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

9th Canadian Symposium on Hepatitis C Virus

9ème Symposium canadien sur le virus de l'hépatite C

February 28, 2020 – 28 février 2020

Le Westin, Montréal. QC

Program and Abstracts
Programme et résumés

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Welcome Message - Message d'accueil

Dear Colleagues,

We are pleased to welcome you to the 9th Canadian Symposium on the Hepatitis C Virus (HCV), in the exhilarating city of Montreal!

Many Canadians infected with hepatitis C virus (HCV) have been cured thanks to the now tremendously successful antiviral therapies. The widespread use and improved access to such treatments are critical steps to reducing the prevalence of chronic HCV infection. However, challenges remain for those affected by HCV such as diagnosing those unaware of their infection status and adequate access to care. We believe that by facilitating communication and supporting interactions between Canadian scientists, clinicians, the affected communities, and policy makers we can overcome these challenges more effectively. In this effort, we are setting a collective intention to eliminate HCV by preventing and treating all HCV-infected individuals.

The Canadian HCV Symposia have provided an ideal forum for such an exchange since 2012. The Canadian Network on Hepatitis C (CanHepC) has a strong record of supporting research training and knowledge translation of HCV research to benefit patients. The network is built on a strong foundation of motivated and collaborative investigators whose work encompasses the social, behavioural, clinical, health, and basic sciences. This multidisciplinary team is vital for the development of programs to combat HCV.

We look forward to learning about your exciting research and work in the HCV field so that together we can shape the future of HCV research and policy in Canada.

Chers Collègues,

Nous vous souhaitons la bienvenue au 9e Symposium canadien sur le virus de l'hépatite C (VHC), dans l'exaltante ville de Montréal!

De nombreux Canadiens infectés par le VHC ont été guéris grâce à l'efficacité des récents traitements antiviraux. L'utilisation répandue et l'amélioration de l'accès à ces traitements sont des étapes essentielles pour réduire la prévalence de l'infection chronique par le VHC. Cependant, d'importants défis subsistent pour les personnes affectées par le VHC, en commençant par le diagnostic de ceux qui ne connaissent pas leur statut d'infection, et l'accès adéquat aux soins. Nous sommes convaincus qu'en facilitant la communication et en soutenant les interactions entre les scientifiques, les médecins, les communautés affectées et les responsables politiques canadiens, nous pouvons surmonter ces défis de manière plus efficace. Dans le cadre de cette initiative, nous adoptons collectivement l'intention d'éliminer le VHC par la prévention et le traitement de toutes les personnes infectées par le VHC.

Les symposiums canadiens sur le VHC représentent un forum idéal pour ce type d'échanges depuis 2012. Le Réseau Canadien sur l'Hépatite C (CanHepC) a fortement contribué à soutenir la formation en recherche et le transfert de connaissances sur la recherche sur l'hépatite C, pour le bénéfice des patients. Le réseau est construit sur une base solide de chercheurs motivés et collaboratifs dont les travaux englobent les sciences sociales, comportementales, cliniques et fondamentales. Cette équipe interdisciplinaire est cruciale pour le développement de programmes de lutte contre le VHC.

Nous avons hâte d'en apprendre plus sur vos recherches et travaux dans le domaine de l'hépatite C, afin de pouvoir, ensemble, façonner le futur de la recherche et des politiques publiques portant sur l'hépC au Canada.

Curtis Cooper, MD, FRCPC
The Ottawa Hospital Research Institute, Ottawa, Canada

Angela M. Crawley, PhD
The Ottawa Hospital Research Institute, Ottawa, Canada

Biographies of Co-Chairs – Biographie des co-présidents

Curtis Cooper, the Ottawa Hospital Research Institute, Ottawa, Canada – Chair

Biography

Dr. Curtis Cooper trained at the University of Saskatchewan (MD 1994). He received certification in Internal Medicine in 1997 and in Infectious Diseases in 1999 while at the University of Manitoba. He completed an HIV Research Fellowship and Masters of Epidemiology in 2002 while at the University of Ottawa. He is currently an Associate Professor with the University of Ottawa, Infectious Diseases Consultant with The Ottawa Hospital Division of Infectious Diseases, and Scientist with the Ottawa Hospital Research Institute. As a clinical researcher, his research activities encompass viral hepatitis, HIV, and vaccine development. His work is focused on the development of new therapeutic agents and the delivery of treatment that maximizes safety and adherence. He is a principle investigator with the CIHR Canadian HIV Trials Network (CTN) and the CIHR Canadian HIV Observational Cohort (CANOC) as well as President of the Canadian Foundation for Infectious Diseases.

Angela Crawley, The Ottawa Hospital Research Institute, Ottawa, Canada – Co-Chair

Biography

Dr. Angela M. Crawley, Ph.D. is a Scientist at The Ottawa Hospital Research Institute in the Chronic Disease Program. She is also an Assistant Professor in the Department of Biochemistry, Microbiology and Immunology, University of Ottawa, PhD Scientist in the Department of Medicine, The Ottawa Hospital, and an Adjunct Professor in the Department of Biology, Carleton University. Dr. Crawley earned her Ph.D. in veterinary immunology from the University of Guelph. She then completed her postdoctoral fellowship training at The Ottawa Hospital Research Institute, specializing in the immunopathogenesis of HIV infection. Dr. Crawley was the recipient of a CIHR New Investigator Award and an Ontario HIV Treatment Network Junior Investigator Award as she established her independent research program. Her laboratory evaluates the dysfunction of CD8+ T-cells in chronic HCV infection in association with liver fibrosis severity through discovery-based basic science research as well as translational research in collaboration with several clinician scientists. The main focus of the Crawley lab research program is to determine the underlying mechanisms preventing immune restoration in chronic liver disease.
www.crawleylab.ca

Program – Programme

Advances in HCV Research and Treatment Towards Elimination

07h15 - 08h00 Registration, breakfast
Inscription, petit déjeuner

08h00 - 08h15 Welcome and Introductions – Mot de bienvenue
Drs. Angela Crawley and Curtis Cooper, The Ottawa Hospital Research Institute, Ottawa, Canada

Biomedical Research - *HCV Vaccine Development and Related Studies*
Co-Chairs: Drs. Seung-Hwan Lee, University of Ottawa and Che Colpitts Queen's University
CanHepC trainees introducing plenary speakers: Chisom Okwor and Vanessa Meier-Stephenson

08h15 - 08h35 **Vaccines for HCV - where there is a will there is a way**
Dr. Ellie Barnes, Oxford University, UK

08h35 - 08h55 **Progress toward a global prophylactic HCV vaccine**
Dr. John Law, University of Alberta, Canada

08h55 - 09h15 Questions/Panel Discussion

Oral Presentations

09h15 - 09h30 **Differential gene expression of circulating CD8 T cells of cirrhotic HCV-infected individuals identifies pathways associated with lasting dysfunction**
Dr. Angela M. Crawley, Ottawa Hospital Research Institute, Ottawa, Canada

09h30 - 09h45 **The Effect of apoptosis and inflammasome-mediated pyroptosis on HCV infection**
Hannah Louise Wallace, Memorial University, St. John's, Canada

09h45 - 10h00 **Coffee Break – Pause café and poster browsing**

Social, Cultural, Environmental, and Population Health Research – *HCV in underserved populations: modeling and real-life data to inform strategies*
Co-Chairs: Drs. Julie Bruneau, Université de Montréal and Nadine Kronfli, McGill University
CanHepC trainees introducing plenary speakers: Adam Palayew and Yasmin Saeed

10h00 - 10h20 **Tackling HCV transmission among people who inject drugs: insights from modeling**
Dr. Natasha Martin, University of California San Diego, USA

10h20 - 10h40 **Hepatitis C virus care in Canadian correctional facilities: The long road ahead towards HCV elimination**
Dr. Nadine Kronfli, McGill University, Canada

10h40 - 11h00 Questions/Panel Discussion

Oral Presentations

11h00 – 11h15 **Effect of sustained virologic response and opioid agonist therapy on mortality among people living with chronic hepatitis C**
Dr. Prince Adu, University of British Columbia, Vancouver, Canada

11h15 - 11h30 **Community and corrections based point-of-care testing into a provincial hepatitis C elimination framework**
Dr. Lisa Barrett, Dalhousie University, Halifax, Canada

11h30 - 12h30 **Community session** – ***Connecting With Care*: Canadian Models of Hepatitis C Care- A Film Preview and Panel discussion**

Moderator: Melisa Dickie, Director, Hepatitis C Knowledge Exchange

Speakers/panelists:
A Saskatchewan Story, Athakakoop Health Centre: Jodie Albert, Outreach Worker, and Tanys Isbister, Community Health Nurse, Ahtahkakoop Health Centre.

Montreal's many models of care: Martin Pagé, Executive Director, Dopamine; Hugo Bissonnet, Executive Director, and Robert LaMarche, Outreach Worker, Centre Sida Amitié.

Toronto Community Hep C Program: Jennifer Broad, Community Health Worker, and Kate Mason, Researcher, Toronto Community Hep C Program; Jason Altenberg, CEO, South Riverdale Community Health Centre.

12:30 - 14h00 **LUNCH and Poster Session - Présentation des Affiches : CanHepC evaluation of poster from *13h00 to 13h45***

Clinical Research- *Hepatitis C Infection in Pregnancy & Children*
Co-Chairs: Drs. Eve Roberts, Dalhousie University and Hugo Soudeyns, Université de Montréal
CanHepC trainees introducing plenary speakers: Nanor Minoyan and Gillian Kolla

14h00 - 14h20 **DAA use in pregnancy**
Dr. Robert Honegger, Nationwide Childrens's, USA

14h20 - 14h40 **Pediatric perspectives on DAA use**
Dr. Simon Ling, University of Toronto, Canada

14h40 – 14h55 Questions/Panel Discussion

Oral Presentations

14h55 - 15h10 **Efficacy of Sofosbuvir/Velpatasvir (S/V): Impact of treatment adherence**
Dr. Brian Conway, Vancouver Infectious Diseases Centre, Vancouver, Canada

15h10 - 15h25 **Reinfection following successful direct-acting antiviral therapy for hepatitis C infection among people who inject drugs**
Dr. Evan Cunningham, The Kirby Institute, UNSW, Sydney, Australia

Health Services Research – *Blueprint Update and Panel*
Co-Chairs: Drs. Jason Altenberg, South Riverdale Community Health Centre and Naveed Janjua, BCCDC

15h25 - 15h35 **Blueprint Update**
Dr. Jordan Feld, University of Toronto, Canada

15h35 – 15h55 **Elimination Efforts in Nova Scotia and Prince Edward Island**
Dr. Lisa Barrett, Dalhousie University, Halifax, Canada

15h55 – 16h10 Questions/Panel Discussion

Oral Presentations

16h10 - 16h25 **HBV-HCV co infection among immigrants in Ontario, Canada**
Abdool S. Yasseen, University of Toronto, Canada

16h25 – 16h40 **The Health Burden of Hepatitis C Infection Facing the First Nations Population in Ontario: A Research Partnership**
Andrew Mendlowitz, University of Toronto, Toronto, Canada

16h40 – 16h50 CanHepC trainee Awards Ceremony - **Dr. Christopher Richardson**

16h50 – 16h55 Closing Remarks – Mot de la fin
Drs. Angela Crawley and Curtis Cooper, The Ottawa Hospital Research Institute, Ottawa, Canada

16h55 – 17h05 **Canadian Liver Meeting Opening Remarks**
Dr. Marc Bilodeau, Université de Montreal, Montreal, Canada

17h05 – 17h40 **CLM OPENING PRESENTATION - UPDATE ON HCV ELIMINATION IN CANADA AND THE US**
Dr. Andrew Aronsohn, University of Chicago, Chicago, USA

17h40 – 19h30 **Joint CanHepC and Canadian Liver Meeting Reception and CanHepC Poster Tour** hosted by the CanHepC Trainees*

Poster Tour Agenda – Poster Tour Starts at 6 :10pm

Biomedical Poster Tour (6:10pm start) Chair: Rasika Kunden (CanHepC Trainee)	**Social, Cultural, Environmental and Population Health Poster Tour (6:10pm start)** Chair: Zoe Greenwald (CanHepC Trainee)
6:10-6:15 – Sophie Cousineau: **Poster #: CHC-P-001** CLMHCV-1045: Identifying the Role Played by the Poly(rC)-Binding Protein 2 (PCBP2) in the HCV Life Cycle	6:10-6:15 – Adam Palayew: **Poster #: CHC-P-016** HCV-1142: Estimation of an individual-level deprivation index for HIV/HCV coinfected persons
6:15-6:20 – Catia Perciani: **Poster #: CHC-P-004** CLMHCV-1206: Precision-Cut Liver Slice (PCLS) culture: a model to examine HCV interactions with the liver microenvironment	6:15-6:20 – Adelina Artenie: **Poster #: CHC-P-013** CLMHCV-1122: 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
6:20-6:25 – Mohamed Abdelnabi: **Poster #: CHC-P-006** CLMHCV-1129: Neutrophils are the major producers of the pro-fibrogenic cytokine IL-17A in non-alcoholic fatty liver disease (NAFLD)	6:20-6:25 – Sofia Bartlett: **Poster #: CHC-P-012** CLMHCV-1024: Increasing hepatitis C screening & new diagnoses in 10 British Columbia Provincial Correctional Centres from 2010-2019
<<Transition – Attendees move to Clinical or Health Services Poster Tour>>	**<<Transition – Attendees move to Health Services or Clinical Poster Tour>>**
Clinical Poster Tour (6:35pm start) Chair: Jordan Feld (CanHepC Mentor)	**Health Services Research (6:35pm start)** Chair: Lisa Barrett (CanHepC Mentor)
6:35-6:40 – Y. Mendoza (Dr. Sebastiani, presenting author): **Poster #: CHC-P-029** CLMHCV-1050: Non-invasive surrogates of portal hypertension predict decompensation in obese patients with compensated advanced chronic liver disease	6:35-6:40 – William Wong: **Poster #: CHC-P-033** CLMHCV-1049, 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
6:40-6:45 – Valérie Martel-Laferrière: **Poster #: CHC-P-031** HCV-1058: Universal HCV and HIV screening in an Emergency Room – fewer new cases than expected	6:40-6:45 – Gisela Macphail: **Poster #: CHC-P-038** CLMHCV-1151, Hepatitis C (HCV) Re-engagement Strategy after Loss to Follow-up
6:45-6:50 – Curtis Cooper: **Poster #: CHC-P-032** CLMHCV-1184: DAA Treatment Uptake or Outcomes are Not Effected by Alcohol Use: A CANUHC Analysis	6:45-6:50 – Yasmin Saeed: **Poster #: CHC-P-036** CLMHCV-1047, Disparities in health utilities among hepatitis C patients receiving care in different settings
7pm – Poster Tour Completed	**7pm – Poster Tour Completed**

Committees – Comités

9th CSHCV Scientific Committee

Curtis Cooper, The Ottawa Hospital Research Institute, Chair
Angela Crawley, The Ottawa Hospital Research Institute, Co-Chair

Julie Bruneau, Université de Montréal
Melisa Dickie, CATIE
Jason Grebely, The Kirby Institute, UNSW
Nadine Kronfli, McGill University
Carrielynn Lund, Canadian Aboriginal AIDS Network (CAAN)
Selena Sagan, McGill University
Giada Sebastiani, McGill University
Naglaa Shoukry, Université de Montréal
Joyce Wilson, University of Saskatchewan

Alison Marshall, The Kirby Institute, UNSW, Trainee representative
Adam Palayew, McGill University, Trainee representative

Norma Choucha, CRCHUM, Symposium Coordinator

Session Chairs - Modérateurs de sessions

Biomedical Research
Seung-Hwan Lee, University of Ottawa
Che Colpitts, Queen's University

Social, Cultural, Environmental, and Population Health Research
Julie Bruneau, Université de Montréal
Nadine Kronfli, McGill University

Clinical Research
Eve Roberts, Dalhousie University
Hugo Soudeyns, Université de Montréal

Health Services Research
Curtis Cooper, The Ottawa Hospital Research Institute
Angela Crawley, The Ottawa Hospital Research Institute

Abstract Reviewers - Réviseurs des résumés

Biomedical Research

Mohamed Abdel Hakeem, University of Pennsylvania
Che Colpitts, University College London
Angela Crawley, The Ottawa Hospital Research Institute
John Law, University of Alberta
John Pezacki, University of Ottawa
Rodney Russell, Memorial University
Joyce Wilson, University of Saskatchewan

Social, Cultural, Environmental, and Population Health Research

Adelina Artenie, Kirby Institute (Sydney, Australia) & Population Health Sciences Institute (Bristol, UK)
Julie Bruneau, Université de Montréal
Joseph Cox, McGill University
Christina Greenaway, McGill University
Brendan Jacka, Brown University School of Public Health
Carrielynn Lund, CAAN
Sahar Saeed, McGill University

Clinical Research

Marc Bilodeau, Université de Montréal
Brian Conway, Vancouver Infectious Diseases Centre
Curtis Cooper, The Ottawa Hospital Research Institute
Nadine Kronfli, McGill University
Valerie Martel-Laferriere, Université de Montréal
Vanesssa Meier-Stephenson, University of Calgary
Giada Sebastiani, McGill University
Marie-Louise Vachon, Université de Montréal

Health Service Research

Adelina Artenie, Kirby Institute (Sydney, Australia) & Population Health Sciences Institute (Bristol, UK)
Evan Cunningham, The Kirby Institute, UNSW
Jason Grebely, The Kirby Institute, UNSW
Naveed Janjua, University of British Columbia
Mathieu Maheu-Giroux, McGill University
Alison Marshall, The Kirby Institute, UNSW

Speaker Biographies and Abstracts – Biographies des conférenciers et résumés

Biomedical Research

Ellie Barnes, Oxford University, UK

Biography

Ellie Barnes is Professor of Hepatology and Experimental Medicine, University of Oxford. She has a long-standing interest in hepatotrophic viruses, viral pathogenesis, immunology and vaccine development. More recently she has led early human experimental medicine studies with the aims of developing a prophylactic HCV vaccine, including 2nd generation HCV vaccines based on conserved viral genomes, and constructs that encode genetic adjuvants with the potential for wide applicability in cancer and infectious disease. She is also developing a program in HBV using simian adenoviral vectored vaccines for HBV immunotherapy.

Ellie was the Chief Investigator for the UK wide MRC funded consortium STOP-HCV developing stratified medicine to optimise patient clinical outcomes (http://www.stop-hcv.ox.ac.uk/home); the consortium has developed new methods for HCV sequencing, identifying drug resistant subtypes, and is currently supporting stratified medicine studies in Vietnam.

The World Health Organization has set a target to achieve elimination of HCV by 2030-but very few countries are likely to achieve this. An effective preventative vaccine would have a major impact on HCV incidence and would represent a major advance towards global HCV control. Progress in the development of new vaccine platforms to induce high magnitude and broad anti-viral immune responses to HCV means that it should be possible to generate effective HCV vaccines. The major hurdles to achieving this are now political and practical issues around the funding and testing of vaccine candidates.

John Law, University of Alberta, Canada

Biography

Dr. John Law received his Ph.D. in the Department of Cell Biology at the University of Alberta. He continued his post-doctoral training with Dr. Charles Rice at the Rockefeller University in New York City studying the molecular virology of RNA viruses including Hepatitis C virus (HCV). He also has experience in developing methods to identify novel viruses in clinical samples. Currently, he is working as part of a team, led by Drs. Michael Houghton and Lorne Tyrrell, to develop a prophylactic vaccine to prevent HCV infection. His research focuses on characterizing the breadth of vaccine-induced neutralizing antibodies and understanding the mode of protection of these antibodies. His research in the Li Ka Shing Applied Virology Institute in Edmonton is working toward an improved 2nd generation HCV vaccine to prevent global infection in the future.

Social, Cultural, Environmental, and Population Health Research

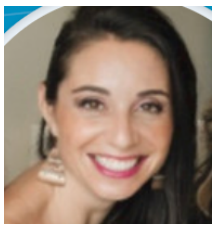
Natasha Martin, University of California San Diego, USA

Biography

Dr. Natasha Martin is an infectious disease economic modeler who develops dynamic transmission models to evaluate the impact and cost-effectiveness of public health interventions. She is currently an Associate Professor in the Division of Global Public Health, Department of Medicine at the University of San Diego and holds an honorary senior lecturer position in the School of Social and Community Medicine, University of Bristol. She is also the co-director of the Biostatistics and Modeling Core of the University of California San Diego Center for AIDS Research (UCSD CFAR). She has worked for 18 years developing mathematical models of disease progression and transmission in both communicable and non-communicable diseases. For the past eight years, her primary research has focused on modeling hepatitis C virus (HCV) and HIV transmission and prevention among high-risk groups such as people who inject drugs (PWID), men who have sex with men, and female sex workers. She is a leading researcher on modeling the impact of HCV treatment as prevention. Additionally, she has experience developing dynamic cost-effectiveness evaluations of case-finding and prevention interventions, and has the only published cost-effectiveness models of HCV case-finding interventions and treatment including both individual and population benefits. She is the principal investigator (PI) of a NIDA-funded R01 using epidemic modeling and cost-effectiveness techniques to optimize HIV and HCV prevention portfolios among people who inject drugs in 108 countries worldwide. Her modeling work informed the WHO guidelines "When to start ART in people living with HIV (2013)", and her work on the impact and cost-effectiveness of HCV treatment among people who inject drugs informed the WHO guidelines on "Hepatitis C testing, care, and treatment (2013)". More recently, her modeling work on HCV elimination was used to inform the WHO "Global Health Sector Strategy on Viral Hepatitis 2016-2021".

Nadine Kronfli, McGill University, Canada

Biography



Dr. Nadine Kronfli is an Assistant Professor in the Department of Medicine, Division of Infectious Diseases at McGill University. As a Junior Clinician Scientist at the McGill University Health Centre, Dr. Nadine Kronfli's research focuses on designing, deploying, and evaluating evidence-based models of care that aim to increase engagement along the HIV and hepatitis C virus care cascades for vulnerable populations, with a particular focus on people in prison and asylum seekers. The ultimate goal of her research is to support the development of evidence-based policies to improve population health with an emphasis on controlling and eliminating HIV and hepatitis C.

Clinical Research

Robert Honegger, Nationwide Childrens's, USA

Biography

Dr. Honegger is an assistant professor of pediatrics at The Ohio State University and serves as an attending physician in the division of pediatric infectious diseases at Nationwide Children's Hospital and primary investigator in the Center for Vaccines and Immunity at the Abigail Wexner Research Institute. His primary research interests center on cellular immunity to the hepatitis C virus (HCV) in pregnancy and childhood, as well as diagnosis, treatment, and prevention of pediatric HCV infection. He has also served as a site investigator for trials of direct acting antiviral therapies for chronic HCV infection in children.

Simon Ling, University of Toronto, Canada

Biography

Dr. Simon Ling graduated in medicine from the University of Edinburgh, Scotland and trained in paediatric gastroenterology in Scotland and Toronto. Following his appointment to SickKids and the University of Toronto in 2003, Dr Ling has served as Head of the Division of Gastroenterology, Hepatology and Nutrition since 2015 and previously as Director of the Paediatric Gastroenterology Training Program. He received the Department of Paediatrics' Richard Rowe Award for Clinical Excellence in Paediatric Medical Care in 2013. Dr. Ling's subspecialty interest is paediatric liver disease and he also maintains a broad expertise in paediatric gastroenterology and endoscopy. His clinical research activities aim to improve our understanding of the progression of chronic liver disease and its complications in children, focusing on children with chronic viral hepatitis B and C, children with cystic fibrosis liver disease (CFLD), and children at risk of variceal bleeding. He collaborates in the Hepatitis B Research Network (HBRN), CanHepC, and the CFLD Research Network.

Health Services Research

Jordan Feld, University of Toronto, Toronto, Canada

Biography

Jordan Feld Associate Professor of Medicine, University of Toronto, Ontario, Canada Dr. Feld attended medical school at the University of Toronto and then completed residency programs in Internal Medicine and Gastroenterology. Following his clinical training, Dr. Feld focused on developing skills in clinical and laboratory research in liver disease, with a particular interest in viral hepatitis. He completed a clinical research fellowship in hepatology and then spent 4 years doing clinical and laboratory research in the Liver Diseases Branch of the National Institutes of Health. He received a Masters of Public Health with a focus on Infectious Diseases as a Sommer Scholar from Johns Hopkins University and has worked extensively abroad, maintaining a strong interest in International Health. Dr. Feld holds the R. Phelan Chair in Translational Liver Research as a clinician-scientist at the Toronto Centre for Liver Disease in the Toronto General Hospital and the Sandra Rotman Centre for Global Health at the University of Toronto. He leads a large clinical research team evaluating new therapeutics and diagnostics for hepatitis B and C virus infections and has led pivotal international trials to establish new treatment paradigms. He serves on the AASLD/IDSA hepatitis C treatment guidance panel and the Panamerican Health Organization Technical Advisory Group on Viral Hepatitis and has co-chaired international congresses including the International Symposium on Viral Hepatitis and Liver Disease, the International Viral Hepatitis Elimination Meeting and HCV2020. He founded and co-chairs the Schwartz-Reisman Liver Research Centre that brings together all senior investigators doing basic and translational research in liver disease at the University of Toronto. His primary laboratory interests focus on understanding virological adaptations to the intrahepatic antiviral immune response.

Lisa Barrett, Dalhousie University, Halifax, Canada

Biography

Dr. Lisa Barrett is an Infectious Diseases Clinician Scientist with the Nova Scotia Health Authority, as well as an Assistant Professor in the Divisions of Infectious Diseases, Microbiology and Immunology, and Laboratory Medicine and Pathology at Dalhousie University in Halifax, Nova Scotia. Dr. Barrett works as a viral immunologist studying chronic viral infections and is involved in hepatitis C studies at the local, national and international level. Dr. Barrett has active trials assessing the hepatitis C care models and immune pathogenesis. Her research spans laboratory based discovery science, clinical research, and implementation science in public health systems with an emphasis on policy influence. She is actively involved in the development and implementation of the PEI HCV program with an elimination target of 2025.

Oral Abstracts – résumés oraux

Biomedical Research

Oral presentation at 09h15 - CHC - O - 43

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

A. Vranjkovic[1], D. Read[2], C. L. Cooper[3,4,5], A. M. Crawley[1,6,7,*]

[1]Chronic Disease Program, OTTAWA HOSPITAL RESEARCH INSTITUTE, [2]University of Ottawa, [3]Clinical Epidemiology , OTTAWA HOSPITAL RESEARCH INSTITUTE, [4]Division of Infectious Diseases, The Ottawa Hospital, [5]Epidemiology and Community Medicine, University of Ottawa, [6]Biology, Carleton University, [7]Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Canada

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. Upregulated 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.

Disclosure of Interest: None declared

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Oral presentation at 09h30 - ID: CHC - O - 42

The Effect of Apoptosis and Inflammasome-Mediated Pyroptosis on HCV Infection

H. L. Wallace[1,*], L. Wang[1], C. Davidson[1], K. Hirasawa[1], R. S. Russell[1]
[1]Biomedical Sciences, Memorial University, St John's, Canada

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 wildtype 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.

Disclosure of Interest: None declared

Social, Cultural, Environmental, and Population Health Research

Oral presentation at 11h00 - ID: CHC - O - 44

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.

Disclosure of Interest: None declared

Oral presentation at 11h23 - ID: CHC - O - 45

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.

Disclosure of Interest: L. Barrett Grant / Research support for: Abbvie, Gilead, Consultant for: Merck, ViiV, Abbvie, Bristol Myer Squib, Gilead , Paid Instructor for: Abbvie, Merck, Gilead, F. Gallagher: None declared, J. Dirk: None declared, G. Arora: None declared, B. Goodall: None declared, M. Bonn: None declared, J. Boudreau: None declared, S. Oldford: None declared, C. Heinstein: None declared

Clinical Research

Oral presentation at 14h55 - ID: 15 CHC - O - 47

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.

Disclosure of Interest: T. Magel: None declared, D. Smyth Grant / Research support for: Merck, Gilead, Consultant for: Merck, Gilead., Speakers bureau from: Merck, Gilead., D. Webster Grant / Research support for: AbbVie, Gilead, Merck& Co, Pfizer, GSK, ViiV, Consultant for: Abbvie, Speakers bureau from: Merck&co, L. Barrett Grant / Research support for: Abbvie, Gilead, Consultant for: Merck, Abbvie, Bristol Myers Squibb, Gilead and ViiV, Speakers bureau from: Abbvie, Gilead, Merck, K. Stewart Grant / Research support for: gilead, viiv, merck, abbvie, Consultant for: Gilead, Paid Instructor for: gilead, merck, abbvie, A. Wong Consultant for: Merck, Gilead, Abbvie - Regional and Provincial Programming: Merck, Gilead, Abbvie - Clinical Trials: Merck, Gilead, C. Cooper Grant / Research support for: Merck, Gilead, Abbvie and BMS, Speakers bureau from: Merck, Gilead, Abbvie and BMS, M.-L. Vachon Grant / Research support for: AbbVie, Gilead, Merck& Co, Consultant for: AbbVie, Gilead, Merck& Co, S. Borgia Grant / Research support for: AbbVie, Gilead, Merck& Co, Consultant for: AbbVie, Gilead, Merck& Co, A. Ramji Grant / Research support for: Abbvie, Gilead, Intercept, Merck&co., Consultant for: Abbvie, Gilead, Lupin, Intercept,Merck & Co, Speakers bureau from: Abbvie, Gilead, Intercept, Merck &Co, G. Macphail Grant / Research support for: Gilead and Merck&Co., Consultant for: AbbVie, Gilead, Merck& Co, C. Fraser Grant / Research support for: AbbVie, Merck&Co, Gilead, ViiV, Consultant for: AbbVie, Merck&Co, Gilead, ViiV, A. O. Hamour: None declared, L. Bullinckx Grant / Research support for: AbbVie, Gilead, Merck& Co, E. Tam: None declared, J. Feld Grant / Research support for: AbbVie, Gilead, Janssen, Wako/Fujifilm, Consultant for: Abbott, AbbVie, Gilead, Enanta, Roche, S. Lee Grant / Research support for: Abbvie, Gilead, Merck, Novartis, Pendopharm, Oncoustics, Consultant for: Abbvie, Gilead, Merck, Novartis, Pendopharm, Oncoustics, Speakers bureau from: Abbvie, Gilead, Merck., B. Conway Grant / Research support for: AbbVie, Merck&Co, Gilead, ViiV, Consultant for: AbbVie, Merck&Co, Gilead, ViiV

Oral presentation at 15h10 - ID: CHC - O - 46

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.

Disclosure of Interest: None declared

Health Services Research

Oral presentation at 16h10 - ID: CHC - O – 49

HBV-HCV Co infection 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. 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.

Disclosure of Interest: None declared

Oral presentation at 16h25 -

The health burden of hepatitis C infection facing the First Nations population in Ontario: A Research Partnership

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Background: Canada's complex history has left First Nations communities bearing a disproportionate burden of hepatitis C virus (HCV) infection. As a part of Canada's commitment to the World Health Organization (WHO) strategy for eliminating viral hepatitis by 2030, Canada has made Indigenous-led approaches and Indigenous populations a priority focus for national and provincial/territorial HCV strategies. Although a few studies have provided data on HCV infection in specific First Nations communities, these estimates have been limited in their scope and generalizability as First Nations populations in Canada are very diverse. In Ontario, where more than 200,000 First Nations people reside, there has been no study describing the burden of HCV. Province-wide evidence of the impact of HCV on the First Nations population will be a necessary first step to inform policy and/or community actions towards combating HCV infection in Canada.

Purpose: To describe the process of creating a collaborative partnership between First Nations representatives and academic researchers to guide the analysis of administrative health data to measure the burden of HCV infection among the First Nations population in Ontario.

Methods: To examine HCV infection among the First Nations population in Ontario, we linked Public Health Ontario testing records, healthcare administrative data stored at ICES, and the Indian Register, which identifies all registered individuals with First Nations status. Guiding the usage of these administrative datasets is an established process that respects First Nations data governance and the formation of a partnership between First Nations and academic researchers across Ontario. A collaborative research process was developed ensuring the project is First Nations-led and strength-focused. Research agreements outlining ethical conduct and plans for knowledge exchange served to establish commitment between partners and formulate how this research will adhere to First Nations data governance principles. Plans for the co-interpretation of findings with partners were created to facilitate a two-way exchange of knowledge that incorporates both Western and First Nations ways of knowing. Knowledge translation approaches in combination with community-based research practices guarantee that findings can be communicated back to First Nations communities and can promote meaningful change.

Result(s): The Ontario First Nations HIV/AIDs Education Circle (OFNHAEC) was an advisory group and partner in this research. Quarterly meetings between the research team and OFNHAEC incorporate cultural understandings in study conception, design, analysis, and interpretation of results. To facilitate mutual co-learning between partners, land-based trainings and gatherings were attended by the research team to understand contextual roots potentially underlying the burden of infection. Collaboration with the Chiefs of Ontario facilitated the review of the project for adherence to First Nations principles of OCAP® (Ownership, Control, Access, and Possession), which are standards for First Nations data, and the dissemination of findings across the province.

Conclusion(s): This partnership serves as a starting point in understanding the impact of HCV infection among the First Nations population in Ontario. Only by working in partnership can we fully address HCV infection in the context of First Nations people's unique determinants of health and well-being.

Posters – Affiches

Biomedical Research

CHC - P - 006

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.

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3. Fabre, T., et al. Type 3 cytokines IL-17A and IL-22 drive TGF-beta-dependent liver fibrosis. Science immunology 3(2018).
Disclosure of Interest: None declared

CHC - P – 002

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.

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CHC - P – 008

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.

Disclosure of Interest: None declared

CHC - P – 005

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[1] and innate immune signalling.[2] 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,[3] 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)[4] and inhibition of the antiviral effector protein kinase R (PKR).[5] 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.[6]

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.

Reference(s): [1]Rasaiyaah et al. (2013) *Nature 503*, 402-405; [2]Liu et al. (2017) *eLife 6*, doi: 10.7554/eLife.24425; [3]Hopkins et al. (2013) *J. Hepatol. 57*, 47-53; [4]Romero-Brey et al. (2012) *PLoS Pathog. 8*, e1003056; [5]Pflugheber et al. (2002) *Proc. Natl. Acad. Sci. USA 99*, 4650-4655; [6]Yamane et al. (2019) *Nat. Microbiol. 4*, 1096-1104
Disclosure of Interest: None declared

CHC - P – 001

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 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.

Disclosure of Interest: None declared

CHC - P – 009

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.

Disclosure of Interest: None declared

CHC -P – 050

Tracking Nanoparticle Biodistribution in an Immunocompetent Woodchuck Tumor Model

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Background: Our overarching goal is to design a nanoparticle (NP)-based therapy to treat hepatitis-induced hepatocellular carcinoma (HCC) and eventually other types of liver disease. A necessary first step towards this goal is to establish a biologically relevant animal model for pre-clinical testing. Non-primate models are conventionally used to assess the biomedical utility of nanomaterials. However, current *in vivo* liver tumor models lack an intact immunological background, and the tumours in these animals do not develop spontaneously. Given that the success of treatments in clinic rely on biologically relevant animal models for pre-clinical testing, we are focusing on establishing the most biologically relevant animal model to test new HCC therapies. The pre-clinical Woodchuck Hepatitis Virus (WHV)-induced liver cancer model effectively recapitulates the entire disease course of hepatitis B virus (HBV)-induced HCC. In this model, tumors develop spontaneously as a result of chronic WHV infection and importantly, these animals are fully immunocompetent.

Purpose: A necessary step towards designing a NP-based treatment for HCC is to fully characterize the biodistribution of inert NPs in woodchucks. Therefore, we characterized the biodistribution of 60 nanometer (nm) gold NPs at the organ, cellular and subcellular level in this animal system.

Methods: We intravenously injected 10 animals (6 chronically infected with WHV, 4 healthy) with 60 nm gold NPs. Inductive coupled plasma mass spectrometry (ICP-MS) was used to determine the biodistribution of these particles at the organ level. Flow cytometry was used to determine which immune cell type takes up these particles. Transmission electron microscopy and confocal microscopy was used to determine the subcellular distribution of these particles. Finally, we performed bulk RNA-sequencing to determine the transcriptional differences between cells that take up the particles compared to those that do not.

Results: We find that the liver and spleen are the primary organs that sequester intravenously injected gold NPs. We find that these particles accumulate in the lysosomes of the macrophages lining the sinusoid of the liver. Finally, we identified that immunoregulatory macrophages have a higher propensity to take up NPs than inflammatory macrophages.

Conclusions and Significance: The large discrepancy between pre-clinical animal models and clinical performance and translation is largely attributed to the lack of tumor models that can recapitulate human cancers. Woodchucks are the only animal system that develops tumours spontaneously as a result of chronic virus infection. By determining the biodistribution of NPs in this animal system, we hope that this will establish the basis to test future NP-based therapies for the treatment of HCC.

CHC - P – 010

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[1]. 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[2-4]. DDX3X has been shown to be essential for HCV viral replication[5] and is linked to HCV-associated hepatic steatosis through influences on lipid metabolism pathways[6]. Interestingly, all of these processes are mediated by host protein interaction with the 3'-UTR of HCV[6-7]. Furthermore, elevated levels of DDX1 and DDX3 are associated with oncogenesis highlighting these host proteins as important targets[8-12].

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.

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Disclosure of Interest: None declared

CHC - P – 003

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.
Disclosure of Interest: None declared

CHC - P – 004

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 6mm 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 days 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.

Reference(s): McGilvray I, et al., Gastroenterology 2012; MacParland SA, et al., Nat Commun 2018
Disclosure of Interest: None declared

CHC - P – 007

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.

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Disclosure of Interest: None declared

Social, Cultural, Environmental and Population Health Research

CHC - P – 013

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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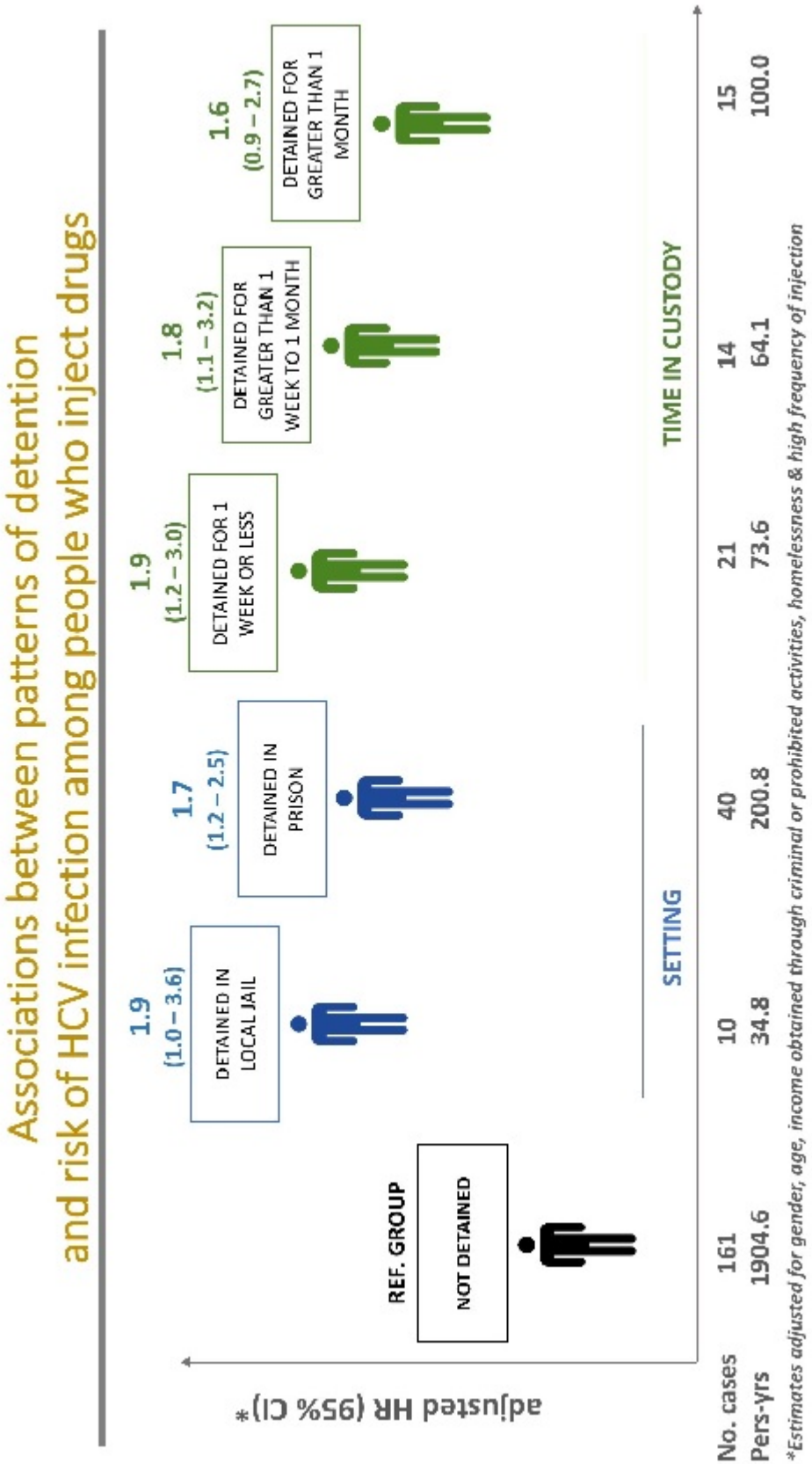
Background: Recent incarceration has been linked to a high risk of hepatitis C virus (HCV) infection among people who inject drugs (PWID) [1]. Although research surrounding this topic mainly focused on long-term incarceration, many PWID frequently experience short-term detention episodes [2] - a context where access to care and harm-reduction is particularly limited [3]. 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.

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).

Image:


Associations between patterns of detention and risk of HCV infection among people who inject drugs
adjusted HR (95% CI)*
REF. GROUP
NOT DETAINED
1.9 (1.0 – 3.6)
DETAINED IN LOCAL JAIL
1.7 (1.2 – 2.5)
DETAINED IN PRISON
1.9 (1.2 – 3.0)
DETAINED FOR 1 WEEK OR LESS
1.8 (1.1 – 3.2)
DETAINED FOR GREATER THAN 1 WEEK TO 1 MONTH
1.6 (0.9 – 2.7)
DETAINED FOR GREATER THAN 1 MONTH
SETTING
TIME IN CUSTODY
No. cases 161 10 40 21 14 15
Pers-yrs 1904.6 34.8 200.8 73.6 64.1 100.0
*Estimates adjusted for gender, age, income obtained through criminal or prohibited activities, homelessness & high frequency of injection

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.

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[2] Malakieh J. Adult and youth correctional statistics in Canada, 2017/2018. Ottawa, Canada: Statistics Canada, **2019**. Available at: https://www150.statcan.gc.ca/n1/en/pub/85-002-x/2019001/article/00010-eng.pdf?st=EK430Mhb. Accessed September 2019.
[3] Small W, Wood E, Betteridge G, Montaner J, Kerr T. The impact of incarceration upon adherence to HIV treatment among HIV-positive injection drug users: a qualitative study. Aids Care **2009**; 21(6): 708-14.

Disclosure of Interest: None declared

CHC - P – 019

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 to the World Health Organization (WHO) to call for HCV elimination 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=8834) 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.

Disclosure of Interest: None declared

CHC - P – 012

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.

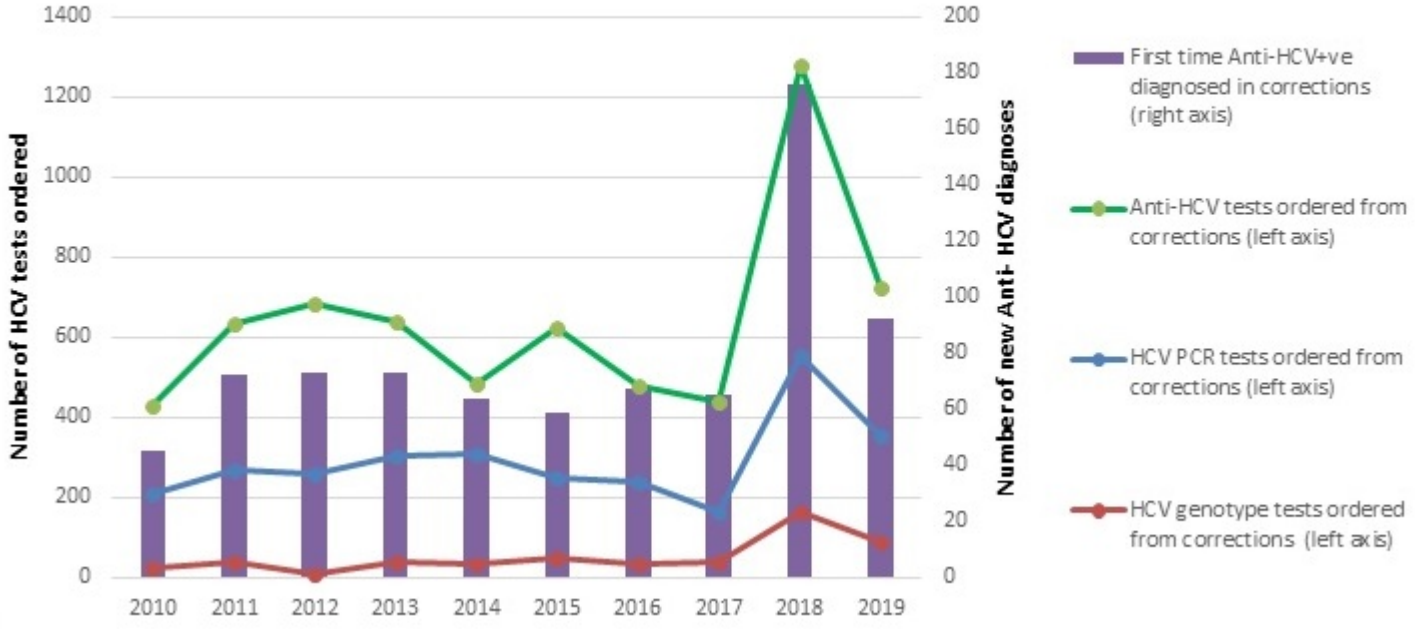
Purpose: To evaluate efforts to increase HCV screening in BC provincial corrections after the transfer of health services from BC Corrections to PHSA in October 2017.

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.

Image:

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



Conclusion(s): Transfer of health services from BC Corrections to the PHSA led to a precipitated 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.

Disclosure of Interest: None declared

CHC - P - 024

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's (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 testing and treatment.

Purpose: In Atlantic Canada, point-of-care-testing (POCT) for hepatitis C 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.

Disclosure of Interest: M. Bonn Grant / Research support for: Grant from Gilead for Peer Led Project, M. Bonn Grant / Research support for: Gilead Grant for Project

CHC - P – 017

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: Hepatis 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 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.

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CHC - P – 014

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.

Image:

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

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

Reference(s): Acknowledgements: Dr Mel Krajden and Dr Naveed Zafar Janjua provided technical support to access and validate data sources without receiving funding from AbbVie Inc. Medical writing support was provided by Ivane Gamkrelidze, employee of Center for Disease Analysis, who contributed to the data analysis and/or the drafting of the abstract. AbbVie Inc. provided funding for this medical writing support.

Disclosure of Interest: J. Feld Grant / Research support for: received consulting fees from AbbVie Inc., Enanta, Gilead, Janssen and Roche. He also received research support from AbbVie Inc., Abbott, Gilead, Janssen and Wako/Fujifilm., Y. Rahal Shareholder of: may own AbbVie stock or stock options, Employee: Employee of AbbVie Corporation, Canada, C. Robert Shareholder of: may own AbbVie stock or stock options, Employee: Employee of AbbVie Corporation, Canada, Y. Sanchez Gonzalez Shareholder of: may own AbbVie stock or stock options, Employee: Employee of AbbVie Inc., H. Razavi Grant / Research support for: Received funding from AbbVie Inc. for this project. Also received research funding from AbbVie, Gilead, and Intercept

CHC - P – 026

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.

Disclosure of Interest: None declared

CHC - P – 023

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.

Disclosure of Interest: K. Harland Grant / Research support for: Gilead Sciences, Abbvie, Merck, Speakers bureau from: Gilead Sciences Canada , J. LeBlanc Grant / Research support for: Gilead Sciences, AbbVie, Merck, S. Materniak Grant / Research support for: Gilead Sciences, AbbVie, Merck, D. Webster Grant / Research support for: Gilead Sciences, AbbVie, Merck, Speakers bureau from: Gilead Sciences, AbbVie, Merck

CHC - P – 011

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.[1] 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.[2,3] 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.[4]

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.

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Disclosure of Interest: None declared

CHC - P – 021

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.

Disclosure of Interest: None declared

CHC - P – 028

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% [1].
This cohort may have higher rates of cognitive dysfunction that persist after SVR [2], and recent BC CDC data also suggests a 17-year reduction in life expectancy [3].

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 [7,8,9,10] which has critical schema functions [11], 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 [4, 5], mood, learning, memory (anomic aphasia), and other critical functions [6] 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.

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Disclosure of Interest: None declared

CHC - P – 020

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.

Image:

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.

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.

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CHC - P – 022

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.

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CHC - P – 015

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], 68% HCV Ab+) contributed 6363 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.

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CHC - P – 016

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 socio-economic 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.

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CHC - P – 025

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:

- A web portal for service providers to find the latest resources on hepatitis C among Canadian immigrants.
- 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.
- 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 ensures 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*.

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Disclosure of Interest: None declared

CHC - P – 027

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 wholestic 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.

Reference(s): 1.Government of Saskatchewan. Population and public health programs & services in Saskatchewan 2015-2016 report. Regina (SK); 2017. 61 p. Report No: 1
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Disclosure of Interest: None declared

CHC - P – 018

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.

Disclosure of Interest: None declared

Clinical Research

CHC - P – 029

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

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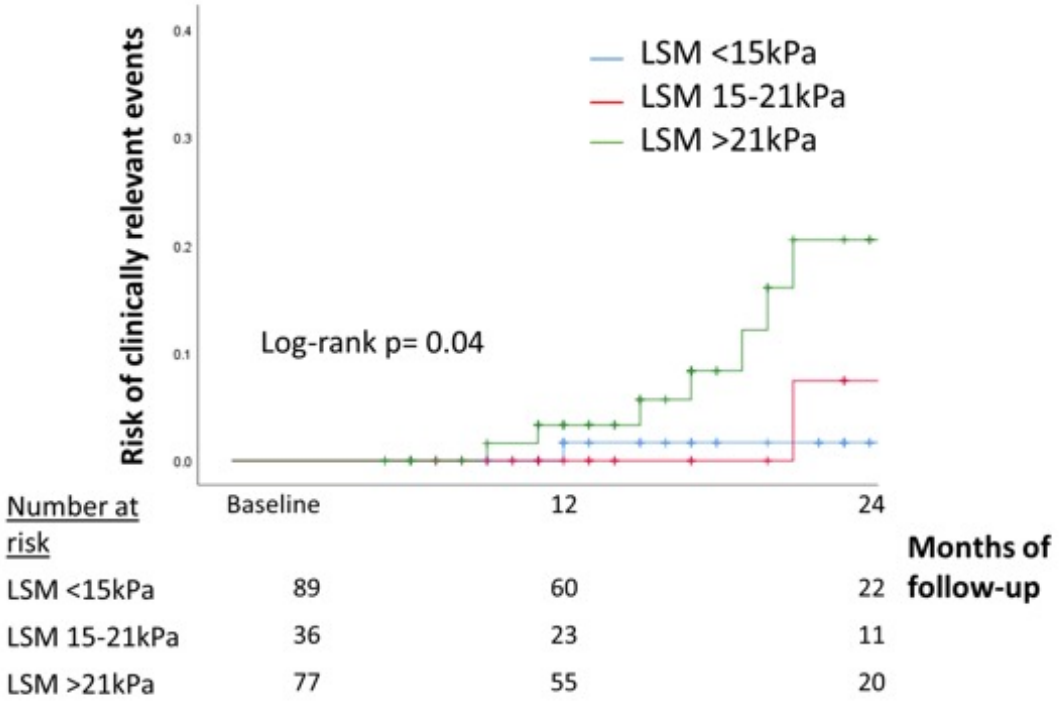
Background: Portal hypertension (PH) is a major driver of progression to clinical decompensation in compensated advanced chronic liver disease (cACLD), as such it should be identified as soon as possible and treated as needed. In patients with cACLD requiring the use of extralarge (XL) probe for liver 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/m2; 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).

Image:



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.

Disclosure of Interest: Y. Mendoza: None declared, S. Cocciolillo: None declared, G. Murgia: None declared, T. Chen: None declared, C. Margini: None declared, G. Sebastiani Grant / Research support for: Merck, Consultant for: Intercept, Novartis, Novonordisk, Speakers bureau from: Gilead, Abbvie, A. Berzigotti: None declared

CHC - P – 032

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 precluded 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/month) is collected. Patient ccharacteristics 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.

Disclosure of Interest: C. Cooper Grant / Research support for: Gilead, Abbvie, Merck, BMS, Consultant for: Gilead, Abbvie, Merck, BMS, Speakers bureau from: Gilead, Abbvie, Merck, BMS, M.-L. Vachon Consultant for: Abbvie, Viiv, Gilead, Merck, B. Conway: None declared, A. Wong: None declared, A. Ramji: None declared, S. Borgia Consultant for: Gilead, Abbvie, Speakers bureau from: Gilead, Abbvie, E. Tam: None declared, L. Barrett: None declared, D. Smyth: None declared, J. Feld Grant / Research support for: Abbvie, Gilead, Janssen, Wako/Fujifilm, Consultant for: Abbott, Abbvie, Gilead, Enanta, Roche, S. Lee: None declared

CHC - P – 030

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 ³20,000 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 ³0.75; 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.

Disclosure of Interest: Y.-S. Lim Consultant for: Gilead Sciences: Advisory Committee or Review Panel; Bayer Healthcare: Advisory Committee or Review Panel, H. Chan Consultant for: Roche: Advisory Committee or Review Panel; Aligos: Advisory Committee or Review Panel; Arbutus: Advisory Committee or Review Panel; Gilead: Advisory Committee or Review Panel; ContraVir: Advisory Committee or Review Panel; Janssen: Advisory Committee or Review Panel; Vaccitech: Advisory Committee or Review Panel; VenatoRx: Advisory Committee or Review Panel; Vir Biotechnology: Advisory Committee or Review Panel, Speakers bureau from: Gilead: Speaking and Teaching;, W.-K. Seto Grant / Research support for: Gilead Sciences: Grant/Research Support, Consultant for: AbbVie: Advisory Committee or Review Panel;Gilead Sciences: Advisory Committee or Review Panel, Speakers bureau from: AbbVie: Speaking and Teaching;Gilead Sciences: Speaking and Teaching, Q. Ning: None declared, K. Agarwal Grant / Research support for: MSD: Grant/Research Support, Consultant for: Springbank: Advisory Committee or Review Panel; shinoigi: Advisory Committee or Review Panel; arbutus: Advisory Committee or Review Panel, Speakers bureau from: Gilead: Speaking and Teaching;, H. Janssen Grant / Research support for: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Medimmune, Merck, Roche, Consultant for: AbbVie, Arbutus, Benitec, Bristol-Myers Squibb, Gilead Sciences, Glaxo, Janssen, Medimmune, Merck, Roche, Vir-Bio, C. Pan Consultant for: Gilead Sciences, Speakers bureau from: Gilead Sciences: Speaking and Teaching, W. Chuang: None declared, N. Izumi Speakers bureau from: Eisai: Speaking and Teaching; Bayer: Speaking and Teaching; Gilead: Speaking and Teaching; AbbVie: Speaking and Teaching; Otsuka: Speaking and Teaching, S. Fung Consultant for: Gilead Sciences Inc.; Abbvie, Speakers bureau from: Merck, D. Shalimar: None declared, M. Brunetto Grant / Research support for: AbbVie, BMS, Gilead, Fujirebio, Consultant for: AbbVie, Janssen, Roche, Speakers bureau from: AbbVie, Gilead, J. Flaherty Employee: Gilead Sciences Inc., S. Mo Employee: Gilead Sciences Inc., C. Cheng Employee: Gilead Sciences Inc., L. Lin Employee: Gilead Sciences Inc., A. Gaggar Employee: Gilead Sciences Inc., G. Subramanian Employee: Gilead Sciences Inc., P. Marcellin Grant / Research support for: Gilead, Merck, Abbive,Eiger, Assembly Biosciences, Consultant for: Gilead; Eiger; Hebabiz, Speakers bureau from: Mylan, E. Gane Consultant for: AbbVie, Gilead, Janssen, Novartis, Roche and Merck, Speakers bureau from: Abbie, Gilead, Janssen, Novartis, Roche, Merck, J. Hou Grant / Research support for: Johnson&johnson, BMS, Consultant for: BMS, Gilead, Roche, Johnson&johnson, Arbutus, Abbvie, M. Buti Consultant for: Roche, Arbutus, Gilead, Spring Bank

CHC - P – 031

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 center, 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.

	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%)

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.
Disclosure of Interest: V. Martel-Laferriere Grant / Research support for: Gilead, Merck, Abbvie, Cepheid, Consultant for: Gilead, Merck, J.-G. Baril Consultant for: Merck, ViiV, Gilead, I. Alarie: None declared, J. Cote: None declared, J. Leblanc: None declared, E. Jourdenais: None declared, D. Horth: None declared, C. Tremblay Grant / Research support for: Gilead, Consultant for: ViiV

Health Services Research

CHC - P – 041

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.[1] 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.[2,3] 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.

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Disclosure of Interest: None declared

CHC - P – 035

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 (1). 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.

Reference(s): 1. Mason et al. Int J Drug Policy. 2015;26(10):1007-13.
Disclosure of Interest: None declared

CHC - P – 038

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.

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CHC - P – 034

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.

Disclosure of Interest: R. Milenkovski Shareholder of: Gilead Sciences Canada, Employee: Gilead Sciences Canada, P. Douglas Employee: Gilead Sciences Canada

CHC - P – 037

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.

Disclosure of Interest: R. Milenkovski Shareholder of: Gilead Sciences Canada, Employee: Gilead Sciences Canada, P. Douglas Employee: Gilead Sciences Canada

CHC - P – 036

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).

Image:

Table 1. EQ5D-3L health utilities in chronic hepatitis C 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
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.

Disclosure of Interest: None declared

CHC - P – 033

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 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.

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

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

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.

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CHC - P – 039

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.(3) 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.

Reference(s): (1) Kwong JC, Ratnasingham S, Campitelli MA, Daneman N, Deeks SL, Manuel DG, Allen VG, et al. The impact of infection on population health: results of the ontario burden of infectious diseases study. PLoS One 2012;7:e44103.
(2) Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, Parish B, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med 2011;364:2199-2207.
Disclosure of Interest: None declared

CHC - P – 040

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.

Reference(s): (1) Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, Parish B, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med 2011;364:2199-2207.

Disclosure of Interest: None declared

Viral Hepatitis

CLM - P – 135

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.

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CLM - P – 168

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[1]. 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[2]. 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[2], 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[3] 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.

Reference(s): 1. Doering TA et al, *Immunity 2012 ;37(6):1130-44.*
2. Rosenberg BR et al, *PLoS Pathogens 2018 ;14(9):e1007290.*
3. Swadling L. et al, *Sci Transl Med. 2014* [SN1] ;6(261):261ra153.

Disclosure of Interest: None declared

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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 bloodborne 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.
Disclosure of Interest: None declared

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