.78 (0.71)	25%	23%	0.64	0.85	0.78 (0.72)	40%	25%
FIB-4 + NFS	0.60	0.95	0.77 (0.71)	8%	20%	0.56	0.82	0.67 (0.65)	15%	30%
FIB-4 + VCTE	0.69	0.93	0.81 (0.72)	0%	17%	0.67	0.66	0.66 (0.64)	0%	34%
FIB-4 + NFS + VCTE	0.62	0.94	0.78 (0.71)	0%	20%	0.62	0.74	0.68 (0.64)	0%	31%

Impaired hepatic leukocyte recruitment and increased thrombin generation during acute bacterial challenge in a mouse model of non-alcoholic fatty liver disease (NAFLD)

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BACKGROUND: NAFLD includes a spectrum of diseases from minor steatosis to steatohepatitis and often progresses into fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The rapid emergence of NAFLD is associated with rising obesity rates, especially in the western world. Many studies indicate that excess adipose tissue has the ability to alter immune responses and impact host defense to pathogens. Epidemiological studies report increased risk of nosocomial infection, and decreased vaccine efficacy in patients with a BMI >30. NAFLD patients experience increased recurrent bacterial infections, and mouse models have shown increased mortality to bacteremic sepsis.

PURPOSE: NAFLD is the most common form of chronic liver disease in North America. Despite the extensive research in physiological changes in the liver during NAFLD progression, the immunological modifications to the hepatic compartment have not been fully identified. Further, pathogen challenge to the fatty liver has not been extensively performed. Here, fatty liver mice are challenged with *Staphylococcus aureus* to assess the immune response.

METHOD: C57bl/6 male mice were fed a high fat diet (HFD) for 5 months to induce a fatty liver phenotype. Mice were then injected intravenously with *Staphylococcus aureus* (strain: USA300, $5x10^7$ colony forming units, CFU). At 6 or 24 hours post-injection (hpi) experiments were performed to assess bacterial dissemination (bacterial CFU counts in various organs) and liver damage by quantifying plasma alanine aminotransferase enzymes (ALTs). Using intravital microscopy (IVM), neutrophils, platelets, and active thrombin were visualized to assess inflammation/coagulation within the liver compared to mice fed a standard diet (SD). Activation of the coagulation cascade was measured via ELISA detection of plasma thrombin-antithrombin (TAT).

RESULT(S): Results show fewer neutrophils but increased platelets aggregates in HFD mice at both 6 and 24 hpi compared to controls, results that have been confirmed by flow cytometry. Interestingly, thrombin activity was detected in uninfected HFD mice by IVM and confirmed via ELISA for TAT. Increased TAT in uninfected mice was accompanied by increase in plasma ALTs, suggesting baseline liver tissue damage in these mice. Finally, bacterial loads in liver, lung and spleen were not statistically different between groups.

CONCLUSION(S): These findings indicate an elevated platelet activation in fatty liver, likely contributing to baseline hepatic inflammation seen in NAFLD patients.

Modelling non-alcoholic fatty liver disease burden in Canada, 2019–2030

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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) account for a growing proportion of liver disease cases globally, including cirrhosis. In Canada, NAFLD/ NASH is the most common liver disease, and NAFLD/ NASH are rapidly becoming the leading indication for liver transplantation in North America. Key risk factors for the development of NAFLD/ NASH include obesity and diabetes.

PURPOSE: Given the increasing prevalence of obesity and the aging population, a crucial need exists to better forecast the country-wide burden of liver disease related to fatty liver to inform public health agencies, and guide organization of healthcare to deal with this growing epidemic.

METHOD: To address this need, a Markov model was employed to forecast fibrosis progression from

F0 (no fibrosis) to F4 (compensated cirrhosis), and subsequent progression to decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant, and liver-related death among the Canadian NAFLD population. Historical trends for obesity prevalence among adults were used to estimate longitudinal changes in the number of incident NAFLD cases. Ranges were included for key inputs to produce 95% uncertainty intervals (UI) for model estimates. Surveillance data on liver disease and HCC incidence, and published estimates for NAFLD and NASH prevalence were utilized to build and validate our model projections.

RESULT(S): The model projected that prevalent NAFLD cases would increase through 2030 when there were an estimated 9,305,000 (8,550,000–9,875,000) NAFLD cases, an increase of 20% from 2019 (7,757,000 [7,138,000–8,232,000] cases). Increases in advanced fibrosis cases were relatively greater with prevalent stage 3 (F3) cases increasing by 65% to 357,000 (219,000–511,000) in 2030, while prevalent F4 cases increased by 95% to 195,000 (120,000–309,000) cases in 2030. In parallel, incident cases of HCC and decompensated cirrhosis were projected to increase by up to 95% by 2030, while annual NAFLD-related deaths would double by 2030 to 5,600 (3,200–9,000) deaths.

CONCLUSION(S): Increasing rates of obesity and diabetes, in combination with an aging population, translates into NAFLD-related cases of cirrhosis, HCC, and related mortality strikingly increasing over the next decade in Canada. Therefore, prevention efforts aimed at reducing the incidence of NAFLD, as well as slowing fibrosis progression among those already impacted should be top priorities to decrease disease burden.

Lenvatinib for the first-line treatment of advanced or unresectable hepatocellular carcinoma: A cost-effectiveness analysis from a Canadian perspective

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BACKGROUND: Survival rates for advanced or unresectable hepatocellular carcinoma (uHCC) are low, and sorafenib is currently the only systemic therapy funded for first-line treatment in Canada. Lenvatinib, an oral multikinase inhibitor, recently received a funding recommendation by the pan-Canadian Oncology Drug Review (pCODR). In the Phase III REFLECT trial, lenvatinib met the primary endpoint of non-inferiority in overall survival (OS) versus sorafenib (13.6 months versus 12.1 months; hazard ratio 0.92; 95% confidence interval 0.79–1.06) and demonstrated superiority in secondary endpoints progression-free survival, time to progression and objective response rate. A greater proportion of sorafenib patients received post-progression therapies, which may explain the longer median OS in the sorafenib arm of REFLECT compared with previous studies.

PURPOSE: To evaluate the cost-effectiveness of lenvatinib versus sorafenib for the first-line treatment of uHCC, from the perspective of the Canadian Ministry of Health.

METHOD: A partitioned survival model was developed to model the incremental costs and benefits (quality-adjusted life-years [QALYs]) associated with lenvatinib treatment, with health states representing progression-free disease, progressed disease, and death. Trial results were used to estimate the proportion of patients in each health state over time, with extrapolation performed to estimate health state membership beyond the trial period. Adjustment was made for baseline imbalances between trial arms, including baseline alpha-fetoprotein concentration, body weight and Child-Pugh score. Utility values in each health state were determined using EQ-5D-3L data captured in REFLECT, and adverse events included in the model were Grade 3 or 4 treatment-emergent adverse events occurring in ≥5% of patients in either treatment arm. To reflect confidential listing agreements that may exist between manufacturers and Canadian payers, one scenario explored the impact of reducing the price of sorafenib by 15%. Another scenario adjusted the OS HR for the imbalance in post-progression therapy use in REFLECT and aimed to align with the

Table:

Base-case/ scenario	Incremental costs	Incremental QALYs	ICUR
Base-case	−$5,064	0.17	Dominant
#1 15% sorafenib price reduction	−$1,310	0.17	Dominant
#2 Adjustment for post-progression therapies and regorafenib only post-progression	−$9,391	0.22	Dominant
#3 Scenarios 1 & 2 combined	−$5,141	0.22	Dominant

Abbreviations: ICUR, incremental cost-utility ration; QALYs, quality-adjusted life years.

Canadian HCC landscape by including regorafenib as the only second-line treatment option.

RESULT(S): In the base-case and all scenarios lenvatinib was dominant due to reduced costs and increased benefits versus sorafenib (see table). The reduction in costs was driven mainly by reduced primary drug costs in the lenvatinib arm, and the increase in QALYs was likely due to lenvatinib patients spending more time in the progression-free health state. The adjustment for post-progression therapies balanced the impact of post-progression therapies on OS between treatment arms, resulting in increased incremental QALYs.

CONCLUSION(S): Lenvatinib is a cost-effective first-line treatment option for patients with uHCC in Canada.

Reducing length of stay in patients following a liver transplant

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BACKGROUND:

- There are seven liver transplant centers in Canada, however, data on length of stay (LOS) has not been analyzed in any center.
- Some United States transplant centers have suggested a target of 18 days.
- Prolonged LOS in hospital can result in increased rates of infection, malnutrition, and increased healthcare resource utilization thus a multidisciplinary effort to reduce LOS may improve patient outcomes and reduce costs.
- London health Sciences Centre had a median LOS of 18 days from January 2015–August 2017.

PURPOSE:

- The aim of the current project was to reduce the median LOS by 3 days over a 16-month period.

METHOD: Improvement:

- We used the model for continuous improvement and instituted four Plan-Do-Study-Act (PDSA) cycles to achieve our aim.
- The 1st PDSA cycle (n = 23) included educational sessions among liver transplant team members.
- The 2nd PDSA cycle (n = 9) included development of a liver transplant clinical pathway.
- The 3rd PDSA cycle included institution of a clinical order set (n = 14).
- The 4th PDSA cycle (n = 19) involved a patient oriented clinical pathway instrument.

Information gathered/Approach Taken

- The study took place at University Hospital in London, Ontario from August 2018 – February 2019.
- 1st PDSA – awareness/education among healthcare professionals.
- 2nd PDSA – Initiate clinical pathway for patients and healthcare professionals to follow (if applicable).
- 3rd PDSA – Initiate HUGO Care Set to help facilitate mandatory orders and transfers from ICU.
- 4th PDSA – Clinical pathway individualized to the patient placed in patient rooms.

RESULT(S): Current Status of Project/Project Impact:

- Over a 16-month period we had 49 liver transplants discharged from hospital with a median LOS of 10 days.
- We also analyzed balancing measures and found 30 day and 90 readmission rates to be 18.4% and 22.4%, respectively, which was not significantly different from the 2015–2017 rates of 15.4% and 22.7%.
- Over this brief study period, $540,000 hospital dollars were saved, which is put toward the global hospital budget.

CONCLUSION(S):

- Development of a multidisciplinary care pathway with patient engagement led to improved discharge rates within a target of ten days.
- Balancing measure of increased readmission rates were not clinically significant.
- During the project period we found further areas of intervention that were preventing patient discharges within target times:

A) Education/Managing patient expectations
B) Psychosocial/family support
C) Frailty (lack of rehabilitation homes/hospital transfer facilities)
D) Discharge planning

- Macro hospital level issues will be a future barrier to further improvement.

The role of transferrin receptor 1 (Tfr1) in liver iron sensing and systemic iron homeostasis

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BACKGROUND: Transferrin receptor 1 (Tfr1) mediates uptake of circulating transferrin-bound iron to developing erythroid cells and other cell types. Its critical physiological function is highlighted by the embryonic lethal phenotype of Tfr1 knockout (Tfrc-/-) mice and the pathologies of several tissue-specific knockouts. Tfr1 is highly expressed in the liver, the organ that orchestrates systemic iron homeostasis by producing hepcidin, the iron regulatory hormone.

PURPOSE: The goal of this work was to understand how Tfr1 affects body iron sensing and controls hepcidin expression in the liver.

METHOD: We generated $Tfrc^{Alb\text{-}Cre}$ and $Tfrc^{Tek}$ mice bearing conditional disruption of the Tfrc gene in hepatocytes or liver sinusoidal endothelial cells (LSECs). The animal phenotypes were analyzed under basal conditions and following dietary or pharmacological iron challenges.

RESULT(S): $Tfrc^{Alb\text{-}Cre}$ and $Tfrc^{Tek}$ mice are viable and do not manifest any apparent liver pathology. Nevertheless, liver iron content (LIC) in $Tfrc^{Alb\text{-}Cre}$ mice is lower compared to that of control $Tfrc^{fl/fl}$ littermates, due to reduced capacity of Tfr1-deficient hepatocytes to internalize iron from transferrin. Moreover, the $Tfrc^{Alb\text{-}Cre}$ mice express inappropriately high hepcidin relative to their LIC and are predisposed to iron deficiency anemia. $Tfrc^{Alb\text{-}Cre}$ mice exhibit physiological hepcidin regulation in response to dietary iron manipulations or holo-transferrin injection. We provide evidence that Tfr1-deficient hepatocytes can acquire transferrin-iron via Tfr2, a Tfr1 homologue that binds to holo-transferrin with 25-fold lower affinity. $Tfrc^{Alb\text{-}Cre}$ mice on a high iron diet appropriately upregulate the major hepcidin inducer BMP6 in LSECs and hepcidin in hepatocytes.

CONCLUSION(S): Tfr1 is redundant for basal hepatocellular iron supply but essential for fine-tuning hepcidin responses according to the iron load of hepatocytes. Our data are consistent with an inhibitory function of Tfr1 on iron signaling to hepcidin via its interaction with the hemochromatosis protein HFE. Moreover, they highlight hepatocellular Tfr1 as a link between cellular and systemic iron regulatory pathways. Our preliminary data with $Tfrc^{Tek}$ mice suggest that Tfr1 is not essential for iron sensing and BMP6 production by LSECs; nevertheless, further experiments are underway to clarify specific effects of transferrin-bound iron (TBI) vs non-transferrin-bound iron (NTBI) in the pathway.

A new score including anthropometric measurement for weight Improved prediction of mortality of adolescents on the liver transplantation waiting list: US nationwide study

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BACKGROUND: The Model for End-Stage Liver Disease (MELD) was adopted for liver transplant (LT) allocation to adolescents with chronic liver disease (CLD) without published validation in children. Pediatric CLD is associated with poor growth than may affect implementing MELD in adolescent patients.

PURPOSE: Therefore, we aimed to assess the performance of MELD, MELD Na, Pediatric End-Stage Liver Disease (PELD) score in predicting adolescent LT-wait list mortality, and to evaluate incorporating height and weight into MELD at the time of registration to improve prediction of mortality in listed adolescents for LT.

METHOD: Adolescents (12–17 years of age) registered for their first LT in the United States between January 2003 and December 2015 were identified using the united network for organ sharing (UNOS) database. Patients listed for multiple organs, Status 1A or 1B, and those who were granted exception points were excluded from the analysis. Area under receiver operating curve (AUROC) and C-statistics were used to evaluate the discrimination of MELD, MELD Na and PELD for the prediction of wait-list mortality at 6 and 12 months, weight and height and their Z scores at time of registration were examined by univariate analysis and later incorporated into a multivariate regression analysis to obtain the new model termed Adolescent PELD.

RESULT(S): A total of 946 adolescent patients fulfilled our eligibility criteria. We randomized our cohort into derivation (n = 473) and validation cohorts (n = 473). Both cohorts had similar age (median 15 for both, p = 0.56), female sex (54% vs. 52%, p = 0.27), weight (56 vs. 57 kg, p = 0.52) and height (161 vs 160 cm, p = 0.66) respectively. Z scores for weight and height and laboratory variables (Na, creatinine, INR, bilirubin) were similar between cohorts. Median follow up was 6 months (IQR 1–21) for both cohorts. Overall 100 (11%) patients died while waiting LT (50 in each cohort) while 437 (46%) patients had LT (209 in derivation cohort and 228 in validation cohort). Only z score for weight was a significant predictor in univariate and multivariate analysis to predict 6 months mortality on LT waitlist. Therefore, we created a new prediction model incorporating Z score for weight with MELD score (Adolescent MELD). In derivation cohorts, Adolescent MELD performed better than PELD, MELD and MELD Na to predict 12 months mortality (AUROC: 0.78 [0.71–0.86], 0.67 [0.59–0.75], 0.74 [0.66–0.83] and 0.75 [0.65–0.84], p < 0.05 for all comparisons respectively). Similarly, Adolescent MELD performed better than most of the other scores in predicting 6 months and 12 months mortality in our validation cohort, Table 1.

Table 1: AUROC (95% CI) of PELD, MELD, MELD Na and Adolescent MELD in predicting mortality of adolescents on the LTx waiting list in the validation cohort

The Score	6-month mortality	12-month mortality
PELD	0.73 (0.66–0.81) ¥	0.67 (0.59–0.75) ¥
MELD	0.77 (0.70–0.85) ¥	0.71 (0.63–0.80) ¥
MELD Na$	0.73 (0.64–0.82) ¥	0.71 (0.63–0.80)
Adolescent MELD	0.81 (0.73–0.88)	0.75 (0.67–0.82)

***** *P < 0.05 compared to PELD*
¥ *P < 0.05 compared to Adolescent MELD*

CONCLUSION(S): Incorporating the anthropometric measurement Z score for weight improved the accuracy of MELD and the prediction of mortality on the LT waiting list.

Performance of noninvasive fibrosis tests among NAFLD patients with normal ALT: Data from a large North American primary care NAFLD pathway

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BACKGROUND: Recent studies risk stratifying NAFLD patients within primary care have focused on patients with elevated transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]).

PURPOSE: Therefore, we used data from the Calgary NAFLD clinical care pathway (CNCCP) to compare performance of noninvasive liver fibrosis tests FIB-4, NAFLD fibrosis score (NFS), and 2-dimensional shearwave elastography (SWE) in NAFLD patients based on having elevated baseline ALT levels.

METHOD: The CNCCP was developed as a partnership to enable primary care physicians (PCP) to risk-stratify NAFLD patients within primary care. PCPs can directly access the CNCCP for their patients with any of the following conditions: overweight, obesity, diabetes mellitus, elevated liver enzymes, or fatty liver detected by prior imaging. Patients with suspected NAFLD (i.e. other causes of chronic liver disease excluded) were then assessed by SWE, ordered directly by PCPs. NAFLD patients with liver stiffness by SWE t 8 kPa (or inconclusive result) were referred to hepatology, and those with SWE <8.0 kPa were managed by their PCPs using a standardized CNCCP management pathway. ALT of 30 U/L for men and 25 U/L for women were considered the upper limit of normal.

RESULT(S): 1,944 NAFLD patients were enrolled in the CNCCP between March-October 2018. Within this patient cohort there were 577 (29.7%) patients with a normal ALT at enrollment in the CNCCP (baseline). NAFLD patients with normal ALT were likely older (median age: 57 vs. 54, $p < 0.001$) than patients with elevated ALT. Patients with normal and abnormal baseline ALT levels were similar according to sex, body mass index (BMI), having diabetes mellitus or hypertension. Patients with elevated ALT levels had similar FIB-4 scores as those patients with normal ALT levels (median 1.01 vs. 0.97, $p = 0.117$), but had lower NFS scores (median: –1.24 vs. –0.71, $p < 0.001$) and higher SWE results (4.5 vs. 4.3 kPa, $p < 0.001$). 26.6% of patients in the normal ALT cohort had FIB-4 >1.30, compared to 33.6% in the elevated ALT cohort ($p = 0.016$). 69.2% of patients with normal ALT levels had NFS >-1.45, compared to 54.7% with elevated ALT ($p = 0.001$). In addition, 3.3% of patients with normal ALT had elevated liver stiffness (SWE S8 kPa), compared to 3.5% with elevated ALT ($p = 0.809$). In adjusted logistic regression analyses, elevated ALT was an independent predictor of FIB>1.30 (adjusted OR 2.09, 95% CI: 1.51–2.91) and NFS >-1.45 (aOR: 0.51: 0.35–0.76), but was not a predictor of SWE >8.0 kPa (aOR: 1.44, 0.87–2.39).

CONCLUSION(S): In a large primary care-driven NAFLD pathway, 1/3 of patients had normal ALT levels (within recommended sex-based cutoffs). Elevated ALT associated inconsistently with serum-based fibrosis markers and liver stiffness. Therefore, risk-stratification of NAFLD patients within primary care should not be limited to patients with elevated transaminases.

Impact of repeat transient elastography within 3 years on clinical management in chronic liver disease

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BACKGROUND: Accurate staging of liver fibrosis severity is important in management of chronic liver disease (CLD) patients. Although liver biopsy is the reference standard for staging liver fibrosis and diagnosis of cirrhosis, this is an invasive procedure associated with complications and other limitations. Vibration Controlled Transient elastography (VCTE) as a non-invasive and simple device is available as a point-of care test, and is increasingly used as an alternative for liver biopsy in diagnosis and staging liver fibrosis/cirrhosis in patients with CLD. Although VCTE is validated for cross-sectional assessment of disease severity, there are no clear guidelines regarding appropriate interval of performing repeat assessments and how this would impact clinical decisions.

PURPOSE: Our aims were to determine temporal changes of Liver Stiffness Measurement (LSM) in patients who have repeat VCTE within a 3-year time frame, and how these results impacted clinical decision making.

METHOD: This single tertiary center retrospective observational study identified 2126 CLD patients (divided to 7 groups based on disease diagnosis)

Table 1: Changes in LSM and influence on management according to CLD

	No. of repeat VCTE	Mean Delta log LSM in kPa (±SD)	Changes in clinical management (%)
Hepatitis B	1132	−0.05 (0.15)	162 (14%)
Hepatitis C	760	−0.03 (0.16)	253 (33%)
Cholangiopathy	426	−0.01 (0.17)	15 (3%)
NAFLD	195	−0.015 (0.17)	22 (11%)
AIH	97	−0.05 (0.21)	6 (6%)
ALD	41	−0.07 (0.24)	11 (26%)

with at least two valid VCTE assessments during their routine clinic follow-up between Jan 1, 2015 and Dec 31, 2017. Data including LSM, etiology of liver disease, demographic factors, and clinical decisions was extracted from the electronic medical record and reviewed by experienced observer. Changes in clinical management included new prescribed therapy or intervention, change to existing therapy. In this study, changes ≥ 30% in LSM were arbitrary defined as significant alteration, given that this not been clearly defined previously in the context of repeat measurement.

RESULT(S): 4942 VCTE were performed on 2126 patients over a period of 3 years, 2816 of which were repeat liver stiffness measurements. The average interval between VCTE was 7.8 months. The mean (± SD) age of our population with repeat VCTE was 51.5 (±13.5) years, with diagnosis of viral hepatitis B or C in 67%, Cholangiopathy 16%, non-alcoholic fatty liver disease (NAFLD) 7%, Autoimmune hepatitis (AIH) 4%, alcoholic liver disease (ALD)2%, other 5%. ALD patients had the greatest variability in repeat LSM (Table 1). Overall and regardless of CLD diagnosis, the results of repeat VCTE influenced clinical management in 17% of cases, among which hepatitis C patients had the highest proportional impact of repeat VCTE, with change in management observed in one-third of cases (Table 1).

CONCLUSION(S): In our cohort, most patients did not have significant changes in management based on repeat VCTE within 3 years, except for patient with hepatitis C and ALD. This impact on hepatitis C patients were mostly due to provincial reimbursement policy for hepatitis C medications at the time of this study. Patients with ALD had the greatest LSM alteration in repeat VCTE readings over a period of less than 3 years.

Evolution of autoimmune cholangitis and primary sclerosing cholangitis in a pediatric cohort

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BACKGROUND: Studies evaluating the natural history of primary sclerosing cholangitis (PSC) in children have often included patients with autoimmune cholangitis (AIC). However, it remains unclear if clinical outcomes are affected by the phenotype of the disease.

PURPOSE: To evaluate whether the clinical presentation of AIC and PSC is associated with different liver related outcomes in a pediatric population.

METHOD: We conducted a single center retrospective review of patients followed for AIC or PSC at the Centre hospitalier universitaire Sainte-Justine in Montreal, Canada, a pediatric liver disease referral center. The files of all patients followed between January 1998 and December 2018 were reviewed. Patients were classified as having either AIC (evidence of large duct disease on cholangiography with histological features compatible with autoimmune hepatitis) or PSC (evidence of large duct disease on cholangiography or histological features compatible with small duct disease) and clinical features at diagnosis, response to treatment and liver related outcomes were compared.

RESULT(S): 40 patients (27 PSC and 13 AIC) were followed for a median time of 47.5 months. Overall, 70% had associated inflammatory bowel disease (IBD), with a similar proportion in both groups (77.8% PSC and 53.8% AIC, p = 0.154). At diagnosis, presence of significant fibrosis at biopsy (45% PSC vs 66.7% AIC p = 0.234) and stigmata of cirrhosis on imagery (10% PSC vs 36.4% AIC p = 0.151) was similar. Liver function tests at baseline were comparable between both groups, however platelet counts were inferior in the AIC group than in the PSC

group (255,000/mm^3 vs 369,000/mm^3, p = 0.015). As expected, IgG counts and auto-immune markers were significantly higher in the AIC group.

80% of patients were treated with Ursodeoxycholic acid at a mean dose of 16.4 mg/kg in PSC and 17.5 mg/kg in AIC (p = 0.614). At diagnosis, significantly more patients with AIC were treated with immunomodulators (76.9% vs 29.6%, p = 0.005) or corticosteroids (84.6% vs 37% p = 0.005). There was no significant difference in the use of Anti-TNF agents at diagnosis (0% in AIC vs 14.8% in PSC p = 0.124) or overall (7.7% in AIC vs 29.6% in PSC P = 0.226).

One year into treatment, GGT and ALT diminished significantly in both groups. However, AST remained significantly elevated in the AIC group and normalization of Bilirubin, AST, ALT and GGT (and IgG levels for AIC patients) at one year was achieved in 55% of PSC patients and in only 15% of AIC patients (p = 0.016). Clinically significant liver related events (cirrhosis, transplantation or cholangitis) occurred more frequently in patients with AIC (53.8% vs 14.8% p = 0.020).

CONCLUSION(S): Patients with AIC and PSC in a pediatric cohort present at a similar stage of liver disease with comparable clinical and biochemical characteristics. However, complete biochemical response to treatment in AIC patients occurs less frequently with clinically significant events occurring more often than in patients with PSC.

Tolerogenic effect of pregnancy in autoimmune hepatitis

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BACKGROUND: Autoimmune hepatitis (AIH) is a disease with a strong female preponderance. Thanks in large part to the success of immunosuppressive treatments, an increasing number of women with AIH are becoming pregnant, thus raising a serious challenge for clinicians. Pregnancy in AIH patients has been associated with spontaneous remission and post-partum flares of disease activity.

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

METHOD: We used our *AIH Research Biobank* to measure immunological parameters in blood samples from AIH patients during and after pregnancy (n = 44 blood samples obtained during 6 pregnancies from 5 AIH patients). The intrahepatic impact of pregnancy on AIH was studied using a murine model of AIH.

RESULT(S): ALT levels were significantly lower during pregnancy than levels before pregnancy or after delivery (p <0.0001). Plasma levels of IL-2 were significantly higher during pregnancy (p <0.001). Expression of IL-2 measured by qPCR in PBMCs were significantly higher during pregnancy (p = 0.0012). Expression of IL-2 in PBMCs rapidly dropped after delivery while expression of IL-16 and IL-21 rapidly increased in PBMCs. Expression of IL-16 and IL-21 by PBMC correlated significantly with ALT levels during and after pregnancy (r = 0.9791, p = 0.0209 and r = 0.7735, p = 0.0145, respectively). Patients also had increased levels of circulating CD4+ regulatory T cells during pregnancy (p <0.001). After delivery, circulating CD4+ Tregs expressed significantly less immunosuppressive CD39 than Tregs from AIH patients (p <0.01) and patients had increased levels of activated HLD-DR+ and CXCR3+ effector CD4+ T cells (p <0.001). In the murine model of AIH, pregnancy led to reduced liver inflammation (p <0.01) and lower ALT levels (p <0.05) as in patients. Intrahepatic expression of IL-10 (p <0.01), levels of liver-infiltrating CD4+ regulatory T cells (p = 0.0205) and IL-2 expressing CD4+ T cells (p <0.05) were all increased during pregnancy while expression of IL-16 and IL-21 by hepatic cells was reduced (p <0.001 and p <0.01, respectively).

CONCLUSION(S): Despite being a pro-inflammatory cytokine, IL-2, expressed at levels as those observed during pregnancy, can promote the expansion of CD4+ regulatory T cells thus leading to an anti-inflammatory response and reduced autoimmune responses. The increase in IL-16 and IL-21 levels close to delivery can, in turn, lead to the recruitment of effector CD4+ T cells and B cell activation that, combined with reduced numbers and

the loss of CD39 expression by Tregs would lead to the post-partum flares of disease activity. A better understanding of the role of these cytokines and regulatory cells could lead to improved clinical management of pregnant and AIH patients in general.

Symptom burden in patients living with primary biliary cholangitis: Indigenous Canadians report significantly higher PBC-40 quality of life scores

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BACKGROUND: Primary biliary cholangitis (PBC) is a chronic liver disease that adversely impacts quantity and quality of life.

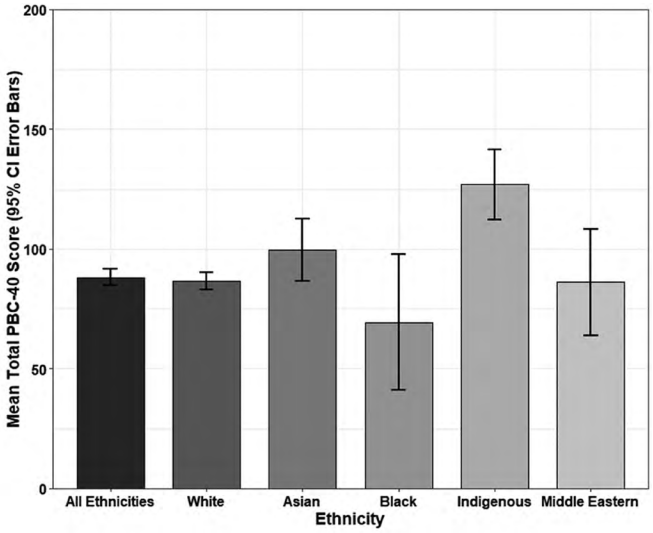
PURPOSE: We aimed to investigate differences in PBC-related quality of life by ethnicity in our multicentre Canadian cohort using the UK-derived PBC-40 questionnaire.

METHOD: The Canadian Network for Autoimmune Liver disease (CaNAL) is a multicentre registry including patients with PBC followed prospectively. Mixed-effects regressions with random intercepts were used to investigate the association of PBC-40 quality of life scores with ethnicity, in participants who completed at least one PBC-40 quality of life questionnaire.

RESULT(S): 318 patients were included from 5 centres in Canada with a mean of 1.2 measurements per patient. Mean (SD) age at first PBC-40 questionnaire was 59.4 (10.3) years, 94% (n = 299) were female, and mean duration of disease was 9.4 (7.7) years. 82% of the cohort were Caucasian (n = 262), 5.7% Asian (n = 18), 3.8% Indigenous Canadian (n = 12), 2.2% Black (n = 7), 2.2% Middle Eastern (n = 7), and 3.8% of various other ethnicities (n = 12). PBC-40 scores slightly lower than those previously published in the literature were identified: out of a maximum score of 200, mean (SD) total PBC-40 scores were 86 (32) for Caucasian patients, 100 (32) for Asian patients, 127 (22) for Indigenous Canadian patients, 69 (37) for Black patients, and 86 (31) for Middle Eastern patients.

Indigenous Canadian ethnicity was associated with a mean total PBC-40 score that was 40 (95% CI 21–59) points higher than other Canadians ($p > 0.0001$). Indigenous Canadians were the only ethnicity whose mean total PBC-40 scores differed significantly from Caucasian patients ($p < 0.0001$). Investigation into which specific PBC-40 domains contributed to these worse scores revealed that Indigenous Canadians had significantly higher scores across all 5 domains of the PBC-40 compared to other Canadians (itch/symptom/fatigue/cognitive/social-emotional: 3.1/4.8/11.7/8.2/12.3 additional points, $p < 0.005$ all domains). These differences in reported quality of life remained after adjusting for sex, age, centre, and duration of disease (itch domain $p < 0.05$, other domains $p < 0.005$) (Figure).

CONCLUSION(S): When applying the PBC-40 in a multi-ethnic Canadian setting, quality of life burden among patients with PBC was substantially higher for Indigenous patients compared to other Canadians. Both the method of assessment, and approaches to improving quality of life in patients living with PBC, must be tailored to the population of patients served.



Assessment of fibrosis and steatosis in patients and healthy volunteers

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BACKGROUND: Non-invasive liver fibrosis and steatosis measurements have been shown allow better disease staging and clinical management, as they are correlated to patient outcomes [Angulo]. We present initial fibrosis and steatosis results using Liver Incytes, a volumetric ultrasound elasticity and attenuation measurement system for the liver [Mueller].

PURPOSE: The purpose of the study was to evaluate the ability of Liver Incytes to discriminate between healthy volunteers (HV) and those with clinically diagnosed non-alcoholic fatty liver disease (NALFD) or hepatitis C virus post sustained viral response (SVR).

METHOD: Liver Incytes is a steatosis and elasticity measurement system (Sonic Incytes, BC, Canada) comprising an ultrasound transducer and a vibration device to generate a multi-frequency (40–70 Hz), steady state shear waves in the patient. The ultrasound elasticity and attenuation is measured over a volume, using an intercostal approach. Volumes are collected in a fan of approximately 30 degrees, at a depth of 15 cm.

Patients and HV were recruited from three clinical sites. HV had no history of liver disease but were not tested for disease at the time of recruitment. Patients were enrolled with either NALFD or HVC post SVR. A FibroScan® (FS) stiffness threshold of greater than 8kPa and controlled attenuation parameter (CAP) greater than 238 dB/m was used to determine the presence of advanced fibrosis and steatosis respectively. On the same day, a FS was completed and used as comparison to the Liver Incytes results.

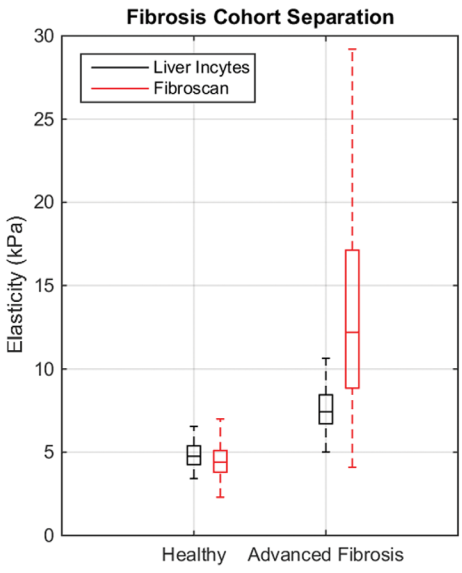
The ability of Liver Incytes to discriminate HV from patients with advanced fibrosis and from patient with steatosis was measured using area under the receiver operating curve (AUROC). A subset of patients also participated in magnetic resonance elasticity (MRE) and proton density fat fraction (MR-PDFF) imaging.

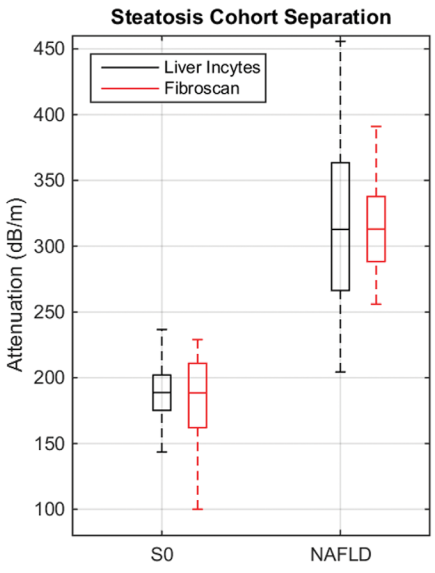
RESULT(S): A total of 50 HV and 48 patients were recruited. The mean [range] age of the volunteers was 27 [19–58] years and 61 [31–75] for patients. 27 of the recruited patients had clinically diagnosed NAFLD and 21 had HCV post SVR.

Median [IQR] stiffness for the HV was 4.8 [1.1] and 7.5 [1.7] kPa for patients on Liver Incytes and 4.4 [1.3] and 12.5 [9.0] kPa when measured with FS. Mean attenuation for the HV and patients was 200 [61] and 298 [98] respectively on Liver Incytes and CAP score was 210 [59] and 295 [96] on FS respectively. The AUROC for Liver Incytes was 0.964 for fibrosis and 0.985 for steatosis, using FS as the gold standard.

Seven patients participated in the MR sub-study. When looking at elasticity, the concordance correlation coefficient was 0.80 for Liver Incytes and 0.20 for FS. The Pearson's coefficient between attenuation and MR-PDFF was 0.98 for Liver Incytes and 0.73 for FS.

CONCLUSION(S): Initial results show that Liver Incytes is able to discriminate HV from patients with advanced fibrosis and steatosis. Initial concordance





and correlation with MRE and MR-PDFF were superior for Liver Incytes compared to FS although numbers are small. Larger clinical trials should be undertaken.

The burden of cirrhosis on the Canadian health care system: A comparison between alcoholic and nonalcoholic cirrhosis patients

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BACKGROUND: Recent studies have indicated an increasing burden of cirrhosis in different health care systems. However, the burden of alcoholic vs. nonalcoholic cirrhosis varies worldwide.

PURPOSE: Therefore, we evaluated the epidemiology of cirrhosis in a Canadian province, and describe the health care utilization patterns of alcoholic vs. nonalcoholic cirrhosis patients.

METHOD: We used a validated coding algorithm to identify cirrhosis patients in the province of Alberta, Canada (population ~4.4 million) from 2008–2018. We classified cirrhosis patients according to etiology (alcoholic vs. nonalcoholic) using the international clinical classification (ICD), versions 9 and 10. Causes of nonalcoholic cirrhosis included viral, nonalcoholic fatty liver and autoimmune chronic liver diseases. Multiple sources of data including inpatient, ambulatory, emergency room visits, and physician billing were linked. Liver-related hospitalizations or emergency department (ED) visits were identified if the primary code was a cirrhosis-related complication including variceal bleeding, ascites, hepatic encephalopathy, hepatocellular carcinoma and spontaneous bacterial peritonitis.

RESULT(S): The overall sex and age adjusted prevalence rate of cirrhosis in Alberta was 68.8 per 10,000 person, while the adjusted incidence rate was 11.2 per 10,000 person. Adjusted incidence and prevalence rates for nonalcoholic cirrhosis were higher than those for alcoholic cirrhosis (Incidence rates 8.6 vs. 2.6 per 10,000 person; Prevalence rates 48.8 vs. 20.0 per 10,000 person). The majority of cirrhosis patients were men (56%), with a median age of 61 years (IQR: 56–64). In our cohort, 31.2% of patients (n = 8,632) had alcoholic cirrhosis. Approximately 38.6% of the cirrhotic patients were hospitalized for cirrhosis-related complications within 1 year after diagnosis, with an estimated median hospitalization cost of $14,133 CAD. The median hospitalization length of stay was 5 days (IQR: 1–19). Liver-related hospitalizations accounted for 59.8% of all hospitalizations, while liver-related ED visits represented 33.4% of all ED visits. Overall 5-year liver-related hospitalization rates for alcoholic cirrhosis were higher than for nonalcoholic cirrhosis (68.5% vs. 42.0%, $p > 0.001$). Similarly, 5-year liver-related ED visits were higher among alcoholic than non-alcoholic cirrhotic patients (28.0% vs. 8.1%, $p < 0.001$).

CONCLUSION(S): In our large Canadian population-based study, nonalcoholic cirrhosis represented two thirds of all cirrhosis patients. However, patients with alcoholic cirrhosis were more likely to visit an ED and be hospitalized for liver-related complications. This data suggests that outpatient resources should be focused on patients with alcoholic cirrhosis to improve acute health care resource utilization.

Impact of depression and antidepressant use on the development of chronic liver disease: A longitudinal UK population-based study

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BACKGROUND: Many studies have evaluated the prevalence of depression, and its' impact on quality of life or response to treatment, among chronic liver disease (CLD) patients. However, the potential impact of depression and antidepressant use on the development of CLD is unknown.

PURPOSE: Therefore, we assessed the impact of depression and antidepressant therapies on the development of chronic hepatitis (CH), alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD).

METHOD: We used The Health Improvement Network (THIN) to identify adult patients with a diagnosis of new-onset depression from 1998 to 2017. The outcome measured was a diagnosis of incident

CH, ALD, or NAFLD. We used a washout period of 3 years to separate indecent from prevalent cases of CLD, and evaluated each CLD of interest separately. THIN is the largest UK-based electronic medical record database for more than 14 million individuals. We used Read Codes to define our outcomes. Poisson regression modelling was performed to evaluate the incidence rate ratio (IRR) of developing each CLD of interest. We adjusted our models for age, sex, socioeconomic status, comorbid conditions, smoking, obesity, and antidepressant use, including atypical antidepressants, mirtazapine, monoamine oxidase inhibitors (MAOI), serotonin norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), serotonin modulators, and tricyclic antidepressants (TCA).

RESULT(S): We identified 220,139 (4.9%) patients with an incident depression diagnosis and 4,248,277 individuals without depression in the THIN database. In our cohort, 898,532 (20.1%) used antidepressants. The majority of prescribed antidepressants were SSRIs (40.2%), TCAs (28.1%), or a combination of antidepressants (26.7%). Incidence rates of CLD and median follow-up duration for each of the CLD cohorts are presented in Table 1. In our adjusted models, depression was significantly associated with greater risk of developing ALD (IRR = 1.26: 1.13–1.40) and NAFLD (IRR = 1.19: 1.12–1.27), but not CH (IRR = 1.05: 95% CI, 88.2–1.27). While most antidepressants independently increased the risk of developing CH, ALD, and NAFLD, using atypical antidepressants was associated with lower risk among ALD patients (IRR = 0.50: 0.37–0.68). Among patients with depression, SSRI was the only antidepressant associated with lower risk of developing CH (adjusted IRR = 0.68: 0.47–0.99).

CONCLUSION(S): Patients with a history of depression were at higher risk of subsequently being diagnosed with ALD and NAFLD. Interestingly, atypical antidepressants were selectively protective from developing ALD in our cohort. These novel findings further our understanding of the link between depression, antidepressants and susceptibility to developing CLD and may lead to new therapeutic approaches.

Baseline liver function and outcomes in the phase III REFLECT study in patients with unresectable hepatocellular carcinoma (uHCC) treated with lenvatinib (LEN) vs sorafenib (SOR)

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Table 1: Incidence rates of CLD cohorts according to depression and antidepressant usage

Cohort	Follow up duration (median, IQR), months	Incidence rates (cases per 1000 person-year, 95% CI)			
		Patients with depression	Patients without depression	Patients using antidepressants	Patients not using antidepressants
Chronic hepatitis (CH), n = 1,883	45 (20.6 – 87.4)	0.108 (0.093, 0.124)	0.055 (0.053, 0.058)	0.095 (0.088, 0.104)	0.05 (0.047, 0.053)
Alcoholic liver disease (ALD), n = 3,939	54.9 (24.7 – 98.7)	0.335 (0.308, 0.363)	0.109 (0.105, 0.113)	0.264 (0.251, 0.278)	0.091 (0.087, 0.094)
Non-alcoholic liver disease (NAFLD), n = 15,125	86.3 (41.6 – 136.7)	0.892 (0.849, 0.937)	0.442 (0.434, 0.449)	0.918 (0.893, 0.943)	0.37 (0.362, 0.377)

BACKGROUND: LEN is approved for first-line treatment of uHCC. Baseline (BL) liver function (Child-Pugh score [CPS] and albumin-bilirubin [ALBI] grade) was prognostic in uHCC patients (pts) who received SOR but has not been assessed with LEN in uHCC.

PURPOSE: Here, we report a post hoc analysis of BL liver function and efficacy/safety outcomes from the phase 3 REFLECT study.

METHOD: Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and safety were stratified by BL ALBI or CPS. OS and PFS were estimated by Kaplan–Meier method. Independent radiologic review utilized mRECIST criteria for ORR. Safety was assessed using NCI-CTCAE, version 4.0.

RESULT(S): Liver function measured by ALBI and CPS seemed to be prognostic for OS and ORR. Median OS was longer in ALBI grade 1 (ALBI-1) vs grade 2 (ALBI-2) pts or for CPS-5 vs CPS-6 on either treatment arm and was longer for LEN vs SOR. ORR was higher in pts with better ALBI or CPS and for LEN vs SOR. Rates of treatment-emergent adverse events grade ≥3 were lower with better BL liver function (ALBI-1 vs ALBI-2: 70% vs 86%; CPS-5 vs CPS-6: 72% vs 86%). Study-drug withdrawal, dose reduction, and dose interruption occurred more often in pts with worse BL liver function (Table).

CONCLUSION(S): This post hoc analysis suggests ALBI (by OS, PFS and ORR) and CPS (by ORR) may be prognostic in uHCC pts and that BL liver function may be linked with efficacy/safety outcomes. This analysis also found that LEN provided benefit vs SOR for uHCC, regardless of BL liver function. The benefit of LEN may be underestimated, as more ALBI-2 pts and fewer ALBI-1 pts received LEN vs SOR.

Table:

Parameter	ALBI-1 LEN (n = 318)	ALBI-1 SOR (n = 340)	HR/OR (95% CI)	ALBI-2 LEN (n = 158)	ALBI-2 SOR (n = 134)	HR/OR (95% CI)	CPS-5 LEN (n = 368)	CPS-5 SOR (n = 357)	HR/OR (95% CI)	CPS-6 LEN (n = 107)	CPS-6 SOR (n = 114)	HR/OR (95% CI)
Median OS, months[a]	17.4	14.6	0.85 (0.70–1.02)	8.6	7.7	0.95 (0.73–1.25)	15.3	14.2	0.91 (0.77–1.09)	9.4	7.9	0.91 (0.67–1.24)
Median PFS, months[a]	7.4	3.6	0.57 (0.47–0.70)	5.5	3.5	0.76 (0.56–1.03)	7.3	3.7	0.63 (0.53–0.76)	7.4	3.5	0.65 (0.45–0.94)
ORR, %[b]	45.0	13.8	5.48 (3.70–8.10)	32.3	9.0	5.37 (2.61–11.06)	42.9	14.0	4.88 (3.37–7.08)	33.6	7.9	5.25 (2.32–11.85)

[a]*Hazard ratio (HR)*; [b]*Odds ratio (OR)*

Ultrasound surface and hepatic vein nodularity as predictors of histologic advanced fibrosis in chronic liver disease

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BACKGROUND: Several serum and imaging elastography methods are used as non-invasive modalities to predict fibrosis stage. Ultrasound (US) uses different parameters such as liver surface (LSN), lobar redistribution (LRD), or hepatic vein nodularity (HVN) to assess morphologic changes in advanced fibrosis.

PURPOSE: Our aim was to investigate the correlation of these ultrasonographic parameters to vibration controlled transient elastography (VCTE) and biopsy-proven advanced liver fibrosis and cirrhosis.

METHOD: This retrospective study included compensated chronic liver disease (CLD) patients with liver biopsy performed at a single tertiary center between 2001—2012 and 2012—2018, along with VCTE and liver ultrasonography within 6 months of biopsy.

RESULT(S): Our study cohort included 158 patients (51.3% males) with mean age of 47.7yrs, and non-alcoholic fatty liver (33.5%) and chronic hepatitis

Table 1: Multivariable regression model for association of VCTE and US parameters with AF and F4

	F3-F4	
Variable	**OR (95% CI)**	**P value**
VCTE ≥12 kPa	14.75 (5.26 – 41.35)	<0.0001
LSN	3.11 (1.07 – 9.04)	0.037
	F4	
VCTE ≥12 kPa	10.75 (4.68 – 24.69)	<0.0001
LSN	5.24 (2.06 – 13.37)	0.001

OR: odds ratio; CI: confidence interval; AF: advanced fibrosis; HVN: hepatic vein nodularity; LSN: liver surface nodularity; LRD: lobar redistribution; VCTS: vibration controlled transient elastography

B (24.1%) as the most common CLD etiology. Advanced fibrosis (AF)(≥F3) was present in 95/158 (60.1%) (F3 n = 28 and F4 n = 67), and 41.8% had VCTE ≥12 kPa. US parameters of LSN (p >0.001), LRD (p <0.001), and HVN (p <0.001) were associated with AF, but in multivariate modeling, only LSN (OR = 6.741, p <0.001) was independently associated with AF. VCTE ≥12 kPa was highly predictive for AF (OR = 20.82, CI: 7.62–56.87) and F4 fibrosis (OR = 16.15, CI: 7.34–35.54), and in a multivariate model of US parameters, LSN (OR = 3.55, p = 0.05) and LRD (OR = 4.88, p = 0.01) were independently associated with VCTE ≥12 kPa. In a combined multivariate model, both VCTE ≥12 kPa and LSN remained independently associated with AF and F4 (Table 1).

CONCLUSION(S): Ultrasound parameters of LSN, LRD, and HVN are associated with AF and higher VCTE scores. However, LSN and VCTE were independently associated with both AF and F4 in our cohort and requires further external and disease-specific validation.

Factors associated with vibration controlled transient elastography failure in a high-volume North American liver clinic

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BACKGROUND: Vibration controlled transient elastography (VCTE) is relatively new to North America and has been adopted into routine practice in our high-volume tertiary clinic.

PURPOSE: We report our experience with VCTE failure as part of standard of care.

METHOD: Electronic medical records were extracted for all VCTE results at a single tertiary center since availability of VCTE from 2014–2019. LASSO regression, a machine learning technique that performs covariate selection, was applied to determine important predictors of VCTE failure. VCTE failure was defined as <10 valid liver stiffness measurements (LSM), valid LSM <70%, or IQR/median >0.3. Eligible variables were probe size, sex, age, operator experience, LSM ≥14kPa, era of test, and interactions. Logistic regression techniques were applied to describe the relationship of identified covariates with VCTE failure.

RESULT(S): 20,459 VCTE tests were performed from 2014–2019. 92.1% of tests were successful. Median patient age was 53.4 years (IQR 42.0–62.0), median LSM was 5.9kPa (IQR 4.6–8.4), 12% had LSM ≥14kPa, 52% were performed on males, and 72% with standard M-probe.

Odds of VCTE failure were higher in females (odds ratio (OR): 1.19, 95% CI (1.01–1.40)), the XL probe (OR: 3.61, (2.95–4.44)), and older patients (OR: 1.02/year, (1.01–1.02)). Odds of failure with the XL probe were higher within females compared to males (OR 3.61 (2.95–4.44) vs 2.84 (1.83–4.41), p <0.05). Less experienced operators had higher failure rates compared to those with >1000 tests (500–1000/250–500/100–250/<100; OR: 1.83 (95% CI 1.46–2.29)/2.80(2.14–3.66)/5.11(3.92–6.68)/5.81(4.51–7.48). Tests before 2017 were more likely to fail despite adjustment for operator experience (OR: 1.91, (1.65–2.22)) (Figure). XL and medium probe were both available throughout 2014–2019.

Additional inclusion of the VCTE result demonstrated that LSM ≥14kPa was associated with failure (OR kPa≥14: 1.41, 95% CI 1.13–1.77, p <0.01).

CONCLUSION(S): VCTE failure was associated with female sex, XL probe, older age, less experienced operators, tests performed before 2017, and kPa≥14. VCTE failure was more likely in the first 3 years since availability at our center, but became

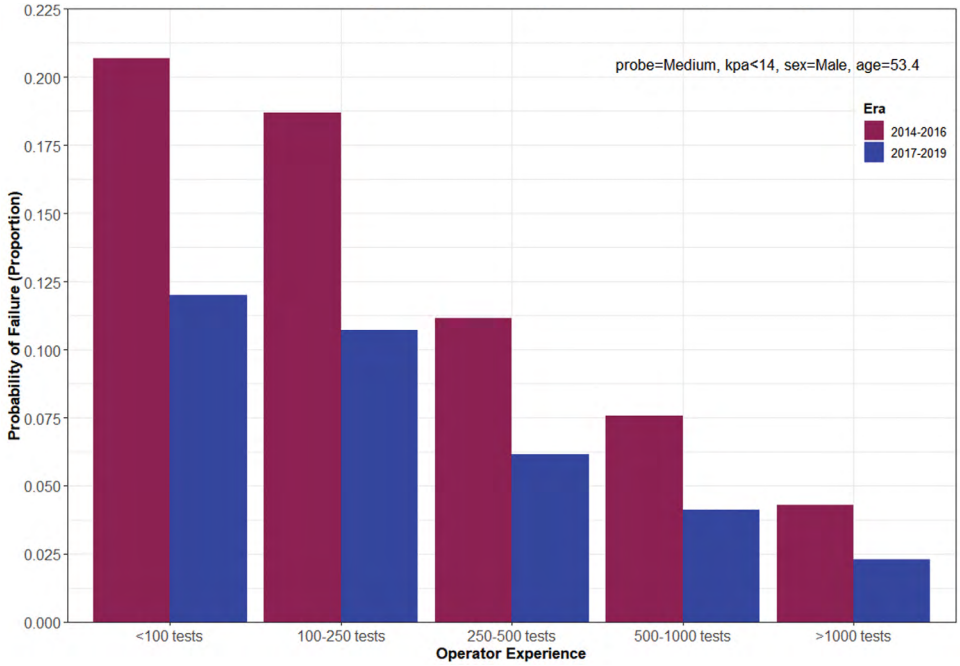

Figure : Probability of transient elastography failure vs operator experience, stratified by era of test

less frequent as operators gained experience and possibly coached new operators. This study highlights importance of the operator learning curve, and indicates that there may be a benefit to having experienced operators perform tests where factors associated with failure are present.

Validation of a hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data

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BACKGROUND: Chronic liver disease (CLD) and cirrhosis are leading causes of death globally with the burden of disease rising significantly over the past several decades. Defining the etiology of liver disease is important for understanding liver disease epidemiology, healthcare planning, and outcomes.

PURPOSE: The aim of this study was to validate a hierarchical algorithm for CLD and cirrhosis etiology incorporating both laboratory and administrative coding in routinely collected healthcare data.

METHOD: Consecutive patients with CLD or cirrhosis attending an outpatient hepatology clinic in Ontario, Canada from 05/01/2013 – 08/31/2013 underwent detailed chart abstraction. Gold standard liver disease etiology was determined by an attending hepatologist as hepatitis C (HCV), hepatitis B (HBV), alcohol-related, non-alcoholic fatty liver disease (NAFLD)/cryptogenic, autoimmune or hemochromatosis. Individual data was linked to routinely collected administrative healthcare data at ICES. Diagnostic accuracy of a hierarchical algorithm incorporating both laboratory and administrative codes to define etiology was evaluated by calculating sensitivity, specificity, positive (PPV) and negative predictive values (NPV), and kappa's agreement.

RESULT(S): 442 individuals underwent chart abstraction (median age 53 years, 53% cirrhosis, 45% HCV, 26% NAFLD, 10% alcohol-related). In patients with cirrhosis, the algorithm had adequate sensitivity/NPV (>75%) and excellent specificity/PPV (>90%) for all etiologies. In those without cirrhosis, the algorithm was excellent for all etiologies except for hemochromatosis and autoimmune diseases.

CONCLUSION(S): A hierarchical algorithm incorporating laboratory and administrative coding can accurately define CLD and cirrhosis etiology in

routinely collected healthcare data. These results should facilitate health services research in this growing patient population.

Retrovirus footprint in primary sclerosing cholangitis; APOBEC3 family expression

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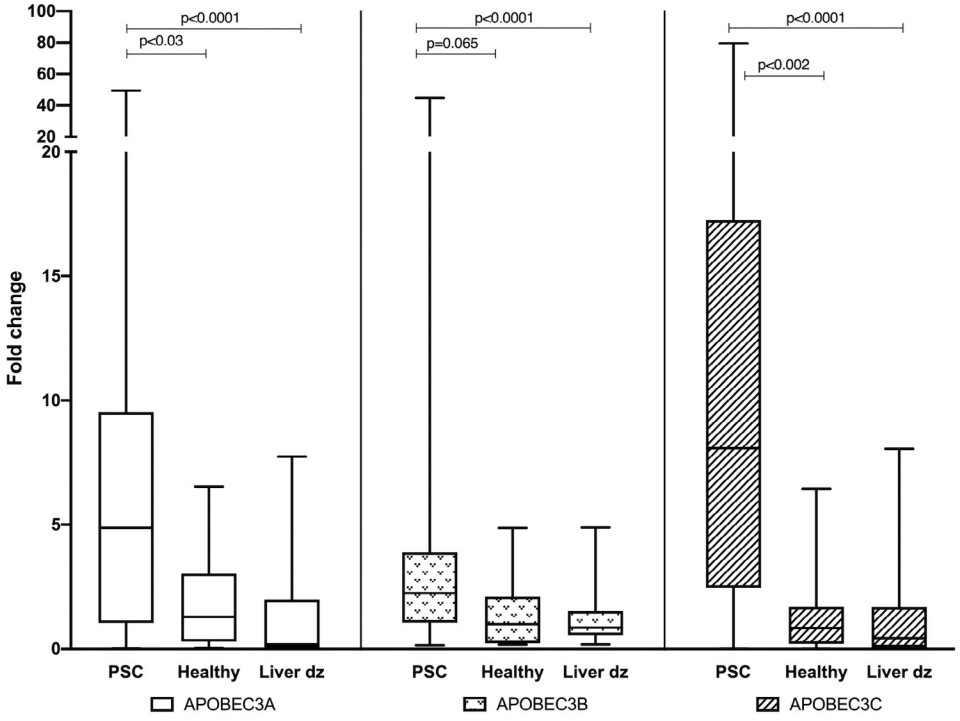
BACKGROUND: Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease characterized of unknown etiology. As a result, there is no reliable biomarker to predict the progression of PSC or therapy to treat disease leading to a sizable proportion of patients requiring liver transplantation. Members from our lab previously found the evidence of retroviral seroreactivity in the serum of PSC patients and therefore we sought further evidence supportive of a potential retroviral etiology. The APOBEC3 (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) family of proteins have cytidine deaminase activity and they restrict retroviral replication by mutagenizing the viral genome during reverse transcription. To investigate the potential role of retroviruses in PSC pathogenesis, we decided to evaluate whether specific members of the APOBEC family were differentially expressed in peripheral blood of PSC patients.

PURPOSE: To evaluate APOBEC3A, APOBEC3B and APOBEC3C expression in PSC patients, patients with other liver disorders and healthy controls.

METHOD: Total RNA from whole blood samples of 30 PSC patients, 48 patients with other hepatic disease and 16 healthy subjects were extracted. Following conversion to cDNA using Superscript II RT, primers complementary to APOBEC3A, APOBEC3B and APOBEC3C were employed for real-time PCR to assess the level of the APOBEC3 family member expression.

RESULT(S): PSC patients demonstrated increased expression of APOBEC3A, APOBEC3B and APOBEC3C vs. liver disease controls, and increased expression of APOBEC3A and APOBEC3C with a trend of increased APOBEC3B compared to healthy controls.

CONCLUSION(S): Upregulation of APOBEC3 proteins in PSC patients suggests the presence of innate immune response triggered by interferon-gamma to activate the retroviral restriction factors.



Optimising trial design in late-stage primary biliary cholangitis: evaluating options for composite clinical endpoint studies

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BACKGROUND: The criteria for participant inclusion, alongside suggested efficacy endpoints, for clinical trials involving patients with late-stage primary biliary cholangitis (PBC) is challenging.

PURPOSE: We sought to model a late-stage PBC clinical efficacy trial to understand better trial-design issues.

METHOD: Patients from the Global PBC database, diagnosed 1990 onwards that were ursodeoxycholic-acid (UDCA) treated for at least one year, were identified. A defined cohort was then modelled over time, of patients who met the following real-world inclusion criteria: cirrhosis and bilirubin >1 and <2×ULN (cirrhosis criteria) or bilirubin >2 and <3×ULN (bilirubin criteria). Patients who met bilirubin criteria may be cirrhotic. Follow-up started at the time the inclusion criteria were met. A clinical event was defined as the first occurrence of decompensation, hepatocellular carcinoma, MELD >15, liver transplantation, death, or cirrhosis for non-cirrhotic patients. To support the selection of bilirubin <3×ULN, the sample size and outcomes of patients with bilirubin >3 and <5×ULN are described.

RESULT(S): A total of 234 patients were included (8% of the total cohort), of whom 119 patients met cirrhosis criteria and 115 patients met bilirubin criteria. Median time from the start of UDCA to inclusion was 3.2 years (IQR 1.3–7.0). There were 211 (90.2%) female patients with mean age at inclusion of 56.1 years (SD 12.0). At inclusion, median bilirubin and ALP were 1.9×ULN (IQR 1.3–2.3) and 2.2×ULN (IQR 1.3–3.4), respectively. Overall, event-free survival at 1, 3, and 5 years was 85.1%, 57.9%, and 40.6%, respectively. The 1-, 3- and 5-year event-free survival was 84.5%, 49.2%, and 32.0% for the bilirubin group and 85.6%, 66.3%, and 48.6% for the cirrhosis group, which were not significantly different (P = 0.07). Of various biochemical markers at 1 year, bilirubin was predictive of event-free survival. In multivariable Cox regression (n = 112), patients with a bilirubin increase at 1 year had an increased risk for a clinical event compared to those with decrease or no change (HR 2.57, 95% CI 1.53–4.32, P < 0.001). In comparison, extending the inclusion to patients with bilirubin >3 and <5×ULN identified an additional 47 patients, with 1-, 3- and 5-year event-free survival of 46.5%, 25.8%, and 20.6%.

CONCLUSION(S): In a late-stage PBC population, a composite event-free survival endpoint may be plausible as an efficacy outcome, albeit still very challenging operationally to recruit to; change in bilirubin values at 1 year could potentially serve as an early determinant of efficacy.

Real-world experience with obeticholic acid (OCA) in Canada: A retrospective analysis of primary biliary cholangitis (PBC) patient characteristics and treatment patterns from the Canadian Patient Support Program

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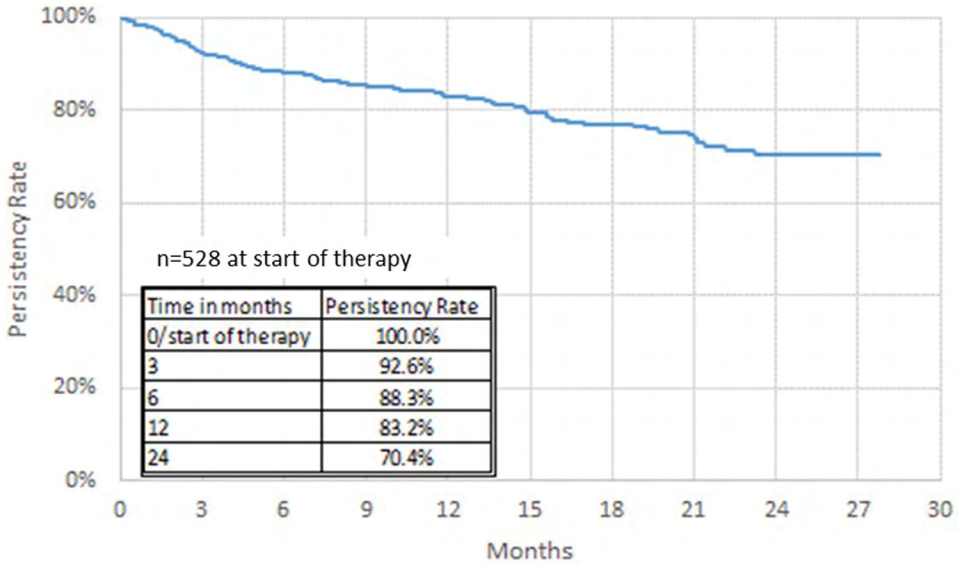

Figure : Ocaliva overall persistence

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BACKGROUND: Obeticholic acid (OCA) is the first licensed 2nd line therapy for patients with primary biliary cholangitis (PBC), that have an inadequate response or are intolerant to ursodeoxycholic acid (UDCA) treatment. OCA received conditional approval by Health Canada in May 2017.

PURPOSE: To date, real-world data on the treatment patterns and tolerability of OCA has been limited. We audited prescriber experience with OCA and characterized OCA treated patients collected through a pan-Canadian Patient Support Program (PSP).

METHOD: Non-identifiable data were obtained from patients enrolled into the PSP, which includes all patients in Canada that received at least 1 dose of OCA between May 2017 and October 2019. Baseline demographics, UDCA treatment history, available serum liver tests, starting OCA dose, dose modification, start and discontinuation dates, and reasons for discontinuation were collected for 528 patients. Patient and prescriber demographic and clinical characteristics were described using summary statistics. The Kaplan-Meier method was used to estimate persistency on OCA, defined as time from first dose to discontinuation. Log rank tests were applied to analyze associations between persistence and treatment patterns.

RESULT(S): Between May 2017 and October 2019, 528 patients started treatment with OCA across Canada. Of patients that initiated OCA, 91% were female, mean age was 57.3 y and median time since diagnosis was 6.7 y. The majority of patients had a baseline ALP >1.67 xULN (84.8%) and total bilirubin

CONCLUSION(S): To date, this is the largest real-world analysis of treatment patterns with OCA. Patient characteristics of disease were consistent with the Phase 3 POISE trial. OCA treatment persistence was good in patients that were up-titrated from 5 mg/d to 10mg/d.

Metabolic alterations of human liver tissue occurring during biobanking procedures

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BACKGROUND: Human biospecimen biobanking is crucial for biomedical research. Sample processing and storage conditions can significantly impact analyses for downstream research, as our previous work on liver metabolism support.

PURPOSE: Here, performed a pilot study to define the metabolic status of human liver tissue during laparotomy prior and after resection.

METHOD: In a pilot study of 5 patients undergoing liver tumor resection, metabolic compounds were measured from non-tumoral liver samples recovered and snap frozen at three timepoints: T1, before liver transection; T2, within the resected specimen at the end of the liver transection; T3, after transport, within the resected specimen in the Pathology lab. Liver tissue metabolome was analyzed using liquid chromatography-mass spectrometry by the CRCHUM metabolomics core facility. Data were analyzed using multivariate and univariate statistical analysis. Selection of putative biomarkers from OPLS-DA model and S-plot was combined to VIP values and univariate statistics. Only variables with strong model contribution and highly statistical reliability were selected as discriminate metabolites.

RESULT(S): Average time for samples collection from skin incision was T1:32.6±3.7min., T2: 113.8±20.6min. and T3:154.2±21.7min. We found significant impact of time of acquisition on the activity of Krebs cycle and on the energetic metabolites: lower levels of isocitrate (T1 vs T3; $P < 0.05$), acetyl-CoA (T1 vs T2,T3, $P < 0.001$), aspartate (T1 vs T2 $P < 0.05$; T1 vs T3 $P < 0.01$) and, in counterpart, increases in glycerol-3P (T1 vs T2; $P < 0.01$, T1 vs T3; $P < 0.001$), lactate (T1 vs T3; $P < 0.01$), succinate (T1 vs T3; $P < 0.01$), glutamine (T1 vs T2; $P < 0.05$, T1 vs T3; $P < 0.01$) as well as alanine (T1 vs T2; $P < 0.05$, T1 vs T3; $P < 0.01$) and leucine (T1 vs T2; $P < 0.01$, T1 vs T3; $P < 0.001$). Levels of ADP (T2 vs T3; $P < 0.05$) and ATP were also lower at later time point (T1 vs T3; $P < 0.05$) whereas AMP level was higher (T1 vs T2; $P < 0.05$, T2 vs T3; $P < 0.001$) while energy charge gradually lower along timeline (T1 vs T3; $P < 0.001$, T2 vs T3; $P < 0.05$). Interestingly, metabolic alterations associated with the timeline process were the greatest source of variation overtaking inter-individual variability.

CONCLUSION(S): In conclusion, the metabolism of non-tumoral human liver is dependent on the time of acquisition. The interpretation of results from samples acquired obtained late in the process should be taken with great caution as they do not reflect the reality of *in vivo* liver conditions.

Liver transplantation (LT) for hepatocellular carcinoma in Alberta: Patients assessed for LT in Calgary wait longer for listing and have increased mortality compared to those assessed in Edmonton

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BACKGROUND: Liver transplant (LT) is an effective cure for certain individuals with hepatocellular carcinoma (HCC). Due to their significant waitlist mortality, HCC patients are awarded MELD exception points while on the transplant waitlist to help prioritize LT. In Alberta, prospective LT patients from around the province as well as from neighbouring provinces are evaluated at two major centres (Calgary and Edmonton) with waitlisting and LT occurring in Edmonton.

PURPOSE: To assess whether evaluation in Calgary versus Edmonton influences: 1) waitlisting for LT; 2) receiving LT; and 3) mortality for individuals with HCC.

METHOD: We conducted a retrospective cohort study of all patients with HCC assessed for LT in Alberta between July 1, 2006 and December 31, 2014 using the LT databases in Calgary and Edmonton. Individuals were classified as having HCC if it appeared as primary, secondary, or tertiary diagnoses. Crude and adjusted logistic regression models and competing risk Cox regression models were performed to identify time from first pre-LT assessment to 1) waitlist placement; 2) transplantion; and 3) death, stratified by initial evaluation location (Calgary and Edmonton). Models were adjusted for age at first visit, sex and separately for MELD and MELD exception points.

RESULT(S): A total of 353 patients with HCC were evaluated during the study period (n = 250, 70.8% initially evaluated in Edmonton and n = 103, 29.2% initially evaluated in Calgary). Of the 103 seen in Calgary, 73 were referred to Edmonton for wailtlist consideration. Sixty-one (85%) of the 73 were waitlisted and 40 (55%) were transplanted. Of the 250 initially evaluated in Edmonton, 177 (71%) were waitlisted and 111 (44.4%) were transplanted. HCC patients accounted for a lower portion of transplants in the Calgary cohort (30.5% vs 36%; p = 0.337). Once waitlisted, there was no significant difference in transplant frequency or post-LT survival between evaluation sites. Intention to treat overall mortality was 56 (54.4%) for those evaluated in Calgary and 107 (42.8%) for those initially evaluated in Edmonton (p = 0.047). Median time to waitlist for those seen initially seen in Calgary was significantly longer at 129 days (IQR 72, 308) compared to 10 days (IQR 3, 46) for those initially evaluated in Edmonton. Median exception MELD points at transplant was 25 (IQR 22, 30) for those evaluated in Calgary and 24 (IQR 22, 28) for those initially evaluated in Edmonton. The competing risk adjusted hazard for waitlisting was significantly lower for those seen in Calgary compared to Edmonton (adjusted hazard ratio [HR] 0.30; 95% CI 0.21–0.41). There was no significant difference in hazard to transplant once waitlisted between sites, even after adjustment for MELD and exception MELD. Individuals initially evaluated in Calgary had higher hazard of mortality (adjusted HR 1.40; 95% CI 1.01–1.95) than those evaluated in Edmonton. When examining just those referred to Edmonton, there was no longer a significant difference.

CONCLUSION(S): Individuals with HCC evaluated in Calgary wait significantly longer to be listed and have higher hazard of mortality than those initially assessed in Edmonton. Patients with HCC seen in southern Alberta need to be referred to Edmonton earlier or eMELD exception point handled differently to ensure equal access to transplantation.

Serum ferritin is not associated with elevated elastography scores in non-alcoholic fatty liver disease

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is common, but only a minority of patients develop severe sequelae such as decompensated cirrhosis and death. Given the high prevalence of the disease and range of severity, risk stratification is critical. Non-invasive risk scores such as the FIB-4 or NAFLD fibrosis score (NFS) are recommended to identify patients that would benefit from transient elastography (TE) and early specialist intervention. Patients with NAFLD usually have elevated ferritin levels as part of a dysmetabolic hyperferritinemia. It is debated if serum ferritin is associated with a more severe presentation of NAFLD or with higher TE scores. In this study we explored the utility of adding ferritin to standard clinical assessment to help better predict risk of fibrosis.

PURPOSE: To identify if serum ferritin is predictive of fibrosis in NAFLD.

METHOD: A retrospective chart review of patients referred for NAFLD to the Vancouver General Hospital hepatology clinic from 2015–2018 who underwent transient elastography was performed. Using a retrospective cohort design, BMI, presence of hypertension, triglycerides, hemoglobin A1C, AST, ALT, platelet count, bilirubin, INR, albumin, ferritin measured within 3 months of transient elastography were collected. We compared ferritin levels against liver stiffness, ALT, AST levels, BMI, hypertension and impaired glucose status. Median levels of ferritin were also compared between patients that had a TE score greater than 8 kPa and all other patients.

RESULT(S): Data was obtained from 317 patients. After removing patients with insufficient data, 224 remained and were used for the study. Mean age was 51.1 years (SD 12.3), 50% were male, mean BMI was 28.9 (SD 5.3), 21.9% had diabetes or impaired fasting glucose. Mean AST and ALT were 39.1 IU/L (SD 39.2) and 56.2 IU/L (SD 49.7) respectively. Median ferritin was 145 mg/L and ranged from 11–3264 mg/L. Median liver stiffness was 5.2 kPa with 14.3% of patients having liver stiffness ≥8.7kPa and 17.4% ≥8.0 kPa. Receiver operating characteristic curve analysis using a

liver stiffness ≥8.0kPa as a gold-standard showed an AUROC of 0.54 for serum ferritin levels. At a cut-off of both 300 mg/L and 450 mg/L fibrosis score did not differ significantly in those with liver stiffness ≥8.0kPa vs <8.0kPa (ferritin ≥300mg/L; p = .099, ferritin ≥450mg/L; p = .12). Ferritin was significantly higher in male patients (198mg/L; vs 91mg/L p = .0001). There was a weak linear association between AST and ferritin levels.

CONCLUSION(S): Elevated serum ferritin is not associated with fibrosis in NAFLD as measured by transient elastography and is not predictive of an elevated transient elastography measurement.

Test-retest reliability of hepatic venous pressure gradient: A study in 215 patients from the control arms of 17 randomized controlled trials

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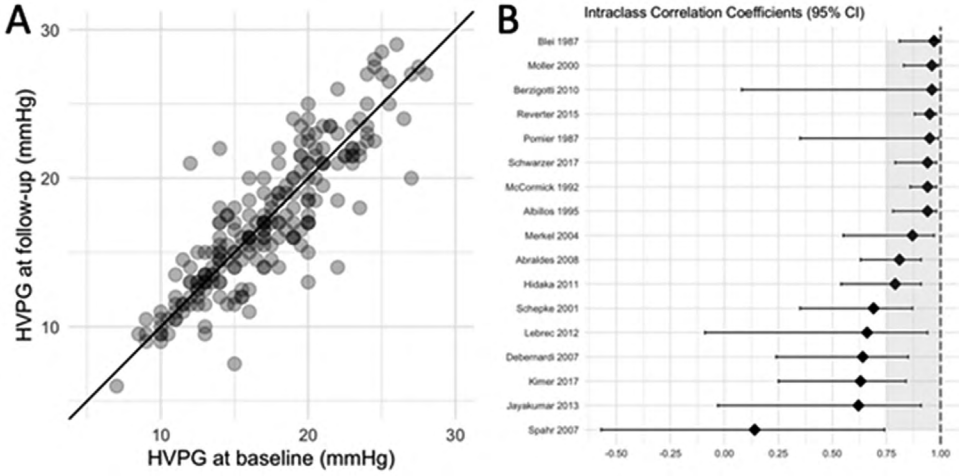
BACKGROUND: Portal hypertension (PH) is a major driver for cirrhosis complications. Portal pressure is estimated in practice by the hepatic venous pressure gradient (HVPG). The assessment of HVPG changes has been used for drug development in PH. Moreover, there is increasing interest in wider use of HVPG as a clinical outcome measure in RCTs for the treatment of cirrhosis. This requires a thorough understanding of the test-retest reliability of HVPG.

PURPOSE: This study aimed at quantifying the test-retest reliability of HVPG in the specific context of RCTs for the treatment of PH in cirrhosis.

METHOD: We performed a systematic search of published RCTs in patients with cirrhosis reporting individual patient-level data of HVPG at baseline and after an intervention, and that included a placebo or untreated control arm. Baseline and follow-up HVPG in the control groups were extracted after digitizing the plots. Test-retest reliability was estimated by the intraclass correlation coefficient (ICC). Pooled ICC and potential associations with study characteristics were estimated with linear mixed models (patient and study as random effects). We considered ICC >0.75 as excellent as recommended for measures with physiological variability.

RESULT(S): Seventeen trials including a total of 215 patients in the placebo/untreated groups had plots with legible individual HVPG changes. Time range between HVPGs was 20 min to 730 days. Fig. A shows the association between baseline and follow-up HVPGs, and Fig. B the ICCs of individual studies. 20% and 8% of the patients showed a ≥10% and ≥20% response, respectively. 11/17 studies showed excellent reliability (>0.75) of repeated HVPGs, and 5 showed moderate reliability. Only one study showed poor reliability (ICC: 0.14). In that study, a wedged catheter was used for HVPG measurement (as opposed to balloon catheter in the other 16 studies). Pooled ICC was excellent (0.87). We did not find an association between reliability and proportion of patients with alcohol-related liver disease, compensated vs



decompensated cirrhosis, multicentric vs single-center studies, year of publication or time between measurements.

CONCLUSION(S): We show in this study that, in the context of RCTs, test-retest reliability of HVPG is excellent. We provide quantitative information on the range of expected reliability parameters that will be useful for sample size calculation and results' interpretation in trials with HVPG as an outcome measure.

Preliminary results of the prevalence of fatty liver disease in the Greater Toronto population

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BACKGROUND: The incidence and prevalence of non-alcoholic fatty liver disease (NALD) and non-alcoholic steatohepatitis (NASH) is on the rise. NAFLD and NASH can lead to advanced liver fibrosis and/or cirrhosis. In order to deal with this epidemic in a timely fashion, it is important to gain a better understanding of the defining characteristics of the affected population and the severity of the disease needs to be achieved.

PURPOSE: The aim of this study was to undertake a retrospective analysis of the Fibroscan results of a diverse patient population in the Greater Toronto Area (GTA) to understand the demographic composition of the population and the prevalence/severity of fatty liver disease within this specific region of southern Ontario, Canada.

METHOD: Retrospective review of 4486 charts was conducted in order to study the condition of fatty liver among a diverse patient population in the GTA. Patient geographical location within the GTA, age, gender, fibrosis and steatosis scores were analysed for these patients through the use of descriptive statistics.

RESULT(S): A retrospective review of 4486 patient charts sourced from the GTA was undertaken to obtain a snapshot of the prevalence of fatty liver

Table: Patient demographic information

	Frequency	Percentage
Gender		
Female	1860	41.5
Male	2344	52.3
Age		
<30	85	1.9
30–39	326	7.3
40–49	759	16.9
50–59	1271	28.3
60–69	1185	26.4
70–79	678	15.1
80–89	145	3.2
>90	7	0.2
Geographical Location		
Mississauga	948	21.13
Toronto	752	16.76
Scarborough	607	13.53
Halton Region	221	4.93
Vaughan	201	4.48
Markham	158	3.52
Burlington	65	1.45
Richmond Hill	64	1.43
Brampton	46	1.03
Newmarket	38	0.85
Durham	25	0.56
London	8	0.18
Peterborough	4	0.09
St. Catherines	4	0.09
Kitchener	2	0.04
Oshawa	2	0.04
Barrie	1	0.02
Hamilton	1	0.02
Unknown	1340	29.86
FibroScan® Results Fibrosis		
F0	973	25.8
F0-F1	712	18.9
F1	582	15.4
F1-F2	373	9.9

	Frequency	Percentage
F2	398	10.5
F2-F3	173	4.6
F3	154	4.1
F3-F4	103	2.7
F4	309	8.2
Steatosis		
S0	129	7.3
S0-S1	53	3.0
S1	248	14.1
S1-S2	73	4.2
S2	366	20.8
S2-S3	243	13.8
S3	647	36.8

disease in the GTA (Table). Geographical distribution spans 18 different cities/ regions in the GTA among 3147 patients for whom the data was available: Barrie (0.03%), Brampton (1.46%), Burlington (2.07%), Durham (0.79%), Hamilton (0.03%), Halton Region (7.02%), Kitchener (0.06%), London (0.25%), Markham (5.02%), Mississauga (30.12%), Newmarket (1.21%), Oshawa (0.06%), Peterborough (0.13%), Richmond Hill (2.03%), Scarborough (19.29%), St. Catherines (0.13%), Toronto (23.90), Vaughan (6.39%). Of the 4486 cases: 52.3% male (2344 patients), 41.5% female (1860 patients), 6.3% unknown (282 patients). In terms of age distribution: <30: 1.9%, 30–39: 7.3%, 40–49: 16.9%, 50–59: 28.3%, 60–69: 26.4%, 70–79: 15.1%, 80–89: 3.2%, <90: 0.2% and age is unknown for 0.7%. Fibroscan® results were registered in 3777 of the cases and the relative proportion of fibrosis staging was: F0- 25.8%, F0 to F1- 18.9%, F1- 15.4%, F1 to F2- 9.9%, F2-10.5%, F2-F3-4.6%, F3-4.1%, 3 to F4- 2.7%, F4- 8.2%. Steatosis results were available in 1759 of the 3777 available Fibroscan results: S0- 7.3%, S0-S1- 3.0%, S1- 14.1%, S1-S2- 4.2%, S2- 20.8%, S2-S3- 13.8%, S3- 36.8%.

CONCLUSION(S): The majority of patients were between the ages of 50 and 69 and were male (52.3%). The majority of the charts where steatosis results were available indicate moderate to severe steatosis. Moderate to severe fibrosis was found in 30% of the cohort of which 8.2% were F4 (cirrhosis).

FINCh: Fibroscan Impact on Non-alcoholic fatty liver disease in children—using randomized placebo-phase design trial

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is thought to be the most common form of paediatric liver disease, the most important risk factor for which is obesity. As obesity rates rise in North America the rates of NAFLD are expected to follow. Lifestyle intervention is the only proven treatment that alters its clinical course. With current management, over 1/3 of adult patients with NAFLD have progressive fibrosis on repeat biopsies. Unfortunately, the experience in our institution suggests that paediatric patients struggle with lifestyle modification adherence despite frequent multidisciplinary appointments.

PURPOSE: The purpose of this study is to determine whether quantifying the amount of scarring in patients' liver by transient elastography (TE) will help improve compliance with lifestyle modifications.

METHOD: We used a randomized placebo-phase design (RPPD) trial to measure the impact of TE results measured by Fibroscan on patient compliance to lifestyle modifications. In this study we collected data on BMI, BMI z-score, liver enzyme values, AST-platelet ratio index (APRI) as well as total cholesterol and triglyceride levels. This information was collected for 9 patients at the time of their initial consultation, at the time of the TE and during a follow-up appointment after the scan results were disclosed. Patients with other active causes of liver fibrosis were excluded.

RESULT(S): In our preliminary analysis 5/9 patients (55%) had a decrease in the BMI Z-score or a slowing in the rate of weight gain between the intervention and follow-up. When patients who already had a decreasing BMI z-score prior to the intervention were excluded, this result increased to 4/6 (67%). Overall, the patients who showed positive results had a higher initial average BMI z-scores of

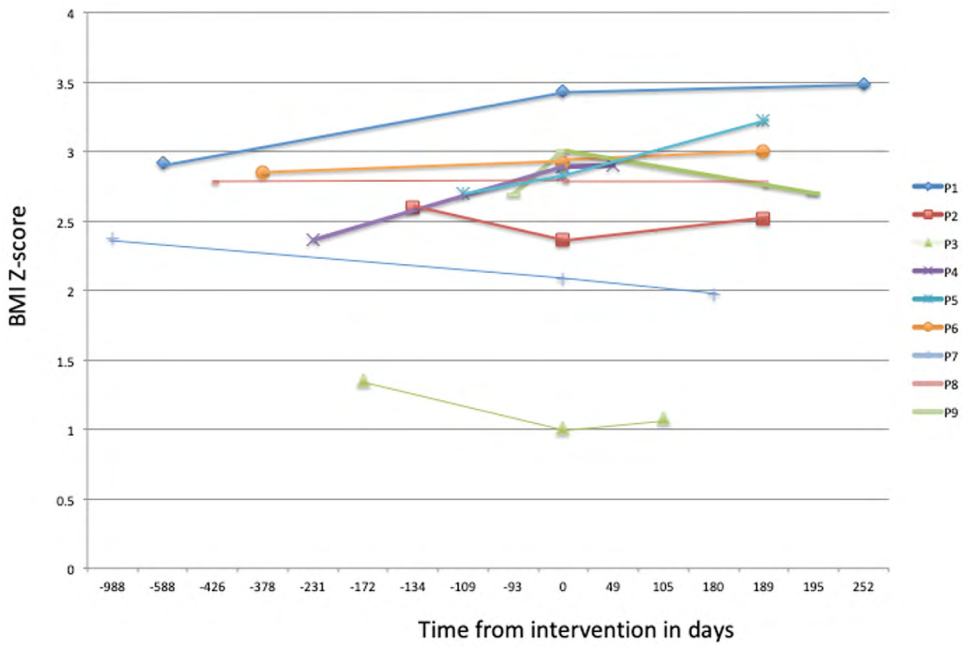

Figure : Trend in BMI z-score over time in study patients before and after the intervention

2.84 vs. 2.28, higher APRI scores of 0.4748 vs. 0.2078 as well as higher liver enzymes, cholesterol and triglycerides. Despite showing BMI z-score improvement a Wilcoxon signed-rank test found statistically significant increases in average ALT (54.9 vs. 72.8, p = 0.018) and cholesterol (3.832 vs. 4.185, p = 0.046) measurements between the time of the intervention and follow-up appointments.

CONCLUSION(S): Paediatric patients with NAFLD who have rising BMI z-scores despite regular appointments may benefit from knowing their hepatic fibrosis scores as measured by TE. Our study is ongoing with the hopes that a larger sample size will help reinforce this notion. Despite weight loss or a slowing in weight gain, many patients continued to have rising liver enzymes and cholesterol levels. This may be attributed to the short time period before follow-up or the fact that additional weight loss may be required to reverse the effects of this chronic condition.

Outcomes of sarcopenic obesity and metabolic syndrome in liver transplant patients

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BACKGROUND: Sarcopenia is associated with a worst prognosis in cirrhotic patients after liver transplantation (LT). As patients gain weight and sarcopenia remains after LT, sarcopenic obesity (SO) develops. Metabolic syndrome (MS), a cluster of factors that increase the risk of heart disease and diabetes, is caused by weight gain. There are limited data about the influence of SO and MS in LT recipients.

PURPOSE: The goal of this study was to examine the impact of SO and MS on outcome after LT.

METHOD: In total, 94 cirrhotic patients who underwent LT at the CHUM – Liver Unit were included. Sarcopenia was assessed at the third lumbar level vertebrae using a CT-scan. Obesity was determined using BMI whereas MS was diagnosed using the presence of ³3 modified NCEP ATP III criteria. The prognostic factors were collected 6 months before and during 1 year after LT through medical records and included number of complications, episodes of infections, length of stay, and frequency of readmissions.

RESULT(S): Most of the patients (~70%) were not obese before LT. Approximately 20% of the patients developed obesity after LT. Among patients who were obese before LT, ~40% of the patients remained obese after LT. SO affected 10% and less of the patients before and after LT. Among patients with MS before LT (64%), ~40% of them was still affected after LT. Among patients who were not affected by MS before LT, 38% developed MS after LT and one patient remained not affected after LT. Prognostic factors were worst in patients with SO and MS before and after LT.

CONCLUSION(S): SO affected a small proportion of patients while MS was prevalent before and after LT. Nevertheless, these conditions were associated with worst prognosis. Strategies to manage SO and MS could help to improve recovery in patients who have undergone LT.

Hepatic steatosis predicts fibrosis in long-term methotrexate use

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BACKGROUND: Methotrexate (MTX) is effective for dermatologic and rheumatologic conditions such as psoriasis (Ps), psoriatic arthritis (PsO) and rheumatoid arthritis (RA). Long-term MTX use may be complicated by hepatic fibrosis, although patient, disease factors and the mechanism remain unclear. Transient elastography (TE) is a non-invasive measure of hepatic fibrosis that is often used as surveillance in this patient population.

Patients with Ps and PsO have higher rates of non-alcoholic fatty liver disease. The controlled attenuation parameter (CAP) measurement is a non-invasive test that correlates with histologic degree of steatosis. To our knowledge, no studies have evaluated hepatic steatosis via CAP scores in MTX use.

PURPOSE: To determine the prevalence of steatosis and significant fibrosis (F≥2) in persons on MTX therapy and to determine the predictive factors for these events.

METHOD: A single centred retrospective cohort study was performed. Patients on >6 months of MTX for a dermatologic or rheumatologic disease who had undergone TE from January 2015 to September 2019 were included. Demographic variables, laboratory investigations, TE and CAP scores were collected. Multivariate analysis was performed to determine predictors of steatosis and fibrosis.

RESULT(S): A total of 177 patients on methotrexate were included. Ps was the most frequent diagnosis (n = 52) followed by RA (n = 50) and PsO (n = 38). Steatosis (CAP ≥245 dB/m) was present in 73.9% of patients. Patients with steatosis had significantly more fibrosis and a higher BMI than those without steatosis (CAP <245 dB/m). Higher CAP score was correlated with increased lifetime dose of methotrexate by Pearson correlation analysis (r = 0.48, p = 0.001) (n = 85 patients). Multivariate regression analysis revealed that diabetes mellitus (OR 10.5, 95% CI 1.38-80.60), hypertension (OR 4.97, 95% CI 1.66–14.84), and BMI >30 (OR 10.1, 95% CI 1.88–37.14) were predictors of steatosis (CAP≥245 dB/m). Predictors of METAVIR≥F2 (TE≥8.0 kPa) by multivariate regression analysis included CAP score of ≥270 (OR 8.36, 95% CI 1.88–37.14), diabetes mellitus (OR 2.85, 95% CI 1.09–7.48), hypertension (OR 5.4, 95% CI 2.23–13.0), dyslipidemia (OR 3.71, 95% CI 1.50–9.18) and alcohol use (OR 3.06, 95% CI 1.2–7.49).

CONCLUSION(S): In patients on MTX for rheumatologic and dermatologic diseases, hepatic steatosis was common and predicted significant fibrosis. Additionally, increasing MTX exposure is correlated with steatosis. Features of the metabolic syndrome including diabetes, hypertension or obesity were predictors of both steatosis and fibrosis (F≥2). Further study is needed to evaluate if steatosis is a mechanism by which fibrosis occurs in patients on MTX, or if it due to other patient factors.

Clinical evaluation of portal-hepatic blood flow at a low-invasive treatment of mechanical jaundice

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BACKGROUND: Many diseases can cause obstructive jaundice and then lead to a series of pathologic disorders. Thus preoperative assessment of liver function is of utmost importance. Traditional assessment is to monitor related indicators of liver function, but it is invasive and needs to be performed repeatedly

PURPOSE: To analyse the features of hepatic hemocirculation in patients with obstructive jaundice before and after eliminating cholestasis

METHOD: The study involved 60 patients with obstructive jaundice aged 42 to 84 years admitted at the Department of Gastroenterology in 1st Republican Therapy Center, Tashkent. The duration of jaundice ranged from 2 to 24 days. Complex ultrasound was performed upon admission and in the dynamics of biliary decompression, which, depending on the cause and level of obstruction, was performed by retrograde or antegrade minimally invasive methods, which excluded the effect on liver anesthesia, surgical trauma, blood loss and other negative factors of open intervention. The control was the results of a survey of 24 healthy individuals in whom mean values of blood flow parameters were accepted, which we accepted as the norm

RESULT(S): The study showed that resistance index (RI) in the hepatic artery was 1.2 times higher than the normal level, and the volumetric blood flow (Q) by IV is reduced to 577.3 ± 34.5 mL/min or by 22% compared with the control value. After decompression of the bile ducts, blood supply to the liver improved. In the first 2–56 days, improvement of hepatic hemodynamics occurred due to an increase of 109.6% ± 6% portal venous blood flow, carrying the bulk of the toxic substances from the intestines, which are formed in excess with acholia and a violation of its functions. Mean values Q in hepatic artery were significantly lower ($p < 0.01$) of the initial level by 19.1% ± 1.6%, although they did not statistically differ ($p > 0.05$) from the indicators in the control group. Dynamics of improving blood supply to the liver during depended much on the functional state of hepatocytes, which confirms the interdependence of circulatory and metabolic disorders. So, in patients with an initial deviation of integral function of liver to 45% of the liver cells coped with the increased toxic load after decompression and the restoration of effective blood flow occurred in them 3–6 days after biliary drainage ducts.

CONCLUSION(S): Thus, we can conclude that biliary decompression in obstructive jaundice is accompanied by a portal toxic load on hepatocytes inhibited during cholestasis, from the initial state of which the further course of hepatargy depends. An analysis of the initial state of the patients made it possible to identify individuals who are especially dangerous with respect to post-decompression inhibition of liver activity.

Validation of FIB-4 scores and liver stiffness measurements (LSM) by VCTE as non-invasive modalities for detection of advanced fibrosis in NAFLD patients

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BACKGROUND: Among patients (pts) with non-alcoholic fatty liver disease (NAFLD), fibrosis has been shown as the only independent predictor of clinical outcomes. Compared to no fibrosis, F3-F4 fibrosis is associated with an increased risk for liver-related events. The risk for all-cause and liver-related mortality also increases with higher stages of fibrosis. Biopsy remains the current standard of care for fibrosis in NAFLD pts but incurs many potential risks and sampling error. Diagnosis using non-invasive techniques (NITs) is critical for identification of pts with advanced fibrosis. Liver stiffness measurements by Fibroscan (LSM-FS) and FIB-4 are two NITs widely available and used for identifying advanced fibrosis in pts with chronic liver diseases.

PURPOSE: To evaluate the performance of LSM-FS and FIB-4 in predicting advanced fibrosis vs biopsy in pts with NAFLD.

METHOD: A retrospective review of pt records from Sept 1995 to Dec 2018 was conducted at a large urban community-based liver clinic to identify pts with NAFLD (n = 1209). Pts with other liver etiologies (significant alcohol use, HIV, HBV, HCV) were excluded. Based on biopsy results, pts were

divided into 2 groups: mild/moderate fibrosis (F0-2), and advanced fibrosis (F3-4). Lab measurements (ALT, AST, platelets) for FIB-4, and LSM-FS were included in the analysis if obtained within 6 months of biopsy in non-cirrhotic pts, and within 1 year in pts with cirrhosis. Correlations between NITs and biopsy were analyzed with the Spearman method. Diagnostic performances of both NITs were assessed using AUROC.

RESULT(S): Of the 1209 NAFLD pts with evaluable data, 82 had reliable paired biopsy and LSM-FS (cohort 1), and 81 with reliable paired biopsy and FIB-4 (cohort 2). In cohort 1, 43 (52%) were male with a mean age of 50; in cohort 2, 48 (59%) were male with a mean age of 43. Spearman coefficients between LSM-FS/biopsy-Metavir and FIB-4/biopsy-Metavir were 0.63 ($p < 0.0001$) and 0.22 ($p = 0.0048$). LSM-FS had a sensitivity of 89% and specificity of 75% in predicting advanced fibrosis; FIB-4 >3.25 had a sensitivity of 33%, specificity of 100% in predicting advanced fibrosis. In our study, AUROC for LSM-FS in predicting advanced fibrosis was 0.873 (95% CI: 0.79–0.93) and for FIB-4 was 0.60 (95% CI: 0.49–0.71).

CONCLUSION(S): Our analysis shows positive correlations between LSM-FS and FIB-4, and stages of liver fibrosis on biopsy. LSM-FS and FIB-4 are both useful in predicting advance liver fibrosis in an outpatient setting. Further studies with a larger cohort of patients are needed to further elaborate on these findings.

Impact of depression and antidepressant usage on the clinical outcomes of chronic liver disease

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BACKGROUND: Depression is common among patients with chronic disease, including those with chronic liver diseases (CLD). The role of depression and antidepressant usage on patient survival in common CLD are unknown.

PURPOSE: In this study, we evaluated the impact of depression and antidepressants on survival among patients with chronic hepatitis (CH), alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD).

METHOD: We used The Health Improvement Network database (THIN), the largest medical database in the UK, to identify incident CH (n = 3,830), ALD (n = 6,073), and NAFLD (n = 21,205) patients between 1989 and 2013, and followed these patient cohorts up to and including the year 2017. Our primary outcome was mortality, and secondary outcome development of decompensated cirrhosis. We evaluated the effect of depression and use of different antidepressants as: never exposed; exposure prior to CLD diagnosis; or current/ after CLD diagnosis. We used Read Codes to define our main exposure and outcomes. Antidepressants included atypical antidepressants, mirtazapine, monoamine oxidase inhibitors (MAOI), serotonin norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), serotonin modulators, and tricyclic antidepressants (TCA). We used multivariate Cox proportional hazards models to identify independent predictors (hazard ratio) of outcomes. Models were adjusted for age, sex, socioeconomic status, comorbid conditions, smoking, and alcohol usage.

RESULT(S): The prevalence of a current depression diagnosis varied among incident CLD patients (CH = 11.0%, ALD = 9.1%, and NAFLD = 5.6%). Antidepressant usage was common among all CLD cohorts (CH = 46.1%, ALD 47.6%, and NAFLD = 40.6%). Median follow-up and mortality rates among the three cohorts are presented in Table 1. In our adjusted models, depression status was not associated with decompensated cirrhosis-free survival or mortality in our three cohorts (Table 1). However, current use of mirtazapine (HR 0.72: 95% CI, 0.59–0.87), SSRI (0.79: 0.70–0.88), and TCA (0.72: 0.64–0.81) antidepressants were independently associated with improved survival among ALD patients. Only SNRI (0.63: 0.41–0.98) use was associated with better survival in the NAFLD cohort. No antidepressant was identified as an independent predictor of better survival among the CH cohort. Neither depression nor antidepressant usage were associated with decompensated cirrhosis-free survival in the CLD cohorts.

CONCLUSION(S): In our large CLD patient cohort, depression and use of antidepressants were

Table 1: Clinical outcomes incidence rates and adjusted hazard ratios for depression in chronic liver disease cohorts

Cohort	Follow up duration (median, IQR), months	Mortality incidence rate (cases per 1000 person-year)	Decompensated cirrhosis incidence rate (cases per 1000 person-year)	Adjusted HR of depression for mortality (95% CI)	Adjusted HR of depression for decompensated cirrhosis (95% CI)
Chronic hepatitis (CH)	46.1 (20.2–86.7)	12.3 (11, 13.7)	4.3 (3.5, 5.1)	0.70 (0.47, 1.04)	0.74 (0.39, 1.38)
Alcoholic liver disease (ALD)	32.3 (13.3–65.1)	70.5 (67.5, 73.6)	37.7 (35.2, 40.4)	0.85 (0.71, 1.01)	0.99 (0.78, 1.26)
Nonalcoholic fatty liver disease (NAFLD)	35.4 (17.2–67.4)	8.9 (8.3, 9.6)	2.8 (2.4, 3.2)	0.84 (0.61, 1.15)	1.10 (0.67, 1.80)

common. Although a diagnosis of depression did not alter survival or risk of decompensation, the use of certain antidepressants significantly improved survival in ALD and NAFLD patients. These findings support further research to determine mechanism whereby certain antidepressant classes can exert a survival benefit in ALD and NAFLD.

Post-partum primary biliary cholangitis (PBC) after resolution of intrahepatic cholestasis of pregnancy (ICP) in First Nation's patients of BC: a case series

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BACKGROUND: PBC is a progressive cholestatic disease characterized by destruction of intrahepatic bile ducts, peri-portal inflammation and fibrosis. PBC is the leading indication for liver transplantation in First Nations of British Columbia. PBC is not classically associated with ICP, but we have empirically noticed a correlation.

PURPOSE: To explore a possible relationship between ICP and PBC in First Nations patients of BC.

METHOD: We present 3 cases of clinically diagnosed ICP in First Nations women who were later diagnosed with PBC post-partum.

RESULT(S): **Case 1:** A 27-year-old woman with history of ICP at 31 weeks during her 3rd pregnancy and family history of PBC presented with ursodiol and cholestyramine responsive pruritis and jaundice 20 weeks into her 4th pregnancy. Bilirubin was 103 µmol/L, ALP 371 IU/L, ANA and AMA negative. Symptoms and biochemistry remained in remission after delivery at 33 weeks. Discontinuation of medications led to recurrent pruritis 4 months later. Bilirubin was 6 µmol/L, ALP 272 IU/L, GGT 153 IU/L and ALT 204 IU/L. Liver biopsy was consistent with PBC, F1. Pruritis has now been refractory to ursodiol, cholestyramine and rifampin.

Case 2: A 30-year-old woman with history of ICP at 20 weeks during 2 prior pregnancies presented with ursodiol responsive pruritis 20 weeks into her 3rd pregnancy. Symptoms and biochemistry remained in remission after delivery at 35 weeks. Post-partum discontinuation of ursodiol led to recurrent pruritis 2 months later. ALP was 876 and AMA >1:640. Re-initiation of ursodiol improved symptoms and biochemical abnormalities.

Case 3: A 30-year-old woman with family history of PBC (mother) presented with ursodiol responsive pruritis and jaundice 20 weeks into her 4th pregnancy. Symptoms and biochemistry remained in remission after delivery at 37 weeks. Post-partum discontinuation of ursodiol led to recurrence jaundice 4 months later. Bilirubin was 68, ALP 1279, total cholesterol 7.72, IgM 18.98, ANA >1:640 and AMA 1:320. Jaundice and biochemical abnormalities persisted despite re-initiation of ursodiol. Obeticholic acid has been initiated.

CONCLUSION(S): First Nations communities of BC are disproportionately affected by PBC, due to both genetic and epigenetic phenomena. We present 3 patients who were diagnosed with ICP that resolved post-partum but with the subsequent development of PBC. The intrapartum cholestasis did not have clinical features of PBC during pregnancy. Although not previously reported, ICP may predispose to PBC in this specific community. It remains to be seen if there is a genetic association. Clinicians must remain suspicious of PBC during pregnancy in this population and ongoing monitoring in the post-partum period is paramount.

NMR metabolic profiling can help discriminate between normal primary hepatocytes and diverging hepatic cancer cell lines

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BACKGROUND: Metabolic alterations are a hallmark of cancer cells. Recent studies suggest that the metabolic reprogramming of cancer cells is essential to support their growth in nutrient-restricted environments. We previously showed that Dt81Hepa1-6 cells, a highly tumorigenic derivative of Hepa1-6 murine cells, display increased metabolic plasticity *in vitro*. Recently, novel omics technologies have been shown to perform multiparametric quantification of metabolic responses in normal and pathological cells.

PURPOSE: To characterize the metabolic pathways active in primary hepatocytes and these two diverging cancer cell lines under proliferative conditions, we examined production and consumption rates of metabolites *in vitro* using a nuclear magnetic resonance (NMR) metabolomic approach.

METHOD: Primary hepatocytes were isolated using the two-step collagenase perfusion method from C57BL/6 mice. Dt81hepa1-6 cells have been isolated after an *in vivo* passage of parental Hepa1-6 cells. Cells were cultured *in vitro* in high glucose DMEM (25mM) with 10% FBS. After 48 hours, medium was collected and cells were snap-frozen. The extraction of intracellular metabolites was performed using an ice-cold $MeOH/CHCl_3/H_2O$ solution. Cell extracts and culture medium samples were analyzed using a cryoprobe Bruker 700 MHz AVANCE NMR spectrometer for both structure elucidation and quantification.

RESULT(S): More than 30 metabolites were identified and quantified in both cellular extracts and extracellular culture medium. Metabolomic analysis revealed distinct metabolic profiles between primary hepatocytes, Hepa1-6 and Dt81-hepa1-6 cell lines. We identified several metabolites that were differentially regulated between normal and cancer cells (that both displayed increased glycolytic activity) as well as metabolites that were specifically associated with the highly tumorigenic Dt81Hepa1-6 cell line. Hence, a significant decrease in glucose, glutamine ($P < 0.01$) as well as a specific increase in lactate, alanine, acetate ($P < 0.001$) were found in the extracellular medium of both cancer cell lines. Interestingly, ketoacids by-products originating from the valine, leucine and isoleucine degradation pathway were found in the Dt81-hepa1-6 medium. Lactate, alanine, creatine and ATP ($P < 0.001$) were also increased in cancer cell compared to primary cells extracts.

CONCLUSION(S): Our metabolomic approach can identify and measure metabolite alterations associated with cellular growth and energy metabolism. Normal and cancer cells can be distinguished according to their respective metabolic profile. The level of tumorigenicity of HCC cells also seems associated with metabolic differences. These results confirm the increased use of glucose by cancer cell lines and demonstrate that NMR-based metabolomics analysis is a powerful approach to characterize the metabolic alterations that occur in cancer cells.

Vitamin D deficiency and its association with clinical outcomes in primary sclerosing cholangitis

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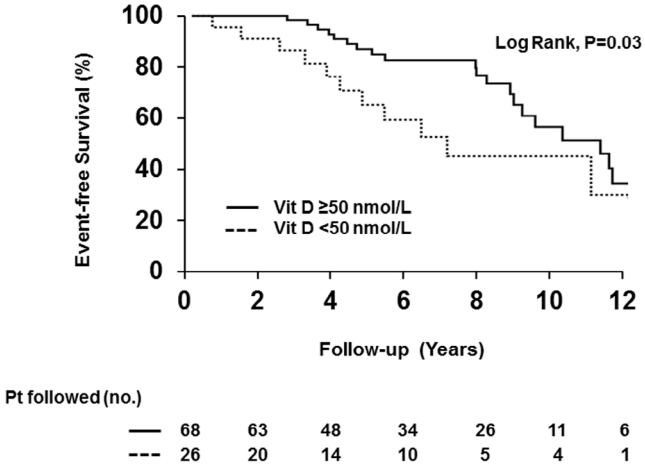
BACKGROUND: Primary sclerosing cholangitis (PSC) is a progressive cholestatic disease involving chronic inflammation and fibrosis of intra- and

extra-hepatic ducts. Vitamin D is a secosteroid implicated in anti-inflammatory and anti-fibrotic pathways, and its deficiency has been associated with worse outcomes in chronic liver disease. Vitamin D status may also influence the course of PSC but studies evaluating this link are scarce.

PURPOSE: To determine the association of vitamin D deficiency with the development of cirrhosis, mortality, and liver transplantation in patients with PSC.

METHOD: Ninety-four patients with the diagnosis of PSC were evaluated and followed by the autoimmune liver disease clinic at the University of Alberta, Edmonton, Canada. Clinical data were recovered from medical charts. Vitamin D status was defined by the serum concentration of 25-hydroxyvitamin D3. Patients with levels <50 nmol/L (10 ng/mL) were defined as deficient. Univariate and multivariate analyses were constructed using the Cox proportional hazards regression models. Event-free survival was defined as time from vitamin D assessment to the time of liver transplant or death.

RESULT(S): Mean age at PSC diagnosis was 32±14 years, with 67% of patients being male. The mean vitamin D level was 69±33 nmol/L (range, 4–163 nmol/L) and 26 patients (28%) had vitamin D deficiency (<50 nmol/L). Among 85 patients without cirrhosis at diagnosis, 43 patients (51%) developed cirrhosis. By univariate Cox analysis, serum ALP, albumin, bilirubin and vitamin D deficiency were predictors of cirrhosis development. Vitamin D deficiency was independently associated with higher risk of developing cirrhosis (HR 2.11, 95% CI 1.002–4.44, P = 0.049) after adjusting for other predictors. Median time to develop cirrhosis was shorter in patients with vitamin D deficiency (6.8 years; 95% CI, 1.7–11.8) compared to those without (10.8 years; 95% CI, 9.2 -12.4; P = 0.007). Over a median follow-up period of 5.6 years, adverse outcomes (liver transplant or death) were observed in 34 patients (36%). Serum levels of albumin, ALP, bilirubin, INR, platelet count, ascites, variceal bleeding and vitamin D deficiency were associated with adverse outcomes in univariate analysis. Vitamin D deficiency was independently associated with higher risk of adverse endpoints (HR 2.87, 95% CI, 1.16–7.12, P = 0.02) after adjusting for confounding factors. Event-free survival was shorter in the patients



with vitamin D deficiency compared to patients without deficiency (7.1 years; 95% CI, 2.4–11.9 *vs.* 11.4 years; 95% CI, 8.9–13.9, P = 0.03, Figure).

CONCLUSION(S): Vitamin D deficiency was frequent in patients with PSC and was associated with progression to cirrhosis, as well as decreased time to liver transplantation and death. The possibility of improving outcomes in PSC by vitamin D supplementation awaits further investigation.

Erythropoietic protoporphyria: an unusual presentation of advanced liver fibrosis during infancy

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BACKGROUND: Erythropoietic protoporphyria (EPP) is a rare orphan autosomal recessive inherited disease caused by ferrochelatase (FECH) mutations. In most cases, a severe pathogenic FECH mutation is inherited from one parent and a mild, low-expression mutation (which is common in the normal population) from the other. This heme synthesis disorder leads to impairment of iron insertion into the protoporphyrin IX ring to form heme, resulting in the accumulation of protoporphyrin

in bone marrow, erythrocytes, plasma, skin and liver. EPP has an estimated frequency of 1:75,000 to 1:200,000. Skin photosensitivity usually begins during infancy. The liver excretes, but is subject to damage by protoporphyrin. Advanced liver disease and liver failure occur in 1%–4% of EPP patients.

PURPOSE: Herein we describe a case of EPP presenting in the first year of life with advanced liver fibrosis. A literature review is performed to identify management strategies and determine optimal treatment options.

METHOD: A chart and PubMed review are performed.

RESULT(S): A 12-month-old girl presented with recurrent painful facial swelling exacerbated by sunlight exposure. Physical exam revealed facial and palmar skin erosions and scaling, associated with firm hepatomegaly. Initial investigations showed elevated metal-free erythrocyte protoporphyrin (50.6 umol/L, (n<2umol/L) consistent with the diagnosis of protoporphyria. Initial CBC was normal and LFTS showed elevations in ALT 133 U/L, AST 138 U/L and GGT 58 U/L with a normal ALP 144 U/L. The total bilirubin was <2umol/L (N). A liver biopsy found marked bridging fibrosis with golden brown pigment within the Kupffer cells. Genetic testing: compound heterozygous mutations in the FECH gene: c.1217G>A; p.Cys406Tyr and c.854A>G; p.Gln285Arg. Within 1 year of diagnosis, there was increasing hepatomegaly and deteriorating liver function.

A living related (father) liver transplant (LRD) under special light filters was performed at 32 months of age. This was followed by a bone marrow transplant 10 weeks later using the identical donor as the LRD. Now nine months post BMT the patient is chimeric with CD3 99% donor and CD33 75% donor. Discontinuation of single agent immunosuppression with tacrolimus is planned.

Mesh search of PubMed identified seven childhood cases of EPP with advanced liver disease. All patients developed liver fibrosis in late childhood unlike our patient who had severe liver involvement during infancy. Four kids were treated with liver transplantation (LT) alone (n = 2) or sequential LT with subsequent stem cell transplant (HST) (n = 2), of which two survived. Of the remaining 3 cases two died before receiving LT. Two cases of EPP with advanced liver fibrosis revealed, as in our case, compound heterozygous severe FECH mutations rather than one severe mutation *trans* to the common low-expression mutation.

CONCLUSION(S): This is a first reported case of EPP with advanced liver disease in infancy. Treatment with sequential liver and then bone marrow transplant using the identical donor has so far been successful. Inheritance of two pathogenic FECH mutations in this case likely account for more severe disease and early onset hepatopathy. While bone marrow transplant offers a cure for EPP its timing and tolerability deserves consideration in relation to the severity of liver disease and need for liver transplantation.

Histological characterization of muscle and adipose tissue in patients with cirrhosis receiving liver transplant

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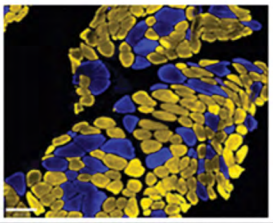
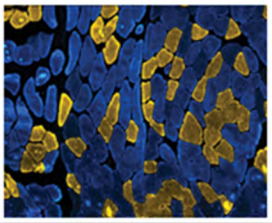
BACKGROUND: Body composition abnormalities are frequent in cirrhosis, and emerging evidence suggests that male sex is a risk factor for sarcopenia development and sarcopenia-related mortality, whereas female patients have a higher risk of losing subcutaneous adipose tissue in cirrhosis. Differences in skeletal muscle substrate metabolism by sex might contribute to this discrepancy.

PURPOSE: To better understand the pathophysiology of sarcopenia, sexual dimorphism in skeletal muscle fiber type and size as well as adipose tissue histological characteristics were investigated.

METHOD: CT images taken at the third lumbar vertebra were used to determine cross sectional areas of muscle, visceral and subcutaneous adipose tissue expressed by cm^2/m^2. Sarcopenia was defined as skeletal muscle index (SMI) <39 cm^2/m^2 in women and <50 cm^2/m^2 in men as published earlier. Biopsies of rectus abdominis muscle, periumbilical subcutaneous adipose tissue and visceral adipose

Histological Characteristics (mean± s.e.m)	Female (n=10)	Male (n=10)	P value
Total muscle fiber area (μm^2)	3604 ± 678	3866 ± 593	0.57
Fiber type I area (μm^2)	3051 ± 539	3506 ± 509	0.23
Fiber type I/IIA area (μm^2)	2239 ± 421	2901 ± 456	0.48
Fiber type IIA area (μm^2)	4584 ± 930	4469 ± 658	0.83
Fiber type IIA/D area (μm^2)	4291 ± 901	3785 ± 809	0.85
Fiber type IID area (μm^2)	2482 ± 416	2435 ± 457	0.81
Fiber type I (%)	58 ± 5	42 ± 6	0.01
Fiber type I/IIA (%)	1 ± 0.2	3 ± 1	0.23
Fiber type IIA (%)	26 ± 3	34 ± 5	0.31
Fiber type IIA/D (%)	13 ± 4	19 ± 5	0.51
Fiber type IID (%)	1 ± 1	3 ± 2	0.54
MyHC type I	59 ± 5	45 ± 6	0.04
MyHC type IIA	40 ± 5	55 ± 5	0.009
MyHC type IID	15 ± 4	22 ± 6	0.63
Immunofluorescence staining of muscle samples for Myosin Heavy Chain type I (yellow) and type IIA (blue)			
Subcutaneous adipocytes area (μm^2)	1546 ± 290	1764 ± 199	0.60
Visceral adipocytes area (μm^2)	1007 ± 129	1085 ± 68	0.36

tissue (omental) were obtained from the incision site at the time of liver transplant (LT) surgery. Muscle fiber boundaries were demarcated using laminin and dystrophin stain for muscle fiber size calculation. Fiber types were classified based on the isoforms of myosin heavy chain (MyHC). Adipose tissue sections were stained with Harris hematoxylin, and counterstained with eosin for histological analysis. Comparison between groups was made using Fisher's exact test and Mann-Whitney U test.

RESULT(S): Of 20 consented patients, 55% were male with a mean age of 50 ± 2 years, MELD score of 20 ± 1 points and mean BMI of 26 ± 1 (kg/m^2) at the time of LT. Sarcopenia was present in 60% of men and 33% of women. Lumbar SMI (cm^2/m^2) was significantly lower in sarcopenic patients compared to non-sarcopenic patients in both males (38 ± 2 vs. 60 ± 4; p = 0.001) and females (29 ± 9 vs. 44 ± 2; p = 0.049). No difference in mean muscle fiber area of total and per fiber type was observed by sex and sarcopenia. Sexual dimorphism was observed in the proportions of fiber types and MyHC isoforms (Figure). Percentage of MyHC type I (59% vs. 45%, p = 0.04) and consequently proportion of type I oxidative fibers (58% vs. 42%, p = 0.01) was higher in females compared to males. MyHC type IIA fibers, however, were more prevalent in males compared to females (55% vs. 40%, p = 0.009). Although visceral adipose tissue index (cm^2/m^2) tended to be higher in males (41 ± 9 vs. 22 ± 5; p = 0.09), no difference in the size of adipocytes by sex was observed for adipose tissue removed from visceral and subcutaneous depots (Figure).

CONCLUSION(S): Higher proportion of muscle type I oxidative fibers that are more resistant to atrophy in females might contribute to the sex differences in sarcopenia prevalence and related complications in cirrhosis.

Role of glutamine in the tumorigenicity of the murine hepatocarcinoma cell line Dt81Hepa1-6

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BACKGROUND: Hepatocellular carcinoma is a primary liver cancer with an aggressive and heterogeneous nature. While the metabolism of glucose in cellular models of this cancer has been widely studied, the importance of glutamine, the

most abundant amino acid, still remains to be investigated.

PURPOSE: This study aims to elucidate the behavior of hepatocarcinoma Dt81Hepa1-6 cell line under various glutamine and glucose conditions. Given the metabolic versatility of glutaminolysis, the hypothesis of this study is that CHC cells have differential activity and phenotype in the presence or not of glutamine. The goals of this study were to elucidate the expression of the key genes involved in glutamine metabolism as well as the influence of this nutrient on the viability and proliferation of the Dt81Hepa1-6 cell line.

METHOD: Dt81Hepa1-6 cells were cultured in different glutamine [0–20mM] and glucose [0–50mM] concentrations over a period of 48 h. Cell viability was assessed using the MTT assay whereas cell doubling time was used to measure cell proliferation and qPCR to evaluate gene expression levels.

RESULT(S): Cell viability was significantly reduced when cells were deprived of glutamine ($P < 0.05$). Proliferation was also significantly affected by decreasing concentrations of glutamine to the point where it was totally stopped in the absence of glutamine irrespective of the presence of high extracellular glucose levels ($P < 0.001$). The pathway responsible for the synthesis of glutamine (glutamine synthetase) was significantly upregulated by glucose in a dose-dependent manner ($P < 0.05$). On the other hand, the breakdown of glutamine into glutamate (glutaminase; GLS1&2) was downregulated with increasing doses of glucose ($P < 0.001$). Next, we investigated glutamine transporters (SLC1A5 and SLC7A5) and found that both were down-regulated by the presence of glucose ($P < 0.05$) whereas SLC7A5 was upregulated by glutamine dose dependently ($P < 0.05$). We finally investigated the metabolism of glutamate: 1) the expression of glutamate dehydrogenase (GLUD) was inversely proportional to the glucose concentration ($P < 0.05$); 2) Transamination of glutamate by its two main enzymes, alanine transaminases (GPT1 and GPT2) and aspartate transaminase (GOT2) was also downregulated by glucose ($P < 0.05$) except for GOT1 which remained unaffected.

CONCLUSION(S): Glucose has a significant impact on the metabolism of glutamine. Our results suggest that the metabolic pathways of glucose and glutamine appear to operate in a symbiotic manner with respect to the metabolism of tumorigenic Dt81Hepa1-6 cells.

Factors associated with dialysis independence in patients with cirrhosis and acute kidney injury requiring dialysis: A population-based study

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BACKGROUND: In patients with cirrhosis and acute kidney injury (AKI), renal replacement therapy (RRT) is typically used as a bridge to liver transplantation (LT). However, many patients do not have the option for LT and the outcomes for these patients in whom RRT is initiated are poorly defined.

PURPOSE: We sought to better characterize outcomes in patients with cirrhosis who require RRT for AKI along with factors associated with dialysis independence in order to inform shared decision-making for this high-risk population.

METHOD: Retrospective cohort study using administrative healthcare data from Ontario, Canada. Adult patients with cirrhosis admitted to hospital from 01/01/2009–12/31/2016 were identified using a validated case definition and followed until 12/31/2017. Patients were included if they had AKI (based on serum creatinine [sCr] criteria) and required RRT during hospitalization. Those with history of LT, kidney transplant, eGFR<15 mL/min or RRT before index hospitalization were excluded. The primary outcome was renal recovery defined as absence of RRT for at least 30 days. The association between clinical factors and renal recovery was evaluated using multivariate competing risks regression with death and LT considered competing events to dialysis independence.

RESULT(S): 722 patients met inclusion criteria (median age 61 years [IQR 54–68], 62% male, 52% viral hepatitis, 25% NAFLD, 18% alcohol, median MELD 26 [IQR 22–34]). 193 (27%) had renal recovery, 20 (3%) received LT, and 589 (82%) died after a median follow-up of 19 days. The cumulative incidence of renal recovery at 1, 3, 6, and 12 months was 3%, 22%, 25% and 26% respectively (figure). After competing risk

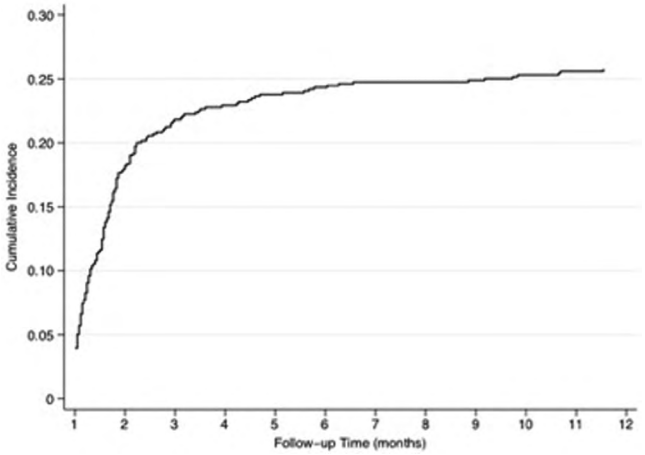

Figure : Cumulative incidence of renal recovery in patients with cirrhosis and AKI who started renal replacement therapy (n = 722)

analysis, factors associated with an increased likelihood of renal recovery were admission to a teaching hospital (sHR 1.53, 95% CI 1.10–2.11) and absence of sepsis (sHR 2.12, 95% CI 1.52–2.96) while factors associated with a decreased likelihood of renal recovery were older age (sHR 0.93 per 5 year increase, 95% CI 0.88–0.99), higher baseline sCr (sHR 0.98 per 10 unit increase, 95% CI 0.96–0.99), and higher MELD (sHR 0.68 per 5 unit increase, 95% CI 0.61–0.75).

CONCLUSION(S): Renal recovery occurred in only 1 in 4 patients with cirrhosis requiring RRT with dialysis independence being least likely in older patients with high baseline sCr admitted with sepsis. These results provide information regarding prognosis in this population and should be useful in shared decision making.

FIB4 or NFS can reliably predict fibrosis in sub-groups of NAFLD patients

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is a heterogenic spectrum of disease associated with steatosis and fibrosis of the liver. The non-invasive evaluation of patients with serum biomarkers and/or transient elastography (TE) is suggested. Models of care are being sought to triage severity of fibrosis with accessible and in-expensive tests. It is unclear if certain sub-group of NAFLD patients maybe best evaluated by different screening biomarker tests.

PURPOSE: To determine if Fib4 and/ or NAFLD Fibrosis Score (NFS) scores can predict stage of fibrosis in different sub-groups of NAFLD patients.

METHOD: A retrospective study between January 2018 and March 2019, data of 350 persons diagnosed with NAFLD based on clinical, imaging or TE (by Fibroscan) was reviewed. Data collected included, demographics, co-morbidities, physical, laboratory and TE measurements. The TE scores were used as the 'gold-standard' for defining various stages of fibrosis and was defined as >F2 (kPa>8), > F3 fibrosis (kPa >9.5), and >F4 (kPa >12). The FIB4 and the NFS were used as screening tools for predictability of fibrosis in sub-groups of NAFLD patients evaluated.

RESULT(S): We retrospectively studied 350 patients with diagnosis of NAFLD. Mean age of patients was 52.5 years; 200 (57%) were female, 98 (28%) patients had DM, 130 (37%) had dyslipidemia, 112 (32%) had HTN, and 130 (37%) had obesity (BMI >30).

TE (Fibroscan) revealed that overall 83 (24%) had fibrosis ≥F2, 42 (12%) had ≥F4 fibrosis, and 255 (73%) patients had CAP > 270.

Specific patient factors were significantly associated with CAP score >270, included BMI >30 (OR: 7.84), DM (OR: 2.45), and alcohol use (OR: 1.87). However, other risk factors including age > 60, male gender, HTN, and dyslipidemia were not associated with CAP > 270. Interestingly, percentage of patients with fibrosis ≥F2 was significantly higher in patients with DM (40%) compare to non-DM (18%), and in obese (38%) compare to non-obese (18%) ($p < 0.05$).

FIB4 >1.30 (OR: 1.96, and OR: 2.36) and NFS >–1.45 (OR: 10.00, and OR: 8.96) were predictive for fibrosis ≥F2 in NAFLD patients with DM or obesity, respectively. NFS is has a higher predictive value than FIB4 for fibrosis in both DM and Obese patients. When both FIB4 >1.30 and NFS >–1.45, predictability for ≥F2 fibrosis was higher (OR: 12.33). 24 (8%) patients had ≥F3, and a FIB4 <1.30 or NFS<-1.45.

CONCLUSION(S): Both FIB4 and NFS are useful to evaluate stage of fibrosis compared to TE as a 'gold-standard'. The NFS has a higher predictive

value for significant fibrosis (≥F2) than FIB4 in both DM and obesity sub-groups of NAFLD. The combination of FIB4 and NFS improves the predictive value for significant fibrosis. Larger sample sizes are needed to study if particular biomarkers are best suited to certain subgroups of NAFLD patient types.

Prevalence and associated factors of non-alcoholic fatty liver disease in South Asian women with polycystic ovary syndrome: A prospective study using transient elastography

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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease globally, affecting 25% of general population, and the leading indication for liver transplantation in women. Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy in women of reproductive age, with prevalence of up to 10%. PCOS seems a risk factor for NAFLD due to common pathogenetic pathways including insulin resistance and obesity. PCOS is more frequent in women from South Asian descents. Data on NAFLD in this population are scarce.

PURPOSE: Primary: Determine the prevalence of NAFLD and significant liver fibrosis, as well as cofactors of NAFLD, among premenopausal South Asian women with PCOS.

SECONDARY: Estimate the prevalence of severe steatosis and evaluate subsequent lifetime atherosclerotic cardiovascular disease (ASCVD) risk.

METHOD: We performed a prospective study at the Obstetrics and Gynecology Department of McGill University Health Centre. Consecutive South Asian women diagnosed with PCOS according to Rotterdam criteria were invited to participate by undergoing a transient elastography (TE) examination with controlled attenuation parameter (CAP) as part of a screening program for liver disease. Patients with significant alcohol consumption, those who had secondary causes of hepatic steatosis, and/or failed TE examination were excluded. Clinical, serological, and biochemical evaluation were performed at enrollment. AUDIT-C was applied for each participant to define any alcohol intake. NAFLD was defined as CAP >248 dB/m, severe steatosis as CAP >292 dB/m, and significant liver fibrosis (stage >2 out of 4) as TE measurement >8.0 kPa. Cofactors of NAFLD were determined through multivariate logistic regression analysis. Lifetime ASCVD risk was estimated using the American College of Cardiology risk estimator.

RESULT(S): 101 PCOS patients (mean age 36.3 years) were included. Prevalence of NAFLD, severe NAFLD, and significant liver fibrosis were 61.4%, 36.6% and 6.9%, respectively. Elevated ALT was observed in only 9.9% of patients with NAFLD. After adjusting for PCOS duration, insulin resistance measured by HOMA-IR and free androgen index (FAI), cofactors independently associated with NAFLD were higher waist circumference (adjusted odds ratio [aOR] 1.08, 95% CI 1.01–1.17), higher triglycerides (aOR 7.15, 95% CI 1.52–33.55) and ALT (aOR 2.52, 95% CI 1.04–6.11) (see Table.1).

Table 1: Logistic regression analyses of factors associated with steatosis in PCOS patients

Variable	Unadjusted OR	aOR
PCOS duration (per year)	1.12 (1.00–1.24) *	1.17 (0.99–1.38)
Waist circumference (per cm)	1.13 (1.07–1.20) **	1.08 (1.01–1.17) *
HOMA-IR	3.08 (1.81–5.24) **	1.77 (0.85–3.68)
FAI	1.23 (1.03–1.47) *	1.04 (0.86–1.28)
Triglycerides (per mmol/L)	9.24 (2.95–28.90) **	7.15 (1.52–33.55) *
ALT (per 10 IU/L)	3.57 (1.63–7.83) *	2.52 (1.04–6.11) *

Odds ratios (OR) and 95% confidence intervals are shown for each variable analyzed in univariable and multivariable logistic regression analysis.
** P < 0.05; ** P < 0.001*

NAFLD subgroup had higher lifetime ASCVD risk than no NAFLD counterpart, with 31% and 23%, respectively (p = 0.004).

CONCLUSION(S): Despite the young age, NAFLD diagnosed by TE with CAP is a frequent comorbidity in South Asian women with PCOS and is strongly associated with features of metabolic syndrome. Non-invasive screening strategies could help early diagnosis, cardiovascular risk stratification and initiation of interventions, including weight loss, correction of dyslipidemia and linkage to care.

Diabetes is associated with the development of hepatic encephalopathy in cirrhotic patients

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is strongly associated with type II diabetes (T2D) and has become the main cause of cirrhosis. Both NAFLD and T2D are associated with cognitive and neurological impairments. T2D has been established as a risk factor for first-time development of overt hepatic encephalopathy (HE) in cirrhotic patients. Moreover the onset of HE in diabetic patients with cirrhosis develops earlier compared to cirrhosis patients without T2D. However it remains unclear whether NAFLD-induced cirrhosis increases the risk for HE.

PURPOSE: The present study aims to address the association between NAFLD, T2D and HE.

METHOD: Our retrospective study includes 102 cirrhotic patients on the liver transplant list at the Liver Unit of the Montreal University Hospital Center. Patients were classified by etiology of cirrhosis; 1) NAFLD and 2) non-NAFLD. Demographic data, blood biochemistry, clinical information on T2D-related comorbidities and cirrhosis complications (including number and severity of HE episodes) were collected. These factors were statistically associated with HE episodes.

RESULT(S): Our cohort comprised 20 (19%) NAFLD and 82 (79%) non-NAFLD patients presenting with similar MELD and Child-Pugh scores. The prevalence of T2D was higher in NAFLD vs non-NAFLD cirrhotics (15 (75%) vs 24 (29%) respectively) and was associated with comorbidities such as cardiac disease, dyslipidemia, hypertension and obesity. Among non-NAFLD cirrhotics, 47 (57%) patients had a history of HE whereas 8 (40%) were found in the NAFLD cirrhotics ($p > 0.05$). Since T2D is already known as a risk factor for HE, we subdivided both NAFLD and non-NAFLD groups into non-T2D and T2D subgroups. HE was significantly more prevalent in patients with T2D: in the NAFLD group, 5 (25%) T2D patients had developed an episode of HE compared to 3 (15%) patients without T2D ($p < 0.05$); in the non-NAFLD group, 16 (67%) patients had T2D and HE compared to 31 (53%) HE patients without T2D ($p < 0.001$). Fasting glycemia levels analysis in the 4 sub-groups of patients revealed increased levels in patients with history of HE and T2D, regardless of NAFLD etiology; in the NAFLD group 8.60 ± 0.84 mmol/l in patients with HE and T2D vs 6.00 ± 1.35 mmol/L in patients with HE without T2D ($p < 0.01$); in the non-NAFLD group: 9.23 ± 0.93 mmol/L in patients with HE and T2D vs 5.82 ± 0.27 mmol/L in patients with HE without T2D ($p < 0.001$).

CONCLUSION(S): Our results sustain the association between T2D and HE and suggest high glucose might play a pathological role in the development of cognitive decline. NAFLD is not a risk factor for the development of HE. These interesting results provide new insights in the role of T2D in the development of HE and further studies are required to understand the mechanisms underlying the relationship between diabetes and HE. Furthermore, identifying patients who are at higher risk of developing HE is imperative to initiate early treatment strategies to protect neurological decline in patients with cirrhosis.

Prevalence of liver diseases in referred patients of varying ethnic backgrounds within the Toronto Liver Centre

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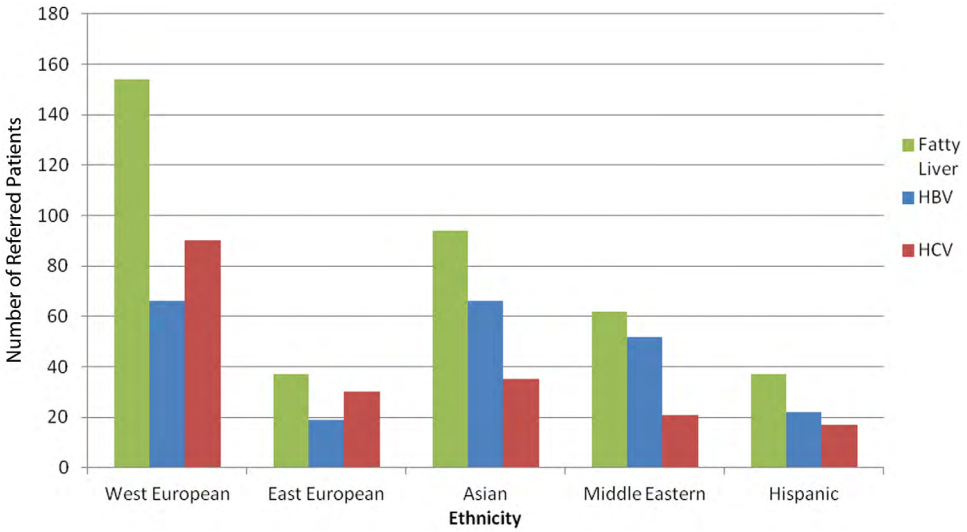

Figure 1 : Prevalence of disease across ethnicities in referred patients

BACKGROUND: The correlation between the prevalence of several liver diseases and factors such as gender and age has already been established in previous studies. The role of ethnicity in liver diseases has not been well studied, specifically in patient population within the Greater Toronto Area.

PURPOSE: In this retrospective investigation, the prevalence of three major liver related diseases: non-alcoholic fatty liver disease (NAFLD), hepatitis B (HBV), and hepatitis C (HCV) are comparatively analyzed in relation to the ethnic background of referred patients to the Toronto Liver Centre.

METHOD: This is a retrospective chart review. The inclusion criteria consisted of patients with HBV, HCV, and NAFLD referred for FibroScan evaluation to the Toronto Liver Centre. A total of 802 patients were included. We determined the closest ethnicity based on first and last names of individual patients. Names with uninterpretable ethnicity were excluded in the data. Five major ethnic backgrounds were identified which included the West Europeans, East Europeans, Asians, Hispanics and the Middle Easterns. A graphical representation of patients with three major liver diseases across five ethnic categories were constructed (Figure 1). An analysis of available data was done to look at the relation between ethnic backgrounds and the prevalence of each of the liver diseases.

RESULT(S): As indicated in Figure 1, of the total 802 single-time referred patients: 310 were West European, 86 were East European, 195 were Asian, 135 were Middle Eastern and 76 were Hispanic. Within the West European sample population, there were 66 patients with HBV (21.3%), 90 with HCV (29.0%) and 154 with NAFLD (49.7%). East European population had 19 patients with HBV (22.1%), 30 HCV (34.9%), and 37 with NAFLD (43.0%). As for the Asian population, there were 66 patients with HBV (33.8%), 35 HCV (17.9%), and 94 NAFLD (48.2%). The Middle Eastern population had 64 patients with HBV (34.0%), 21 HCV (14.0%) and 62 NAFLD (45.9%). Lastly, the Hispanic population had 22 patients with HBV (28.9%), 17 HCV (22.4%) and 37 NAFLD (48.7%). Based on these percentages, the proportion of patients with NAFLD did not differ significantly between ethnic groups. It can be noted, however, that the prevalence of NAFLD was greater than that of both HBV and HCV across all ethnicities. In contrast, the proportion of patients with HBV varied between ethnic groups. However, Asian and Middle Eastern groups demonstrated similarly large proportions of HBV affected patients relative to all other ethnicities ($p < 0.1$ for both). In HCV related cases, data were inconclusive due to the large fluctuation in proportions and therefore, lack of identifiable pattern between each group.

CONCLUSION(S): A graphical and statistical analysis revealed a correlation between ethnicity and the prevalence of HBV induced liver disease, with the highest proportion in Asian and Middle Eastern groups. Conversely, the data yielded no results indicating ethnicity as an attributable factor for NAFLD or HCV liver disease prevalence.

Characteristics and outcomes of patients with primary sclerosing cholangitis at a Canadian tertiary care center

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BACKGROUND: Primary sclerosing cholangitis (PSC) is a chronic inflammatory disorder of the biliary tree, without any recognized treatment. Chronic inflammation and duct destruction results in biliary fibrosis which can lead to cirrhosis. Liver transplantation remains the only option for advanced disease. PSC is relatively prevalent in the Caucasian population and thought to be uncommon in Asian populations.

PURPOSE: To assess the characteristics and disease course of patients with PSC at a multi-ethnic tertiary care center.

METHOD: A retrospective chart review was conducted.

RESULT(S): A total of 85 cases were seen between 2012–2018 with a median age of 34 (range 14–60) years for those found to have IBD, and 42 (range 16–73) years for those with PSC. There was an almost equal gender distribution with 46 males (54.1%) and 39 females (45.9%). 66 subjects (77.6%) of the total cohort were non-Hispanic Whites, only 3 (3.5%) were East Asian and 8 (9.5%) were South Asian. 92% of those affected (79 patients) were non-smokers, and all with reported alcohol intake had none to moderate alcohol consumption. The initial diagnosis was IBD in 30 cases, and PSC in 49 cases. Co-existing liver diseases were present in 19 patients (22.4%), with autoimmune hepatitis (AIH) being the most common in 12 cases (14%), IgG4 disease in 4 cases (4.7%); NAFLD in 6 cases (7.1%), and no cases of PBC. 70 of the cases were using ursodeoxycholic acid with good symptomatic or biochemical response, and 21 cases received a liver transplant. 2 had recurrent PSC and 1 patient required a second transplant. 6 patients developed cholangiocarcinoma and 4 developed colorectal cancer. Only 50% of patients were undergoing annual MR screening scans. 1 of the patients developed malignancy after transplantation. Of those with IBD (46 patients, 54.1%), 33 had 'ulcerative colitis-like' disease, whereas 12 had 'Crohn's-like' disease. 28 patients of those affected with IBD received mesalazine, 9 received corticosteroids, 11 required colorectal surgery. 8 patients required used of biologics, which included 3 receiving infliximab, 2 receiving adalimumab, 1 receiving golimumab, and 2 receiving vedolizumab. None of the patients in this cohort received ustekinumab or tofacitinib. 5 patients developed pouchitis after total colectomies performed for IBD.

CONCLUSION(S): The incidence of PSC appears to be more common in South versus East Asians in Vancouver, Canada. The majority of patients were non-smokers, and all with no to moderate alcohol consumption. Liver transplantation, cholangiocarcinoma and colon cancer were not uncommon. We intend to use this database of patients to investigate disease progression and novel therapeutics.

New insights on the impact of sex on chronic liver disease and hepatic encephalopathy

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BACKGROUND: The impact of sex differences on chronic liver disease (CLD) and hepatic encephalopathy (HE) is unknown. The majority of animals used in research are male since the main difficulty with using female animals is the potential impact of the estrous cycle which increases intra-group variability. The bile duct ligated (BDL) rat is a well-characterized model of CLD and HE in males, which has not been investigated in females.

PURPOSE: Therefore, we aimed to characterize a female BDL model of CLD and HE and compare to male BDL rats.

METHOD: Female rats underwent either BDL (n = 8) or Sham (n = 8) surgery. After 5 weeks, we assessed estrous cycle phase (by cellular cytology), anxiety (open field test), motor incoordination (rota-rod test) and night-time activity. We also assessed body weight, body composition (MRI), gastrocnemius muscle weight/circumference, grip strength, plasma ammonia and liver enzymes.

Results from female BDL rats were compared to historical laboratory data from male BDL rats.

RESULT(S): Female BDL rats had increased markers of liver injury: ALP, AST and bilirubin ($p < 0.001$) and impaired markers of liver function (increased ammonia and decreased albumin ($p < 0.001$)) compared to female Shams. Furthermore, Female BDL rats did not differ in body weight, muscle circumference/weight and grip strength but had decreased fat mass ($p < 0.0001$) and increased lean mass ($p < 0.005$) compared to female shams. All results were comparable to male BDL rats except for plasma ammonia levels which were significantly lower in females ($p < 0.01$). Moreover, male BDL rats had decreased fat mass, lean mass, muscle circumference/weight and grip strength. BDL surgery in female rats induced a dysregulated estrous cycle compared to sham (increased metestrus phase [$p < 0.01$]). However, similar to male BDL rats, female BDL rats had increased anxiety ($p < 0.005$), motor incoordination ($p < 0.05$), and decreased night activity ($p < 0.05$), independent of the estrous cycle phase.

CONCLUSION(S): We demonstrated BDL surgery in females leads to hepatic and neurological impairment comparable to male BDL rats (similar intra-group variability). Interestingly, female BDL rats developed unique features. Contrary to male BDL vs. Shams, body weight and muscle mass did not differ between female BDL and Shams. Since muscle mass plays an important compensatory role in regulating ammonia levels, this could explain the reason why blood ammonia levels in female BDL rats are significantly lower compared to male BDL rats. We expect that this model will provide new insights on the effect of sex differences on the pathogenesis of CLD and HE and help to personalize HE treatment.