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

6th Canadian Symposium on Hepatitis C Virus

6ème Symposium canadien sur le virus de l'hépatite C

March 3, 2017 – 3 mars 2017

The Fairmont Banff Springs Hotel,
Banff, AB

Alberta and New Brunswick Ballrooms

Poster session: New Brunswick extension

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 6th Canadian Symposium on the Hepatitis C Virus (HCV).

The advent of highly effective HCV treatments, and their widespread use, has led to great advances in the care of many Canadians afflicted by hepatitis C. However, many individuals living with this viral disease lack access to care. We believe that strengthening communication and supporting interactions between Canadian scientists, clinicians, the affected communities, and policy makers are essential to effectively respond to the challenges of preventing and treating all hepatitis C patients.

The Canadian HCV Symposia have provided an ideal forum for such an exchange. The Canadian Network on Hepatitis C (CanHepC) has contributed to research training and knowledge translation of hepatitis C findings to benefit patients. Importantly, CanHepC has developed a network of motivated and collaborative investigators whose work encompasses the social, behavioural, clinical, and basic sciences. This multidisciplinary collaboration is crucial for the development of programs to eradicate HCV.

We would like to welcome you to the beautiful town of Banff during Canada's 150 year anniversary!

We look forward to learning about your exciting research and work in the field of hepatitis C, and discussing how we can shape the future of hepatitis C research and policy in Canada.

Chers Collègues,

Nous vous souhaitons la bienvenue au 6e Symposium canadien sur le virus de l'hépatite C (VHC). L'instauration de traitements hautement efficaces contre le VHC, ainsi que leur utilisation étendue représente un avancement significatif pour plusieurs Canadiens souffrant de l'hépatite C. Cependant, un grand nombre d'individus infectés par ce virus n'ont pas facilement accès au soin de santé. Nous croyons qu'il est primordial de renforcer la communication et les interactions entre les scientifiques, les médecins, les communautés affectées et les responsables politiques afin de répondre aux défis rencontrés pour prévenir et traiter l'hépatite C partout au Canada.

Le symposium canadien sur le VHC représente un forum idéal pour ce type d'échanges. Le Réseau Canadien sur l'Hépatite C (CanHepC) a contribué à la formation en recherche et au transfert de connaissances sur l'hépatite C pour le bénéfice des patients. De manière importante, le CanHepC a développé un réseau de chercheurs motivés collaborant sur des travaux englobant les sciences sociales, comportementales, cliniques et fondamentales. Ces collaborations interdisciplinaires sont cruciales pour le développement des programmes requis pour éradiquer le VHC.

Nous vous souhaitons la bienvenue dans la magnifique ville de Banff en ce 150e anniversaire de la Confédération canadienne !

Nous avons hâte d'en apprendre plus sur vos recherches et travaux concernant l'hépatite C. Nous discuterons des orientations possibles pour la recherche et les politiques sur l'hépatite C au Canada.

Lorne Tyrrell, MD, PhD, Chair
University of Alberta

Carla Coffin., MD, MSc, FRCPC, Co-Chair
University of Calgary

Biographies of Co-Chairs

Dr. Lorne Tyrrell, University of Alberta, Edmonton, Canada – Chair

Biography

D. Lorne Tyrrell OC, AOE, MD, PhD, FRCP, FRSC, FCAHS is a Distinguished University Professor at the University of Alberta. He is the Founding Director of the Li Ka Shing Institute of Virology and has focused his research since 1986 on viral hepatitis. His work on the development of antiviral therapy was supported by CIHR and Glaxo Canada. It resulted in the licensing of the first oral antiviral agent to treat chronic hepatitis B infection – lamivudine – in 1998. Today, lamivudine is licensed in over 200 countries worldwide for the treatment of HBV. He has also been involved in the establishment of a biotech company—KMT Hepatech Inc. based on the first non-primate animal model for HCV.

Dr. Tyrrell was the Dean of the Faculty of Medicine and Dentistry from 1994-2004. Since leaving the Deanship in 2004, Dr. Tyrrell has taken on a number of important board positions in healthcare in Alberta and Canada. These include the Chair of the Board of the Institute of Health Economics, Chair of the Gairdner Foundation Board, and member of the Research Advisory Council for the Canadian Institute for Advanced Research. He also has been appointed to the Science Advisory Board to Health Canada.

For his studies on viral hepatitis, Dr. Tyrrell has received numerous prestigious awards including the Gold Medal of the Canadian Liver Foundation (2000), Officer of the Order of Canada (2002), Alberta Order of Excellence (2000) and Fellow of the Royal Society (2004). He was inducted into the Canadian Medical Hall of Fame in April 2011 and was awarded the Killam Prize Health Sciences in May 2015.

Dr. Carla Coffin, University of Calgary, Calgary, Canada – Co-Chair

Biography

Carla Coffin MD, MSc, FRCPC is Associate Professor, Cumming School of Medicine, University of Calgary and Medical Director of the Calgary Liver Unit. Dr. Coffin received her MSc and MD from Memorial University of Newfoundland. She completed training in Internal Medicine and Gastroenterology at the University of Calgary and an American Association for the Study of Liver Diseases Advanced Hepatology Fellowship at the University of California San Francisco. Dr. Coffin is a Canadian Institutes of Health Research New Investigator Clinician Scientist. Her clinical and laboratory research is focused on chronic and occult hepatitis B virus (HBV) pathogenesis in the context of hepatitis C and/or HIV co-infection, non-alcoholic fatty liver disease (NAFLD), and pregnancy.

Program – Programme

Delivering a Cure for Hepatitis C Infection: What are the Remaining Gaps?

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

08h00 - 08h15 Welcome and Introductions – Mot de bienvenue
Dr. Naglaa Shoukry, Université de Montréal, Montréal, Canada

Biomedical Research
Co-Chairs: Dr. Selena Sagan and Dr. Angela Crawley

08:15 - 08h45 Opening Keynote: Addressing the Next Challenges in Virus-Host Interactions and Liver Disease
Pr. Thomas Baumert, Université de Strasbourg, Strasbourg, France

08h45 - 09h05 Imaging Immunity In Vivo
Dr. Paul Kubes, University of Calgary, Calgary, Canada

Oral Presentations – Présentations orales

09h05 - 09h15 Solute Carrier NTCP Regulates Innate Antiviral Immune Responses Targeting HCV Infection of Hepatocytes
Dr. Che Colpitts, University of Strasbourg, Strasbourg, France

09h15 - 09h25 Intrahepatic IL-22 Correlates with Advanced Liver Fibrosis and Sensitizes HSCs to TGF-β Signaling in a p38-dependent Manner
Thomas Fabre, Centre de recherche du CHUM, Montréal, Canada

Clinical Research
Co-Chairs: Dr. Carla Coffin and Dr. Curtis Cooper

09h25 - 09h55 Hepatitis C: Difficult to Cure Patients
Pr. Jean-Michel Pawlotsky, Université Paris Est, Paris, France

09h55 - 10h25 Coffee Break – Pause café

10h25 - 10h45 Towards Eradication of Hepatitis C
Dr. Morris Sherman, University Health Network, Toronto, Canada

Oral Presentations - Présentations orales

10h45 - 10h55 Novel E2 Glycoprotein Tetramer Detects Hcv-Specific Memory B Cells
Dr. Maude Boisvert, Centre de recherche du CHUM, Montréal, Canada

10h55 - 11h05 Evaluation of Xpert® HCV Viral Load Point-of-care Test for Detection of HCV Infection by Venipuncture-collected and Finger-stick Capillary Whole-blood Samples
Dr. Jason Grebely, University of New South Wales, Sydney, Australia

Health Services Research
Co-Chairs: Dr. Naveed Janjua and Dr. Wendy Wobeser

11h05 - 11h35 Changing Minds: Popular Culture & Vaccination Myths
Pr. Tim Caulfield, University of Alberta, Edmonton, Canada

11h35 - 11h55 Surveillance Systems to Support a Public Health HCV Response
Dr. Mark Tyndall, University of British Columbia, Vancouver, Canada

Oral Presentations - Présentations orales

11h55 - 12h05 HCV in the Real World: Adherence During Directly Acting Antiviral HCV Treatment Amongst Active Drug Users at a Community Based Program in Toronto
Mary Guyton, RN, Toronto Community Hep C Program, Canada

12h05 - 12h15 Development of a Provincial HCV Elimination Strategy
Dr. Lisa Barrett, Dalhousie University, Halifax, Canada

12h15 - 13h30 Lunch – Diner: Cascade Ballroom

Social, Cultural, Environmental, and Population Health Research
Co-Chairs: Dr. Dan Allman and Dr. Julie Bruneau

13h30 - 14h00	Strategies to Enhance Prevention of Hepatitis C Infection and Reinfection in People who Inject Drugs **Dr. Holly Hagan, New York University, New York, USA**
14h00 - 14h20	Addressing Barriers to Integrating Evidence-Based Public Health and Addiction Treatment Interventions **Dr. Evan Wood, University of British Columbia, Vancouver, Canada**

Oral Presentations - Présentations orales

14h20 - 14h30	Short Injection Cessation Episodes as Opportunities for Hepatitis C Prevention **Emmanuel Fortier, Université de Montréal, Montréal, Canada**
14h30 - 14h40	Hepatitis C Treatment and Care in Big River First Nation Community: Barriers to Accessing Healthcare Services **Dr. Mamata Pandey, Regina Qu'Appelle Health Region, Regina, Canada**
14H40 - 15h10	Coffee Break – Pause café
15h10 - 16h10	Hepatitis C in Indigenous People Panel and Audience Discussion – Table ronde et discussion avec l'audience Panel discussion members: Carrielynn Lund, CAAN, Renee Masching, CAAN, Norma Rabitskin, CAAN **Chair: Dr. Alexandra King, Simon Fraser University, Vancouver, Canada**
16h10 - 16h30	Universal Access to Direct-Acting Antiviral Therapies in Australia: Early Lessons **Dr. Greg Dore, University of New South Wales, Sydney, Australia**
16h30 - 17h10	Achieving "Access for all" in Canada: How will we get there? Panel and Audience Discussion – Table ronde et discussion avec l'audience Panel discussion members: Greg Dore, UNSW, Jean-Michel Pawlotsky, U. Paris Est, Jordan Feld, U of Toronto, Mel Krajden, U of British Columbia, Patricia Bacon, Action Hepatitis Canada. **Chair: Dr. Jason Grebely, University of New South Wales, Sydney, Australia**
17h10 - 17h15	Closing Remarks – Mot de la fin **Dr. Lorne Tyrrell, University of Alberta, Edmonton, Canada**
17h15 - 19h15	Cocktail and Poster Session – Cocktail et présentation des affiches: New Brunswick extension

Posters can be hung up during lunch time and PM coffee break

CATIE Learning Institute

As part of the CanHepC knowledge translation efforts, we are proud to partner with CATIE on an initiative called the HCV Symposium Learning Institute.

CATIE works with front line organizations across Canada to provide up-to-date, unbiased information about HIV and hepatitis C. Together, as part of the HCV Learning Symposium, we have invited frontline workers and community based leaders in HCV care to attend the HCV Symposium. The Learning Institute participants will work with CanHepC trainees to pull out key outcomes from the symposium and share these back in their regions and communities.

CATIE and CanHepC will also be co-hosting a webinar on March 15th and March 27th. These webinars will summarize the key outcomes of the Symposium. For further information please visit the CATIE website.
CATIE and CanHepC are proud to have community representatives amidst our broad range of participants at the Symposium.

http://www.catie.ca/en/home

Committees – Comités

Organizing Committee - Comité organisateur

Lorne Tyrrell, University of Alberta, Chair
Carla Coffin, University of Calgary, Co-Chair

Jason Grebely, University of New South Wales
Mel Krajden, University of British Columbia
Alexandra King, Simon Fraser University
Selena Sagan, McGill University
Naglaa Shoukry, Université de Montréal
Thomas Fabre, Université de Montréal, Trainee representative

Norma Choucha, CRCHUM, Symposium Coordinator

Session Chairs - Modérateurs de sessions

B**iomedical Research**
Angela Crawley, University of Ottawa
Selena Sagan, McGill University

Clinical Research
Carla Coffin, University of Calgary
Curtis Cooper, University of Ottawa

Health Services Research
Naveed Janjua, University of British Columbia
Wendy Wobeser, Queen's University

Social, Cultural, Environmental, and Population Health Research
Dan Allman, University of Toronto
Julie Bruneau, Université de Montréal

Abstract Reviewers - Réviseurs des résumés

Biomedical Research

Che Colpitts, Université de Strasbourg
Thomas Fabre, Université de Montréal
Sonya McParland, University of Toronto
Thomas Michalak, Memorial University
John Pezacki, University of Ottawa
Rodney Russell, Memorial University
Selena Sagan, McGill University
Joyce Wilson, University of Saskatchewan

Clinical Research

Lisa Barrett, Dalhousie University
Marc Bilodeau, Université de Montréal
Carla Coffin, University of Calgary
Curtis Cooper, University of Ottawa
Alexandra King, Simon Fraser University
Thomas Michalak, Memorial University

Health Services Research

Maryam Darvishian, University of British Columbia
Jason Grebely, University of New South Wales
Naveed Janjua, University of British Columbia
Mel Krajden, University of British Columbia
Alexandra King, Simon Fraser University
Alison Marshall, University of New South Wales
Rosie Thein, University of Toronto
Wendy Wobeser, Queen's University

Social, Cultural, Environmental, and Population Health Research

Dan Allman, University of Toronto:
Julie Bruneau, Université de Montréal
Carrielynn Lund, Canadian Aboriginal Aids Network
Renee Mashing, Canadian Aboriginal Aids Network
Gerry Mugford, Memorial University
Sahar Saeed, McGill University

Speaker Biographies and Abstracts – Biographies des conférenciers et résumés

Biomedical Research

Pr. Thomas Baumert, Université de Strasbourg, Strasbourg, France

Biography

Thomas F. Baumert, MD is Professor of Medicine, head of the Inserm Institute of Viral and Liver Diseases, the Laboratory of Excellence HEPSYS and Chair of Hepatology at the Center at the University of Strasbourg, France. He received his MD from the University of Heidelberg. Following his doctoral thesis at the German Cancer Research Center in Heidelberg and his internship in Internal Medicine at the University of Munich, he was a postdoctoral fellow at Harvard Medical School and the National Institutes of Health, Bethesda. Following completion of his clinical training at the University Hospital Freiburg, he relocated to the University of Strasbourg as Professor of Medicine to create a new Inserm research unit with a highly recognized program in translational medicine. He holds a secondary affiliation as a research scholar the BROAD Institute of MIT and Harvard and the Massachusetts General Hospital. His laboratory focuses on preventive and therapeutic approaches for viral infection and chronic liver disease using a functional genomics and systems biology approach. He has received several awards including the Prix Galien. He has published more than 200 scientific articles including Cell, N. Engl. J. Med., Nature Medicine, Nature Biotechnology as a senior author. He is an inventor on 15 patents and patent applications. His research is supported by the National Institutes of Health, the EU including an ERC Advanced Grant as well as industry.

Abstract

Addressing the Next Challenges in Virus-Host Interactions and Liver Disease

Chronic hepatitis C virus (HCV) infection is a leading cause of liver disease and hepatocellular carcinoma (HCC). HCC is the second leading and fastest rising cause of cancer death world-wide. While direct-acting antivirals (DAA) efficiently cure chronic infection, new challenges arise: globally, antiviral therapy is only available to a fraction of infected patients. Many patients remain undiagnosed and/or live in countries where therapy is unattainable demonstrating the need for a vaccine. Patients with defined genotypes, advanced liver disease or prior non responders may need alternative therapies. Moreover, despite viral cure, patients with advanced fibrosis remain at high risk for the development of HCC. Thus, the study of HCV-host interactions will be essential to identify alternative therapeutic targets, inform on vaccine design and elucidate the pathogenesis of liver disease and cancer. Since fibrosis/cirrhosis-driven carcinogenesis is the mechanism of HCC development common to all major etiologies, HCV-induced liver disease can serve as a model to decipher the pan-etiology sequence of molecular events underlying disease progression and HCC. Here, we review recent advances in virus-host interactions and discuss how the investigation of viral pathogenesis will enable to discover new targets for prevention and treatment of liver disease and HCC.

Dr. Paul Kubes, University of Calgary, Calgary, Canada

Biography

Paul Kubes, PhD is a Professor at the University of Calgary Faculty of Medicine and Founding Director of the Snyder Institute for Chronic Diseases. He also holds a Canada Research Chair in Leukocyte Recruitment in inflammatory disease.

Dr. Kubes has received numerous awards including the CIHR Investigator of the Year in 2011 for his basic science work on how the brain affects immunity. He has also received the Alberta Science and Technology Award and the Henry Friesen Award. Dr. Kubes has published basic science work in Cell, Science and the Nature journals and also has publications in both clinical journals including Lancet and more translational journals (JCI). His latest work has uncovered a key role for peritoneal cavity macrophage in healing visceral organs.

Dr. Kubes has extensive review experience with CIHR having been part of numerous committees including the Immunology panel, Cardiovascular A and B panel, the CIHR scholar panel and the Banting postdoctoral panel. He also served as a member of CIHR Governing Council and is chair of the college chairs. In addition, he has reviewed for NIH and he co-chairs the Gairdner Research Committee.

Abstract

Imaging Immunity in Vivo

Liver failure and infections are intimately linked. This is because the liver functions as a firewall for any bacteria, viruses and other pathogens that breach our barriers and enter the blood stream. Using cutting edge imaging, we can visualize the incredibly dynamic and rapid event that occurs to eradicate potential infections. Kupffer cells found intravascularly in sinusoids have the capacity to bind pathogens directly or indirectly via complement or antibodies from the mainstream of blood. This leads to significant but sometimes not complete eradication of the infecting pathogens. In certain cases the pathogen can survive inside these cells and promotes secondary infections. Neutrophils are summoned and can release their DNA in the sinusoids in an attempt to prevent dissemination of pathogens to other organs. iNKT cells are presented with glycolipid antigens on the Kupffer cells via CD1d and begin to make interferons and other molecules that help fight infections. In striking contrast, in sterile injury, Kupffer cells also help summon neutrophils but DNA is not released and the neutrophils begin to dismantle injured and dead vasculature and help in revascularization. iNKT cells produce no interferon but rather make IL4 and help switch the system from an inflammatory to a healing phenotype. Macrophage that are key for helping repair infiltrate the liver from the peritoneal cavity in the first few hours and allow healing to take place.

Clinical Research

Pr. Jean-Michel Pawlotsky, Université Paris Est, Paris, France

Biography

Jean-Michel Pawlotsky, MD, PhD is Professor of Medicine at the University of Paris-Est. He is the Director of the National Reference Center for Viral Hepatitis B, C and Delta and of the Department of Virology at the Henri Mondor University Hospital in Créteil, France, and Director of the Academic Department "Viruses, Immunity and Cancers" (INSERM U955). He focuses on teaching, diagnosis and research in virology, primarily hepatitis viruses. Dr Pawlotsky earned his medical degree in Hepatology and Gastroenterology in 1992. In addition, he earned a Thesis in molecular virology from the University of Paris, France, and he is a graduate in virology from the Pasteur Institute in Paris and microbiology from the University of Paris. Dr Pawlotsky is active in numerous professional societies, and has been acting as the Secretary General of the European Association for the Study of the Liver (EASL) between 2005 and 2009. He is a member of the Scientific College and President of Scientific Commission 4 (CSS4) and Concerted Action 33 (AC33) of the French National Agency for Research on AIDS and Viral Hepatitis (ANRS). Dr Pawlotsky has been an Associate Editor of *Hepatology*, the official journal of the American Association for the Study of Liver Diseases (AASLD), between 2001 and 2006, and is currently an Associate Editor of *Gastroenterology*, the official journal of the American Gastroenterological Association (AGA). He is a member of the Editorial Board of the *Journal of Hepatology*, *Therapeutic Advances in Gastroenterology,* and *European Gastroenterology and Hepatology Review.* Dr Pawlotsky's noted career contributions include the publication of over 450 articles and book chapters in his areas of expertise and over 500 invited lectures at international meetings.

Abstract

Hepatitis C: Difficult to Cure Patients

New treatment regimens based on the use of combinations of hepatitis C virus (HCV) direct-acting antiviral (DAA) drugs now yield high rates of cure of infection. However, some patients remain difficult to cure. They include patients with decompensated cirrhosis, who have a contraindication to the use of protease inhibitors, patients infected with HCV genotype 3, patients with advanced chronic kidney disease, patients who failed a prior treatment with DAAs and selected resistant viruses. For all these groups, options exist but they are sometimes off-label and/or need careful monitoring in the absence of sufficient safety data. New therapeutic options will be available in 2017-2018. However, not all of them will solve the existing issues and no more drug classes will be available to treat difficult to cure HCV patients. Overall, the vast majority of patients with chronic HCV infection treated with oral DAAs will be cured, but a few of them may remain incurable.

Dr. Morris Sherman, University Health Network, Toronto, Canada

Biography

Morris Sherman, PhD, MB, FRCPC graduated in Medicine from the University of Witwatersrand in Johannesurg South Africa in 1972, and completed his initial training in Internal Medicine at Baragwanath Hospital in Soweto. Dr. Sherman obtained his Internal Medicine qualifications in 1976 and completed his Internal Medicine training at Groote Schuur Hospital, Cape Town South Africa. He undertook training in Gastroenterology and liver disease at Groote Schuur Hospital and then completed a PhD in 1982 in the Liver Research laboratory of the University of Cape Town. In 1982, Dr. Sherman undertook a 2 year post doctoral fellowship at the Albert Einstein College of Medicine in New York. Dr. Sherman joined the Toronto General Hospital as a staff gastroenterologist in 1984.
Dr. Sherman is currently Chairman of the Canadian Liver Foundation and President-elect of the International Liver Cancer Association. He is a past President of CASL and has been the recipient of the CASL Gold Medal Award, the CLF Distinguished Service Award and the Queens Jubilee Medal for services to hepatology in Canada. His major interests are chronic viral hepatitis and hepatocellular carcinoma.

Abstract

Towards Eradication of Hepatitis C

Today's treatment for hepatitis C is remarkably effective, allowing us to cure between 95-100% of patients with a single course of treatment. Hepatitis C is unique in that inhibition of viral replication results in clearance of virus. There is no animal reservoir, so that prevention of human to human transmission together with treatment of existing infection should lead to eradication of the disease over time.

However, there are numerous barriers to achieving this goal.

These include: Knowing the prevalence of hepatitis C and being able to identify those who have the disease, and getting them into care. The costs of the antiviral drugs is also a substantial barrier to widespread uptake of therapy.

Re-infection in 2017 occurs mainly in injection drug users. Sexual transmission is rare, person to person transmission in the absence of parenteral exposure is also rare. Therefore prevention of re-infection requires strategies to reduce the infection rate in injection drug users.

The majority of patients with hepatitis C in Canada however did not acquire their infection though injection dugs and are not at risk of transmitting disease to others. However, they are at at risk for the development of the complications of hepatitis C, namely cirrhosis, liver failure and liver cancer. The proportion of people in this group who have been identified is not known, nor is the proportion of those treated, let alone successfully treated.

In this population strategies have to be developed to identify those infected, such as "baby boomer" screening in addition to screening those with an identified risk. This will require recommendations from Health Canada and from professional societies.

Some populations will require additional strategies, such as First Nations people, in who access to healthcare is spotty and among acceptance of Western medicine is by no means universal.

Pharmaceutical companies are going to have to compromise on price. They have already compromised on price in many countries that cannot afford North American prices. Nor can we in Canada.

Health Services Research

Pr. Tim Caulfield, University of Alberta, Edmonton, Canada

Biography

Timothy Caulfield, LLM, FRSC, FCAHS is a Canada Research Chair in Health Law and Policy, a Professor in the Faculty of Law and the School of Public Health at the University of Alberta and Research Director of the Health Law Institute at the University of Alberta. Over the past several years he has been involved in a variety of interdisciplinary research endeavours that have allowed him to publish over 300 academic articles. He is a Fellow of the Trudeau Foundation and the Principal Investigator for a number of large interdisciplinary projects that explore the ethical, legal and health policy issues associated with a range of topics, including stem cell research, genetics, patient safety, the prevention of chronic disease, obesity policy, the commercialization of research, complementary and alternative medicine and access to health care. Professor Caulfield is and has been involved with a number of national and international policy and research ethics committees. He has won numerous academic awards and is a Fellow of the Royal Society of Canada and the Canadian Academy of Health Sciences. He writes frequently for the popular press and is the author of two recent national bestsellers: *The Cure for Everything: Untangling the Twisted Messages about Health, Fitness and Happiness* (Penguin 2012) and *Is Gwyneth Paltrow Wrong About Everything?: When Celebrity Culture and Science Clash* (Penguin 2015).

Abstract

Changing Minds: Popular Culture & Vaccination Myths

There is a ridiculous amount of science-free health and wellness advice floating around in popular culture. And much of this information is conflicting, misleading or just plain crazy. Indeed, these are strange times. Vaccination myths won't die. Bizarre celebrity health recommendations remain ridiculously popular. There is a growing market for unproven therapies. In this presentation Caulfield will explore why and how health information gets so twisted – especially in the context of vaccinations. This will include a consideration of the role of celebrity culture, social media, the erosion of public trust, our cognitive biases and the embrace of pseudoscience by some research institutions. He will conclude by reviewing what the best available evidence says about how to counter this trend.

Dr. Mark Tyndall, University of British Columbia, Vancouver, Canada

Biography

Mark Tyndall, MD, ScD, FRCPC is the Executive Medical Director of the BC Centre for Disease Control and Professor at the UBC School of Population and Public Health. He also serves as a deputy Provincial Health Officer for British Columbia and is the Director of the UBC Centre for Disease Control Research Institute. Prior to coming to Vancouver, he was the Chief of the Division of Infectious Diseases at the University of Ottawa and a Senior Scientist at the Ottawa Hospital Research Institute. His career awards include the Michael Smith Foundation for Health Research Senior Scholar Award and the Ontario HIV Treatment Network Applied Research Chair. He is an author on over 200 peer-reviewed publications, with a focus on HIV care and prevention, drug use, and public health intervention research.

Dr. Tyndall received his Medical degree and internal medicine training at McMaster University and his infectious diseases fellowship training at the University of Manitoba. He received a doctoral degree in epidemiology from Harvard University with a focus on health and human rights. From 1999 to 2010 he was the Program Director for Epidemiology at the BC Centre for Excellence in HIV/AIDS and was co-lead investigator on the evaluation of Insite, North America's first supervised injection site. He has conducted numerous community-based research projects in Vancouver and Ottawa, including epidemiologic studies of HIV and Hepatitis C transmission, antiretroviral access among injection drug users, and health care utilization among marginalized populations. Dr. Tyndall is a strong advocate and leader for public health in Canada and has fostered a number of community-based collaborations that have led to health policy changes.
http://www.bccdc.ca/util/about/UBCCDC/People/Faculty/Dr.+Mark+Tyndall.htm

Abstract

Surveillance Systems to Support a Public Health HCV Response

The introduction of a new generation of oral Hepatitis C treatment has dramatically changed the approach to Hepatitis C management in Canada. While there is an opportunity to cure people of the virus the approach should be based on sound public health principles and requires a rigorous surveillance system to assess competing health risks, the timing of treatment, the completion of therapy, reinfection rates and the long-term outcomes of people who are treated. In BC, the Hepatitis Testers cohort provides an example of a comprehensive surveillance program that is essential to support the role out of Hepatitis C treatment.

Social, Cultural, Environmental, and Population Health Research

Dr. Holly Hagan, New York University, New York, USA

Biography

Holly Hagan, PhD is a Professor at New York University Rory Meyers College of Nursing and Co-Director of the NIH Center for Drug Use and HIV Research at NYU. She received her doctorate in Epidemiology from the University of Washington School of Public Health and Community Medicine. Dr. Hagan's research has principally focused on the infectious disease consequences of substance use, and her main interest is in reducing the burden of hepatitis C virus infection in people who inject drugs. She is currently the Principal Investigator on an NIH RO1 that uses the methods of implementation science to optimize HCV control strategies in the United States at the national, regional and local level. Dr. Hagan is also PI on a case-control study of the onset of drug injection in rural New York State. She is a member of the WHO Global Burden of Disease Study Diseases and Injuries Group, and she served on the Institute of Medicine Committee on the Prevention and Control of Viral Hepatitis in the United States.

Abstract

Strategies to Enhance Prevention of Hepatitis C Infection and Reinfection in People who Inject Drugs

Background: Elimination of HCV infection in PWID cannot be achieved solely through HCV treatment; prevention of primary infection and re-infection must be maintained and improved to reduce the burden of disease in this population.
Methods: Systematic synthesis of the literature describing HCV infection and re-infection events in PWID, with meta-analysis; calculation of attributable risk estimates.
Results: Pooled global HCV incidence in PWID since 2008 is 17.2/100PY. Re-infection post successful HCV treatment in PWID is relatively low in the immediate post-treatment period but higher with longer follow-up (10% after 5 years). Syringe and equipment sharing each increase the risk of HCV infection approximately 2-fold, and the risk increases as HCV prevalence rises. More primary HCV infections are attributable to equipment sharing (20-60%) than syringe sharing (2-40%) because a greater proportion of PWID share equipment (50%) vs. syringes (10-20%). "High syringe coverage" combined with medication-assisted treatment reduces the risk of HCV infection by approximately 70%, but only a small minority of PWID have access to this combination of interventions. Evidence suggests that cooker and cotton distributed/PWID at syringe access programs in the US is low relative to syringes/PWID, and this may explain in part the persistence of cooker/cotton sharing.
Conclusion: The need for safe injection education, syringe and equipment access programs and supervised injection facilities persists. New approaches to expanding the reach and effectiveness of effective safe injection interventions will be reviewed, including methods to prevent re-infection post-HCV treatment.

Dr. Evan Wood, University of British Columbia, Vancouver, Canada

Biography

Evan Wood, MD, PhD, FRCPC, Dip. ABAM is a Professor in the Department of Medicine at the University of British Columbia where he holds the university's Canada Research Chair in Inner City Medicine. Dr. Wood is an internal medicine and addiction medicine physician, an active National Institutes on Drug Abuse funded investigator and is the Principal Investigator of the British Columbia node of the CIHR funded Canadian Research Initiative on Substance Misuse.

Abstract

Addressing Barriers to Integrating Evidence-Based Public Health and Addiction Treatment Interventions

Past research has described the substantial proportion of the global burden of disease that results from substance use disorder. This includes community concerns (e.g. impaired driving, drug-associated crime) as well as major public health challenges (e.g. blood-borne infections and overdose mortality). In this context, the last decade has seen the development of a growing range of innovative tools have been developed that enable physicians and allied health practitioners to identify, prevent and treat addictive disorders. This includes new knowledge on medications and psychosocial interventions. Unfortunately, while the science of addiction medicine continues to advance rapidly, the medical community has historically done a poor job of translating research into improved care of these patients. As a result, most individuals do not receive addiction care and, among those that do, care is often not consistent with evidence-based standards. This presentation will describe historical barriers to quality addiction care. It will also highlight the importance of integrating public health (e.g. harm reduction) and addiction treatment interventions and describe recent advances that are helping to improve systems of care for persons with substance use disorder.

Panel Discussion: Hepatitis C in Indigenous People

Chair: Dr. Alexandra King, Simon Fraser University, Burnaby, Canada

Biography

Alexandra King, MD, FRCPC, is a member of the Nipissing First Nation (Ontario). She is an Internal Medicine Specialist with a focus on HIV/AIDS, hepatitis C (HCV) and HIV/HCV co-infections. She works at the Lu'ma Medical Centre, an Indigenous health and wellness centre providing excellence in wholistic care using both Indigenous and Western healing approaches. As a First Nation researcher, Alexandra is a Principal Investigator on various CIHR research grants related to Indigenous people and HIV, HCV and co-infections. Other research interests include Indigenous wellness; Indigenous research ethics; peer-based navigation, support and research; landbased cultural healing and wellness retreats; and land-based research. She works in communitybased research and intervention research grounded in Indigenous epistemology, culture and wellness. She serves on many local and national initiatives, including the CanHepC: the Interagency Coalition on AIDS and Development, and the CIHR Canadian HIV Trials Network (CTN) Working Group for Health for People Who Use Drugs (co-lead), and the CIHR HIV/AIDS Research Advisory Committee (CHARAC).

Ms. Renée Masching, Canadian Aboriginal AIDS Network, Dartmouth, Canada

Biography

Renée Masching is First Nation from Southern Ontario. Professionally Renée's energies are dedicated to Aboriginal health. Her work in the Aboriginal HIV and AIDS community began in 1995 and she is honoured to contribute with dedication and determination. She earned her degrees in Social Work at McMaster University, with a CIHR research award for her Masters. Renée's research interests focus on community-based research frameworks, Indigenous knowledge and community health with an emphasis on HIV and AIDS. Presently, Renée is the Director of Research and Policy with the Canadian Aboriginal
AIDS Network and she lives with her husband, sons and pets by the ocean in Mi'kmaq Territory.

Ms. Norma Rabbitskin, Sturgeon Lake First Nation, Canada

Biography

Norma Rabbitskin is a fluent Cree speaker from Big River First Nation, Saskatchewan. She is currently employed by Sturgeon Lake First Nation as a Senior Health Nurse over seeing three streams: community health; primary care and home care program and assists with program development. She volunteers her time serving as Board member for CAAN and All Nations Hope Network (Regina). Her passion is assisting and being at service in developing community based programs that are strongly grounded in the healing value of re-engaging in traditional healing practices, parenting skills, acquiring traditional life-skills teachings from Elders /Knowledge keepers while maintaining the vitality of language in knowledge building and achieving Wellness in one's life.

Ms. Carrielynn Lund, Canadian Aboriginal AIDS Network, Edmonton, Canada

Biography

Carrielynn is a Métis consultant whose primary focus is on assisting Aboriginal communities to identify and address health and social issues that have a negative impact on children and their families. She has done extensive work in the area of heath research, particularly with Aboriginal youth and resilience and research ethics. Her extensive committee work includes service on the Aboriginal Healing Foundation (Treasurer), the Canadian Institute of Health Research Ethics Standing Committee and the Health Canada/Public Health Agency of Canada Research Ethics Board. Carrielynn sits on the Realize Board of Directors, contributes substantially to the CIHR review and process development and is highly skilled working within Network environments. Using her lived experience with Hep C, she works with researchers, organizations and governments to promote the inclusion of people living with Hep C in meaningful ways.

Dr. Greg Dore, University of New South Wales, Sydney, Australia

Biography

Gregory Dore, MBBS, PhD, FRACP, MPH is Head, Viral Hepatitis Clinical Research Program, Kirby Institute, UNSW Australia, and Infectious Diseases Physician, St Vincent's Hospital, Sydney, Australia. He has been involved in viral hepatitis and HIV epidemiological and clinical research, clinical care and public health policy for 20 years. He has developed extensive national and international collaborations, and is internationally recognized in the areas of HCV natural history and epidemiology, therapeutic strategies for acute and chronic HCV infection, particularly among people who inject drugs, and HCV elimination strategies.

He holds large-scale ongoing public sector research funding from U.S. National Institutes for Health and Australian National Health and Medical Research Council (NHMRC).

Professor Dore has been President of the Australasian Society for HIV Medicine (ASHM), a member of NHMRC Council, and is a NHMRC Practitioner Fellow.

Professor Dore established the St Vincent's Hospital viral hepatitis service in 1999, and has led its development into one of the leading national and international hepatitis C treatment services, with a particular focus on marginalised populations including people who inject drugs and homeless persons.

Abstract

Universal Access to Direct-Acting Antiviral Therapies in Australia: Early Lessons

Major recent advances in hepatitis C virus (HCV) therapeutic development, with availability of highly curative well tolerated directing-acting antiviral (DAA) regimens, have raised the prospect that treatment will provide considerable individual and population-level impact, including potential treatment as prevention. Australia has established the foundation to achieve elimination of HCV as a major public health issue, including WHO goals of 80% treated, 90% reduction in HCV incidence, and 65% reduction in liver disease mortality, within the next decade. Key elements of this foundation include: a high HCV diagnosis rate (80%); Australian Government subsidisation of DAA therapy for all adults with chronic HCV infection, without liver disease stage or drug and alcohol use restrictions; approval for all medical practitioners to prescribe DAA therapy; several DAA regimens funded; a well-established harm reduction framework that should provide access to PWID and reinfection risk reduction; and a sophisticated surveillance system to enable ongoing monitoring and evaluation of HCV elimination strategies. In the initial five months (March – July 2016) of the DAA program an estimated 26,000 patients initiated therapy, equivalent to 12% of the chronic HCV population. Prescriber patterns over this period demonstrate and increasing proportion of DAA prescriptions by primary care and other non-specialist physicians. Preliminary data also suggests a high proportion (>60%) of people with HCV-related cirrhosis have initiated DAA therapy, and that treatment uptake among people who inject drugs (PWID) is considerable, both key priority populations.

Panel Discussion: Achieving "Access for all" in Canada: How will we get there?

Chair: Dr. Jason Grebely, University of New South Wales, Sydney, Australia

Biography

Jason Grebely, PhD is an Associate Professor in the Viral Hepatitis Clinical Program at the Kirby Institute, UNSW Australia. Jason's research focuses on the epidemiology and treatment of HCV, with a focus on people who inject drugs.

Dr. Patricia Bacon, Action Hepatits Canada, Canada

Biography

Patricia Bacon, PhD is the Executive Director for Blood Ties Four Directions Centre in Whitehorse Yukon, an organization committed to eliminating barriers and creating opportunities for people to have equal access to health & wellness and to live in community with dignity. Patricia has been bringing innovative programs that support people who use drugs, people living with HIV and/or HCV and other vulnerable populations to Whitehorse since 2005.

Nationally, she has been a steering committee member of the Canadian Drug Policy Coalition and was the Pacific Regional Representative for the Canadian AIDS Society Board of Directors from 2008 to 2012.

Since 2013, Patricia is the Chair of Action Hepatitis Canada, a national coalition of organizations committed to working towards the elimination of viral hepatitis.

Patricia holds a Ph.D in human sexuality. As a pluralist, Patricia is a strong proponent of sexual and lifestyle diversity.

Dr. Mel Krajden, University of British Columbia, Vancouver, Canada

Biography

Mel Krajden MD, FRCPC is the Director of BC's Public Health Laboratory and the Medical Head, Hepatitis at the British Columbia Centre for Disease Control. He is also a Professor of Pathology and Laboratory Medicine at the University of British Columbia.

Dr. Krajden's clinical research involves integration of hepatitis prevention and care. His laboratory research involves the application of molecular and genomic techniques to: diagnose viruses; assess correlates between infection and clinical disease; monitor antiviral efficacy and track microbial infections for epidemiological purposes. He has extensive clinical trials expertise and is a Co-investigator/Mentor for CIHR funded National Research Training Program (CanHepC).

He spearheads the BC-Hepatitis C Tester's Cohort (BC-HTC) which contains 25 years of de-identified health information for 1.5 million British Columbians. It includes almost all: lab tests/results, medical visits, hospitalizations, prescriptions, cancer and mortality outcomes. This world-class dataset is able to determine net costs of services and health outcomes by different groups and adjust for confounders. The goal is to drive value-based practices from the bench to population level -- translating discovery into practice across a range of health related questions.

Dr. Jordan Feld, University of Toronto, Toronto, Canada

Biography

Jordan Feld, MD, Associate Professor of Medicine, University of Toronto, Ontario, Canada, graduated from medical school at the University of Toronto in 1997 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. Currently, Dr. Feld is clinician-scientist based at the Toronto General Hospital, Toronto Centre for Liver Disease and the McLaughlin-Rotman Centre for Global Health.

Oral Abstracts – résumés oraux

Biomedical Research

Oral presentation at 09h05

01.03

Solute Carrier NTCP Regulates Innate Antiviral Immune Responses Targeting HCV Infection of Hepatocytes

Che C. Colpitts[1, 2], Eloi R. Verrier[1, 2], Charlotte Bach[1, 2], Laura Heydmann[1, 2], Laetitia Zona[1, 2], Fei Xiao[1, 2], Christine Thumann[1, 2], Camille Sureau[3], Yujin Hoshida[4, 5], Catherine Schuster[1, 2], Mirjam B. Zeisel[1, 2], Thomas F. Baumert[1, 2, 6]

1. University of Strasbourg, Strasbourg, France, 2. Inserm U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, Strasbourg, France, 3. INTS, Laboratoire de Virologie Moléculaire, Paris, France, 4. Division of Liver Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA, 5. Liver Cancer Program, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA, 6. Institut Hospitalo-universitaire, Pôle Hépato-digestif, Nouvel Hôpital Civil, Strasbourg, France

Background: Hepatitis C virus (HCV) is still a major global health burden, with approximately 150 million people chronically infected even in the era of highly effective direct acting antivirals (DAAs). Chronically infected individuals are at increased risk for severe progressive liver disease, including cirrhosis and hepatocellular carcinoma. HCV interacts with an extensive network of host factors during infection of hepatocytes, which may provide novel targets for host-directed antivirals. The sodium taurocholate co-transporting polypeptide (NTCP), a bile acid transporter, was recently identified as the first receptor for hepatitis B virus (HBV) *(Yan et al. 2012 eLife)*. NTCP shows great promise as an antiviral target for chronic HBV infection. Interestingly, bile acids have been shown to affect HCV replication steps *(Chhatwal et al. 2012 PLoS ONE)*, although the potential roles of the bile acid transporter NTCP in HCV infection remains unclear. We recently found that NTCP mediates HCV entry into hepatocytes *(Colpitts et al. 5th Canadian Symposium on HCV, Montreal 2016)*.

Purpose: In this study, we aimed to characterize the mechanisms by which NTCP regulates HCV infection.

Method: N/A

Result(s): Exogenous NTCP expression in Huh7.5.1 hepatoma cells enhanced HCV entry, whereas siRNA- or shRNA-mediated knockdown of NTCP inhibited HCV infection in hepatoma cell lines and primary human hepatocytes (PHH). The effect of NTCP on HCV infection was mediated by its bile acid transport activity. Blocking NTCP-mediated bile acid uptake inhibited HCV entry by indirect mechanisms. Genome-wide microarray analyses and validation studies in Huh7.5.1 cells and PHH uncovered a role for NTCP-mediated bile acid transport in the regulation of innate antiviral responses. Blocking bile acid transport induced the expression of interferon-stimulated genes (ISGs), thereby restricing viral infection. In contrast, treatment of cells with bile acid decreased expression of ISGs to enhance viral infection. The effect of NTCP-mediated bile acid transport on HCV infection was dependent on the IFN signal transduction cascade and resulting IFN responses in PHH.

Conclusion(s): Our results uncover NTCP as a mediator of innate antiviral immune responses in the liver, and establish a role for NTCP in the infection process of multiple hepatotropic viruses. Collectively, our findings suggest a novel role for solute carriers in the regulation of innate antiviral responses. Furthermore, these findings enhance our understanding of hepatitis virus-host interactions and highlight NTCP as a novel antiviral target for HBV/HCV infection.

Oral presentation at 09h15

01.04

Intrahepatic IL-22 Correlates with Advanced Liver Fibrosis and Sensitizes HSCs to TGF-β Signaling in a p38-dependent Manner

Thomas Fabre, Manuel Flores, Genevieve Soucy, Bernard Willems, Jean-pierre Villeneuve, Marc Bilodeau, Naglaa Shoukry

CRCHUM, Montreal, QC

Background: Activation of hepatic stellate cells (HSCs) is a key event in the initiation of liver fibrosis. CD4 T cells can modulate positively or negatively this process. Briefly, Th1 cells despite their pro-inflammatory properties have anti-fibrogenic properties in contrast to Th2 cells. We and others have demonstrated that IL-17A produced by Th17 cells has pro-fibrogenic properties as it promotes activation of HSCs via different mechanisms. Th17 cells also produce IL-22, an enigmatic cytokine with proinflammatory and hepatoprotective properties. In addition, IL-10 produced by regulatory T cells (Treg) negatively modulates activation of HSCs.

Purpose: We hypothesized that liver fibrosis progression results from an alteration in the Th17/Treg ratio leading to an imbalance in the pro-fibrotic cytokine profile within the liver.

Method: We examined *ex vivo* the frequency of Th17 and Treg populations and the cytokine profile of intrahepatic lymphocytes isolated from liver biopsy samples (n=32). Then, we validated these data *in vivo* using transgenic mouse models of liver fibrosis and in vitro using primary human HSCs and transcriptomic analysis.

Result(s): We observed increased Th17/Treg ratio in advanced (F4, Metavir) as compared to moderate or non-fibrosis (F0-F2). Furthermore, we observed a bias towards Th17/Th9 cytokine profile in fibrotic livers with viral-hepatitis, whereas the cytokine profile was Th17/Th2 in non-viral hepatitis. All biopsies exhibited a 5-fold increase in IL-22 in fibrotic livers (p=0.0082) irrespective of aetiology. *In vivo*, lack of IL-22 signaling protects against thioacetamide-induced fibrosis. IL-22RA1 Knockout mice have reduced collagen deposition measured by picro-sirius red staining (p=0.0009) and pro-fibrotic genes expression (ACTA2, LOXL2, TIMP-I, TGFb1, COL1A1) in comparison to wild-type littermates. *In vitro* stimulation of primary human HSCs with IL-22 sensitized them to suboptimal doses of TGF-β. RNA-seq analysis demonstrated activation of p38 in HSCs in response to IL-22 and chemical inhibition of p38 suppressed the pro-fibrogenic effect of IL-22.

Conclusion(s): Our results suggest a dysregulated Th17/Treg ratio in advanced fibrosis coupled with distinct cytokine profile dependant on the aetiology of liver disease. Finally, we have identified IL-22 as a common factor in advanced liver fibrosis acting through sensitization of HSCs to TGF-β in a p38-dependent manner.

Clinical Research

Oral presentation at 10h45

02.03

Novel E2 Glycoprotein Tetramer Detects Hcv-Specific Memory B Cells

Maude Boisvert[1], Wanrui Zhang[2], Elizabeth J. Elrod[2], Nicole F. Bernard[3], Jean-Pierre Villeneuve[1, 4], Julie Bruneau[1, 5], Joseph Marcotrigiano[6], Naglaa H. Shoukry[1, 4], Arash Grakoui[2]

1. Centre de Recherche du Centre Hospitalier de l'Universite de Montreal (CRCHUM), Montreal, QC, 2. Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine; Yerkes National Primate Research Center, Emory Vaccine Center, Atlanta, GA, USA, 3. Research Institute of the McGill University Health Centre (RI-MUHC) and Division of Experimental Medicine, McGill University, Montreal, QC, 4. Departement de medecine, Faculte de medecine, Universite de Montreal, Montreal, QC, 5. Departement de medecine familiale et de medecine d'urgence, Faculte de medecine, Universite de Montreal, Montreal, QC, 6. Center for Advanced Biotechnology and Medicine, Dept of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, USA

Background: Hepatitis C virus infection becomes chronic in most cases while a minority (25%) can spontaneously resolve the infection. Specific E1 and E2 antibodies are generated late during acute infection but their role in spontaneous clearance remains debated. Investigation of the humoral responses during acute HCV infection requires identification of HCV-specific B cells.

Purpose: We hypothesized that expression of a biotinylated form of E2 glycoprotein and fluorescent tetramer generation would enable detection of HCV-specific B cells from patient peripheral blood samples.

Method: We have developed an expression vector enabling production and purification of biotinylated HCV E2 ectodomain. Fluorescent tetramers were generated by incubation with fluorescent streptavidin and they were used together with phenotypic B cells surface markers in flow cytometry experiments (FACS). Longitudinal PBMC samples from individuals who became chronically infected with HCV were used to detect HCV-specific B cells. The new B cell tetramer was also used to FACS sort HCV-specific memory B cells to perform B cell receptor (BCR) deep sequencing.

Result(s): Our new tetramer enabled us to detect HCV E2 specific memory B cells in most samples of HCV chronic infection (28/31). In a longitudinal study, we could detect HCV E2 specific B cells in only half of acute infection samples analysed (3/7), suggesting that in some subject the development of the humoral response might be delayed. We successfully isolated HCV E2 specific memory B cells from two samples and performed BCR deep sequencing. The BCR repertoire of both samples was focussed and had accumulated mutations, suggesting amplification of particular clonotypes and affinity maturation process.

Conclusion(s): Finally, our results suggest that our new B cell tetramer will be very useful to study the development of the humoral response to HCV infection. We showed that most infected individuals developed HCV-specific B cell population, but in some cases, HCV-specific B cells could only be detected during the chronic phase of the infection. Future studies examining subjects that spontaneously resolved the infection will enable characterization of the protective immune response and define the role of the humoral response in spontaneous clearance of HCV infection.

Oral presentation at 10h55

02.04

Evaluation of Xpert® HCV Viral Load Point-of-care Test for Detection of HCV Infection by Venipuncture-collected and Finger-stick Capillary Whole-blood Samples

Jason Grebely[1], Francois Lamoury[1], Behzad Hajarizadeh[1], Yasmin Mowat[1], Alison Marshall[1], Sahar Bajis[1], Janaki Amin[1], Julie Smith[2], Michael Edwards[3], Carla Gorton[4], Nadine Ezard[5], David Persing[6], Marika Kleman[6], Philip Cunningham[7], Beth Catlett[7], Gregory J. Dore[1], Tanya L. Aplegate[1]

1. The Kirby Institute, UNSW Australia, Sydney, NSW, Australia, 2. Matthew Talbot Hostel, St Vincent de Paul Society NSW Support Services, Sydney, NSW, Australia, 3. South Western Sydney Local Health District, Cabramatta, NSW, Australia, 4. Cairns Sexual Health Service, Cairns, QLD, Australia, 5. St Vincent's Hospital, Sydney, NSW, Australia, 6. Cepheid, Sunnyvale, CA, USA, 7. St Vincent's Applied Medical Research, Sydney, NSW, Australia

Background: Testing and diagnosis of HCV remains sub-optimal. Point-of-care HCV RNA testing enables the diagnosis of active infection in a single visit.

Purpose: The aim of this study was to evaluate the performance of the Xpert® HCV Viral Load assay from samples collected by venipuncture and finger-stick capillary whole-blood.

Method: Plasma and finger-stick capillary whole-blood samples were collected from participants in an observational cohort recruited from health services in Australia. The sensitivity and specificity of the Xpert® HCV Viral Load test for HCV RNA detection by venipuncture and finger-stick capillary whole-blood collection was compared to the Abbott RealTime HCV Viral Load assay.

Result(s): A total of 150 participants were included in this analysis (median age 44 years, 87% male, 65% with a history of injecting drug use). HCV RNA prevalence was 30% (n=45, 95% CI, 23%, 38%), based on Abbot RealTime. The sensitivity and specificity of the Xpert® HCV Viral Load assay for HCV RNA detection in plasma collected by venipuncture was 100% (95% CI, 92.0%, 100%) and 99.1% (95% CI, 94.9%, 100%), respectively. The sensitivity and specificity of the Xpert® HCV Viral Load assay for HCV RNA detection in samples collected by finger-stick capillary whole-blood was 95.5% (95% CI, 84.5%, 99.4%) and 98.1% (95% CI, 93.4%, 99.8%), respectively.

Conclusion(s): This study demonstrated good sensitivity and specificity of the Xpert® HCV Viral Load test for HCV RNA detection in capillary whole-blood collected by finger-stick and plasma collected by venipuncture compared to the Abbott RealTime HCV Viral Load assay.

Health Services Research

Oral presentation at 11h55

03.03

HCV in the Real World: Adherence During Directly Acting Antiviral HCV Treatment Amongst Active Drug Users at a Community Based Program in Toronto

Kate Mason[1, 4], Zoe Dodd[1, 4], Mary Guyton[3, 4], Bernadette Lettner[1, 4], Tom Barnard[4], Jason Altenberg[1, 4], Jeff Powis[2, 4]

1. South Riverdale Community Health Centre, Toronto, ON, 2. Michael Garron Hospital, Toronto, ON, 3. Sherbourne Health Centre, Toronto, ON, 4. Toronto Community Hep C Program, Toronto, ON

Background: Direct acting antiviral (DAA) treatments for Hepatitis C (HCV) are now widely available with sustained viral response (SVR) rates of >90%. Despite a disproportionately high burden of HCV among people who use drugs, few have historically accessed HCV treatment. A major predictor of response to DAAs is adherence, yet few real world studies of DAAs exist among people who use drugs. Gaining a greater understanding of DAA adherence among people who use drugs is instrumental to adequately addressing the current HCV epidemic.

Purpose: The aim of this study was to evaluate patterns and factors associated with adherence among people who use drugs and who were receiving HCV care and treatment through the Toronto Community Hep C Program, a community-based, multidisciplinary, harm reduction HCV treatment program.

Method: This study was a prospective evaluation of chronic HCV patients initiating DAA treatment without interferon. Self-report medication adherence questionnaires were completed weekly. Pre/post treatment questionnaires examined socio-demographics, program engagement, co-morbidities and substance use. Missing adherence data was counted as a missed dose.

Result(s): 66 participants who completed treatment were analyzed of 73 people enrolled to-date. 74% were male with an average age of 54 years. One third (35%) had cirrhosis. The majority (68%) reported income from disability benefits and 27% had unstable housing. Only 23% received opiate substitution therapy (OST). In the month before treatment, 11% reported injecting drugs, 30% reported non-injection substance use (other than marijuana) and 17% reported heavy drinking (6+ drinks at one time).

86% were treatment naïve. 74% received sofosbuvir/ledipasvir (8-24 weeks) and 23% Sofosbuvir/Ribarvin (12-24 weeks). SVR rates were available in 56 with an intention to treat SVR rate of 87.5%. Only one participant did not complete treatment and two died prior to SVR. Overall, 94% of treatment weeks had no missed doses. One third (35%) of participants had at least one missed dose; however, the average number of missed doses was only 1.6 (sd=1.47). Factors associated with strong adherence included social support ($p < 0.01$), and taking sofosbuvir/ledipasvir ($p=0.01$). Prior history of mental health hospitalization was associated with missed doses ($p = 0.03$). The most common reasons cited for missed doses were "I just forgot" (n=12), drug/alcohol use interfered (n=7) or could not access the pills (n=6).

Conclusion(s): This study provides insight into the HCV treatment adherence patterns of marginalized people who use drugs as well as factors associated with adherence. It demonstrates that, in the context of high rates of substance use, a community-based model of HCV treatment can support adherence and positive HCV treatment outcomes.

Oral presentation at 12h05

03.04

Development of a Provincial HCV Elimination Strategy

Geri Hirsch[1, 2], Yvonne Lynch-Hill[2], Carla Burgess[2], Lynn Johnston[1, 2], Ian Davis[1, 2], Todd Hatchette[1, 2], Kevork Peltekian[1, 2], Marie Laryea[1, 2], Shelly McNeil[1, 2], Sharon Oldford[1], Lisa Barrett[1]

1. Dalhousie University, Halifax, NS, 2. Nova Scotia Health Authority, Halifax, NS

Background: HCV infection is a burgeoning health problem in Canada, and is one of the most frequent causes of liver disease and liver transplant in the country. The Public Health Agency of Canada recognizes blood borne pathogens such as HCV as a major health risk, as well as the value of a public health, elimination-based approach to these public health threats. To effectively move forward with elimination strategies, programmatic approaches to infection prevention, screening, harm reduction, access to care and treatment are essential.

Purpose: To address barriers to care and develop a multi-phase elimination plan

Method: Between September 2015 and August 2016, HCV care providers, government, and HCV community groups partnered to review current practices and design a province-wide HCV model of care in Nova Scotia, Canada. Key nodes that were critical to success were identified and through a longitudinal iterative consensus process, first steps for the program were prioritized and planned

Result(s): The move to a single health authority was viewed as a critical piece of the implementation plan. To achieve elimination, the multi-year program initially focuses on curing already known HCV patients, then expands to newly identified and vulnerable HCV positive people in the general community through non-specialist, in-place providers. Implementation occurs in 3 phases, the first of which includes: central reporting of new HCV cases to the HCV program; coordinated access to standardized care through centralized triage and referral; and strategy assessment through development of a provincial HCV registry and linkage to provincial databases for health care service delivery and patient oriented outcomes data. Initial implementation of the first phase begins in December 2016.

Conclusion(s): HCV elimination in a sustainable and responsible fashion within a public payer system requires vision, innovative partnership, and a solid, grounded strategy. Pragmatic, community-based, evaluation embedded approaches that blend practical research and evaluation design along with motivated providers and community members are all essential to provincial HCV elimination strategy development.

Social, Cultural, Environmental, and Population Health Research

Oral presentation at 14h20

04.03

Short Injection Cessation Episodes as Opportunities for Hepatitis C Prevention

Emmanuel Fortier[1, 2], Andreea Adelina Artenie[2, 3], Didier Jutras-Aswad[2, 4], Élise Roy[5, 6], Jason Grebely[7], Julie Bruneau[1, 2]

1. Department of Family and Emergency Medicine, Faculty of Medicine, Université de Montréal, Montréal, QC, 2. CHUM Research Center, Centre hospitalier de l'Université de Montréal, Montréal, QC, 3. Department of Social and Preventive Medicine, School of Public Health, Université de Montréal, Montréal, QC, 4. Department of Psychiatry, Faculty of Medicine, Université de Montréal, Montréal, QC, 5. Addiction Research and Study Program, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Longueuil, QC, 6. Institut national de santé publique du Québec, Montréal, QC, 7. The Kirby Institute, UNSW Australia, Sydney, NSW, Australia

Background: In Canada, the majority of new and existing cases of hepatitis C virus (HCV) infection occur among people who inject drugs (PWID). For most, drug injection has been shown to follow a dynamic process characterized by transitions in and out of injection. We have previously shown that short injection cessation episodes are associated with a reduced likelihood of receptive sharing of injection material when resuming drug injection. Given that receptive sharing of injection material is likely to result in parenteral HCV exposure, we hypothesized that engaging in short injection cessation episodes would be associated with a reduced risk of HCV infection.

Purpose: This investigation aimed to assess the association between HCV infection and engagement in short injection cessation episodes, when considering one-month injection cessation periods.

Method: The Hepatitis Cohort (HEPCO) study is an observational cohort study of PWID recruited and followed longitudinally in Montréal (QC, Canada). At 3-month intervals between March 2011 and December 2014, HCV-uninfected (HCV RNA-negative) participants, at-risk of either primary HCV infection (anti-HCV-negative) or reinfection/recurrence (anti-HCV-positive), were tested for HCV. They also completed an interviewer-administered questionnaire eliciting information on sociodemographic characteristics, drug use, drug-related behaviours, and treatments. HCV infections were estimated to occur at the midpoint between the last negative and the first positive test. Drug injection in the past 3 months was categorized as injecting within 0 month (no drug injection), 1 or 2 months (short injection cessation episodes), or all 3 months (no injection cessation). Cox regression analyses with time-dependent covariates were performed. Kaplan-Meier failure curves for multiple-record-per-subject data were estimated and compared using the log-rank test.

Result(s): 311 participants with ≥1 follow-up visit (mean age 40 years, 82% male, 47% anti-HCV positive) contributed 556.7 person-years of follow-up between March 2011 and December 2014. HCV incidence was 11.3 per 100 person-years [95% confidence interval (CI), 8.8-14.4]. At baseline, 60% (n=188) of the participants reported no injection cessation in the past 3 months, 25% (n=79) reported short injection cessation episodes, and 14% (n=44) reported no drug injection. In univariate Cox models, engagement in short injection cessation episodes and no drug injection were significantly associated with a reduced risk of HCV infection [short injection cessation episodes: hazard ratio (HR) 0.36, 95%CI 0.17-0.77; no drug injection: HR 0.23, 95%CI 0.09-0.58] compared to no drug cessation. Associations remained statistically significant for both short injection cessation episodes (HR 0.40, 95%CI 0.19-0.86) and no drug injection (HR 0.30, 95%CI 0.12-0.77) in models adjusted for age, gender, and opioid substitution treatment. There was no evidence of effect modification by the anti-HCV status at baseline. Kaplan-Meier analyses were consistent with Cox regression analyses, with a significant difference between failure curves (P = 0.0002, log-rank test).

Conclusion(s): Engaging in short injection cessation episodes was associated with a reduced risk of HCV infection. Our findings suggest that injection cessation, even for short periods, may trigger subsequent safer behaviours, and could inform harm reduction interventions. Further work is needed to contextualize short injection cessation episodes in the drug injection trajectory.

Oral presentation at 14h30

04.04

Hepatitis C Treatment and Care in Big River First Nation Community: Barriers to Accessing Healthcare Services

Mamata Pandey[1], Marwa Farag[2], Leslie Ann Smith[4], Derek Klein[5], Ruby Mcadam[5], Stuart Skinner[1, 3]

1. Regina Qu'Appelle Health Region, Regina, SK, 2. University of Saskatchewan, Saskatoon, SK, 3. University of Saskatchewan, Regina, SK, 4. Health Canada, Big River First Nation, SK, 5. Big River First Nation, Big River First Nation, SK

Background: Saskatchewan has one of the highest rates of hepatitis C in Canada. Hepatitis C disproportionally affects Indigenous people, with Indigenous populations having rates 4-5 times higher than non-Indigenous populations. Indigenous populations are more likely to inject drugs and engage in high-risk sexual behaviour than non-indigenous population, which increases the chances of acquiring hepatitis C.

Purpose: The purpose of the study was to identify barriers to healthcare access for hepatitis C patients residing in Big River, a rural and remote First Nation community in northern Saskatchewan. The second objective was to identify resources available within Big River First Nation community that can support a mobile clinic that can be employed to bring standardised treatment to residents in their community.

Method: A two hour focus group was carried out with elders, administrative staff, healthcare providers and community representatives at Big River First Nation community. Additionally, 11 individual interviews were carried out with hepatitis C patients to learn about the challenges they face when trying to access healthcare for hepatitis C.

Result(s): Thematic analysis of the focus group and interview data indicates that screening, assessment and treatment for hepatitis C conditions in the community are only available at a tertiary care center approximately 100 km away. A lack of adequate transportation and lack of knowledge about ways to navigate through the urban tertiary care center act as major barriers to accessing healthcare. Patients also mentioned that racism, lack of information on eligibility for treatment, lack of cultural support and issues with confidentiality also sometimes discourage them from seeking healthcare services for their condition. The community members and patients agreed that poverty, addictions and poor living conditions lead to poor health outcomes for residents in Indigenous communities.

A variety of healthcare services are provided to residents through a local healthcare centre at Big River First Nation community. Culturally appropriate and supportive healthcare programs are run by federally funded nursing staff in collaboration with community members. Nursing staff ensure patients are connected with appropriate care, either through the community healthcare centre or through nearby tertiary care centres. Program delivery is guided by the needs of the community as identified or perceived by nursing staff. Chief and Council hold consultation with the community members and residents to inform and discuss health initiatives and prevention programs offered through the community healthcare centre. The Chief, Council and focus group participants all agreed that hepatitis C screening and treatment was a priority and that the nursing staff would be supportive of the implementation of a mobile clinic to bring standardised care to the residents in their community.

Conclusion(s): Systemic and socioeconomic determinants of health continue to hinder access to healthcare services for residents in Indigenous communities. Lack of cultural support, issues with confidentiality and addictions can interfere with screening and adherence to hepatitis C treatment. A mobile clinic implemented with support from the existing nursing staff within the community can improve access to standardised screening and treatment for hepatitis C.

Posters - Affiches

Biomedical Research

P.01

Reprogramming of Exhausted T Cells Following Cure of Chronic Viral Infection

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Background: T-cell exhaustion is a hallmark of immunological failure to control chronic viral infection and cancer. Blocking inhibitory receptors such as programmed death-1 (PD-1) can re-invigorate exhausted T cells (T_{EX}) in animal models of chronic viral infection and in cancer patients. However, clinically, many patients still fail to achieve durable tumor control with checkpoint inhibitors. Thus, a deeper understanding of other molecular pathways and epigenetic mechanisms underlying reversal of T-cell exhaustion is needed. Human chronic infection by HCV represents a unique model, where treatment with novel DAAs leads to complete virological cure even following years of chronic infection. Whether T_{EX} in these cured subjects convert to functional and durable memory cells remains unknown.

Purpose: To investigate whether T_{EX} become "reprogrammed" into more functional effector or memory T cells (T_{MEM}) following cure of chronic disease by non-immunological treatment.

Method: In order to study the reprogramming of T_{EX} following cure of chronic viral infection, we will examine virus-specific T cells from chronic HCV patients cured by DAA treatment and from mice cured of chronic lymphocytic choriomeningitis virus (LCMV). We will determine the cellular, transcriptional, and epigenetic profiles of these cells. Using our well-defined tractable mouse model we will dissect the molecular pathways and mechanisms underlying the changes in T_{EX} following the elimination of continuous exposure to viral antigens. These mechanistic discoveries and predictions from the LCMV model would then be extended and tested in the HCV model in humans.

Result(s): Our data indicate that some markers of exhaustion (including PD-1) are downregulated, while some markers of T_{MEM} may be recovered upon cure of infection. Nevertheless, other aspects of T_{EX} biology do not appear to be corrected simply by eliminating exposure to chronic infection. Ongoing studies are investigating whether these changes are linked to selective recovery of a specific subset of T_{EX}, and whether improvements are accompanied by changes in the epigenetic landscape of these previously-exhausted T cells.

Conclusion(s): We expect these studies to enhance our understanding of the epigenetic signatures and the immunological mechanisms of recovery of T_{EX}. These studies should also identify candidate transcriptional circuits differentially regulated in readily-recovered T cells that could represent novel therapeutic targets for reversal of immune-exhaustion.

P.02

Fluorescent Labeling of the HCV Helicase to Monitor Nucleic Acid Unwinding by FRET

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Background: The hepatitis C virus (HCV) non-structural protein 3 (NS3) contains a helicase activity essential for viral replication. The helicase binds to single-stranded (ss) regions of nucleic acids and unwinds duplexes in an ATP-dependent manner. The mechanism by which the helicase disrupts RNA secondary structure in the viral genome to make way for the replication machinery remains elusive. Several mechanisms have been proposed, which include an active mechanism whereby the helicase actively engages the ss/double-stranded (ds) junction of the substrate to unwind the duplex, and a passive mechanism where the helicase binds and translocates along a ss nucleic acid overhang, taking advantage of transient melting at the ss/ds junction.

Purpose: To generate site-specific fluorescently labeled HCV helicase as a tool to track the movement of the enzyme during unwinding and monitor the dynamics of this process.

Method: The unnatural amino acid p-azido phenylalanine was incorporated in the recombinant HCV helicase during protein expression in *E. coli*. Using a strain-promoted azide-alkyne click reaction we developed a one-step process to screen for both protein expression and reactivity of the azido group from the incorporated unnatural amino acid. After successfully identifying a position in the helicase for incorporation of the unnatural amino acid and fluorescent labeling with a Cy5 fluorophore, we used the site-specific fluorescently labeled enzyme to monitor the location of binding by Förster Resonance Energy Transfer (FRET) to DNA substrates modified with an appropriate Cy3 donor fluorophore.

Result(s): Using our approach to simultaneously screen for protein expression with the unnatural amino acid as well as reactivity of the incorporated unnatural amino acid, we identified a position in the HCV helicase suitable for incorporation of p-azido phenylalanine and fluorescent labeling with a Cy5 fluorescent dye. We then developed a plate-based FRET assay to confirm that we could detect the location of binding on a DNA substrate in a distance-dependent manner. Finally, using single molecule fluorescence microscopy we were able to detect binding by FRET for individual enzyme-substrate complexes.

Conclusion(s): The FRET-based assay has the potential to monitor distinct steps of the unwinding process. Single molecule FRET experiments will provide a deeper understanding of the mechanism by which the helicase interacts with its substrate during unwinding and the dynamics involved in this process.

P.03

The Role of Macrophage Subsets in CD8+T-cell Function in Chronic HCV Infection

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Background: Chronic HCV infection causes generalized $CD8^+$T-cell impairment, not limited to HCV-specific $CD8^+$T-cells. In such an inflammatory hepatic disease, infiltrating monocyte-derived macrophages (MDM) contribute to a micro-environment that could influence cells trafficking through the liver, including $CD8^+$T-cells. These MDM can differentiate into M1 (classically-activated) and M2a, M2b, M2c (alternatively-activated) subsets with pro-and anti-inflammatory functions, respectively. Whether MDM subset generation in chronic HCV infection is altered is unknown. Furthermore, how these subsets influence $CD8^+$ T-cell function needs investigation. We hypothesize that MDM subset phenotypes are altered in chronic HCV infection, thereby contributing to observed generalized $CD8^+$T-cell dysfunction.

Purpose: By investigating the role of macrophage subsets in mediating essential $CD8^+$T-cell functions may provide insight regarding the importance of MDM subsets in the liver. Furthermore, any alteration of MDM subset generation in chronic HCV infection may have consequences for $CD8^+$T-cell function. Research findings can pave the path to immune-therapy that modulates MDM subsets in the liver thereby addressing a potential contributor to dysfunctional $CD8^+$T-cells.

Method: MDM subsets were generated from human peripheral blood collected from healthy controls and individuals with chronic HCV infection. MDM subset phenotypes were confirmed by analyzing surface receptor expression using flow cytometry and quantifying secreted cytokines in culture supernatants by immunobead multiplex assay (Magpix). Autologous co-culture of MDM subsets with isolated $CD8^+$T-cells in health enabled the assessment of resulting $CD8^+$T-cell functions.

Result(s): MDM subset phenotyping in chronic HCV infection suggests M2b cells have a higher percentage of $CD163^+$ than M0 subset whereas in health, they showed no significant difference. The M1 subset has a significantly higher percentage of $CD86^+$ cell compared to M0 cells in HCV infection, whereas no such difference was observed in health. The M2a subset has higher expression (MFI) of CD86 than the M2b subset in health, but not in infection. MDM subsets generated from monocytes of HCV-infected individuals did not produce TNF-α, whereas in health, M0, M1 and M2c cells produced significant amounts of this cytokine. In HCV infection, the concentration of IL-6 in M2a subset supernatants was significantly higher than healthy controls. No differences were observed in the concentrations of IL-10, IL-12p70 and IFN-γ between the subject groups. In uninfected controls, co-culturing $CD8^+$T-cells with M1 macrophages significantly increased the percentage of $perforin^+$, $CD107a^+$ and IFN-$γ^+$ $CD8^+$T-cells, compared to $CD8^+$T-cells alone. In addition, this increased percentage of $perforin^+$ and $CD107a^+$ cells was greater that that induced by M2a cells. Co-culturing with M2c cells significantly increased the percentage of CD107a+ cells compared to $CD8^+$T-cells alone.

Conclusion(s): Phenotypic alterations in health and chronic HCV infection are evident both in terms of surface receptors and secreted cytokines suggesting impairment of MDM subsets. The importance of an M1 phenotype in being able to prime $CD8^+$T-cells and induce perforin and CD107a is evident. How the altered phenotype of MDM subsets in chronic HCV infection will influence the $CD8^+$T-cell function, needs to be further investigated, as it may prove to be a significant mediator of immune dysfunction as the disease progresses.

P.04

Identification of Argonaute Isoforms Involved in Small RNA-Dependent Promotion of HCV Replication

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Background: A liver-specific microRNA, miR-122, protects the Hepatitis C Virus (HCV) genome from degradation and promotes its replication by a poorly understood mechanism. Argonaute (Ago) proteins are host multifunctional proteins involved in the activity of miRNAs, and are also necessary for miR-122 promotion of the HCV life cycle. Humans express 4 Ago isoforms, Ago1-4, but Ago2 has generally been viewed as the primary Ago involved in the HCV life cycle.

Purpose: Identify other Ago isoforms, which, in addition to Ago2, can participate in the promotion of HCV replication dependent on small RNAs.

Method: To investigate the specific role of Ago2 and the impact of the other Ago isoforms in the HCV life-cycle we generated Ago2 knockout (KO) cells using the all-in-one-vector approach of the CRISPR/Cas9 technology. To identify Ago isoforms capable of binding to the HCV 5'UTR depending on small RNAs we performed biotinylated RNA pull-downs using streptavidin magnetic beads and oligoribonucleotide baits representing the 5' 47 nucleotides of HCV RNA conjugated to biotin. Proteins were pulled down from lysates of Huh-7.5 wild-type, miR-122 KO or Ago2 KO cells. Pulled down proteins were resolved by SDS-PAGE and subjected to immunoblotting with Ago-specific antibodies.

Result(s): We generated two cell lines with confirmed biallelic indel mutations in the Ago2 gene. Both showed undetectable levels of Ago2 expression by Western blot. We confirmed that the Ago2 KO cells were devoid of knockdown activity by assaying for small interfering RNAs (siRNAs) directed cleavage activity. Unexpectedly, Ago2 KO cells supported HCV replication but to lower levels (50-70%) than the wild-type cells. This indicates that at least one of the other Ago isoforms is able to sustain high levels of HCV replication when Ago2 is not present. Additionally, we showed that in the absence of Ago2's cleavage activity, perfect match small RNAs directed against miR-122 binding site 1 can promote HCV replication as miR-122 mimics. Our biotinylated RNA pull-down assays confirmed that Ago2 binding to the HCV 5'UTR is dependent on binding of miR-122 or other small RNAs. Interestingly, miR-122 and the other small RNAs preferentially pulled down different Ago isoforms. Specifically, one small RNA that exhibited HCV replication promotion efficiency greater than that of miR-122 showed a preference for association with non-slicer Agos.

Conclusion(s): Our results suggest that miR-122 specific binding pattern is dispensable for HCV replication in the absence of the slicer activity of Ago2 and that in this case other small RNAs that bind to the 5' UTR can substitute for miR-122. In addition, we have determined that Ago isoforms other than Ago2 can support miR-122 promotion of HCV replication, and that some small RNAs may preferentially associate with different Ago isoforms. These results support our hypothesis that isoforms other than Ago2 can promote HCV replication dependent on small RNAs, and suggest preferential loading of small RNAs into the different Ago isoforms. These data will provide information on the mechanism by which miR-122 promotes the HCV life-cycle and also may provide insight into roles of the different Ago isoforms in miRNA activity.

P.05

Development of a Novel Method of Viral Protein Tracking in Host Cells

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Background: HCV contains a perplexing protein that has a number of proposed functions. This protein, termed p7, is essential for virus infectivity in vivo, however its exact function is debated. Current research into the function of p7 has been limited since there are no reliable antibodies available for the visualization of this protein.

Purpose: The ability to label p7 within the context of a replicating virus would allow us to analyze p7 activity in live cells.

Method: Recombinant strains of HCV were engineered to contain the TAG amber codon at various positions within p7. Huh-7.5 cells were transfected first with a DNA plasmid the tRNA and synthetase for unnatural amino acid incorporation, followed by transfection with mutant viral RNAs. The cells were then examined for the presence of viral proteins using immunofluorescence and infectivity was measured by titering infectious virus in culture supernatants.

Result(s): The system has been tested and preliminary results indicated that a viable virus containing the unnatural amino acid has been created. The titer detected indicates that the virus is completing the full life cycle in Huh-7.5 cells. A relatively low viral titer has been measured, as expected, however we will optimize the system to increase the viral titer. Once we established that an unnatural amino acid could successfully be incorporated, we tested for incorporation using a fluorescent unnatural amino acid (ANAP). Initial results indicated that ANAP has been incorporated based on the presence of fluorescence in the transfected cells. We are optimizing the system to reduce cellular incorporation of the fluorescent unnatural amino acid. To increase transfection efficiency, we are creating a stably transfected cell line.

Conclusion(s): We have successfully created a recombinant strain of virus containing an unnatural amino acid which will allow for labeling of p7. The ability to label p7 within the context of a replicating virus will allow us to analyze p7 localization within the cell, as well as co-localization with other viral and cellular proteins, and all of these analyses could theoretically be done in live cells. The strategy employed here will represent a novel approach for visualizing HCV proteins within virus-infected cells and could then be applied to the study of other viruses.

P.06

Investigation of the Protective Role of miR-122 Against Cellular Sensors of RNA at the 5' Terminus of Hepatitis C Virus Genome

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Background: Approximately 200 million individuals worldwide are infected by hepatitis C virus (HCV). MicroRNA-122 (miR-122) is a highly abundant liver-specific microRNA shown to interact at two "tandem" microRNA-binding sites in the 5' end of the HCV genome. This unusual interaction promotes HCV RNA accumulation in both HCV-infected cells and the livers of infected patients. Previous investigation of the stabilization of HCV RNA by miR-122 shows a slowed rate of decay in cells supplemented with miR-122 duplexes. Recent findings demonstrate that miR-122 protects HCV RNA from degradation by exoribonucleases. These results support a model whereby miR-122 acts to shield the 5' terminus of the viral RNA, preventing its degradation or recognition by nucleases or cellular sensors of RNA. The dsRNA-dependent protein kinase (PKR) is activated mainly by long dsRNA, but short RNA stem-loops are able to activate PKR in a 5' triphosphate-dependent manner, which suggests that the 3' overhang created by miR-122 binding to the HCV 5' terminus may also prevent recognition of HCV by PKR. In addition, the LGP2 protein is another RIG-I-like receptor that binds to dsRNA and acts as an on/off switch for RIG-I signaling.

Purpose: We hypothesize that miR-122 forms a distinct complex with host and/or viral proteins that together protect the HCV 5' terminus from recognition by cellular sensors of RNA, such as PKR and LGP2. Herein, we are investigating a protective role for miR-122 against these cellular sensors of RNA.

Method: We are inhibiting PKR and LGP2 expression by siRNA knockdown in Huh7.5 cells, in the presence or absence of miR-122. To investigate the stabilization of the viral RNA in this context, we are montitoring viral RNA accumulation by luciferase assay and northern blot analyses. To investigate the contribution of miR-122, we are using miR-122 site mutants or sequestering miR-122 using an antisense locked nucleic acid inhibitor.

Result(s): We demonstrate that LGP2 expression is increased early during HCV infection in Huh7.5 cells. Knockdown of PKR or LGP2 in the presence of miR-122 has no significant effect on HCV RNA accumulation. Our current focus is on elucidating the effect of PKR and LGP2 knockdown on HCV RNA accumulation in miR-122 site mutants under limited miR-122 conditions or during miR-122 sequestration.

Conclusion(s): We expect that the results will reveal whether miR-122 binding to the 5' terminus of HCV is protective against recognition by the cellular sensors of RNA, PKR and LGP2 and together with our collaborators in the Wilson lab, we are investigating the role of several other cellular sensors of RNA, including IFIT-1, IFIT-5, RIG-I and MAVS. These results will provide insights into whether miR-122 binding to the HCV genome protects the viral RNA from recognition by cellular sensors of RNA and has implications for the mechanisms of miR-122 mediated promotion of HCV RNA accumulation.

P.07

Dissecting the Role of the poly(C)-binding Protein 2 in the Hepatitis C Virus Life Cycle

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

Purpose: We aim to clarify the role of PCBP2 in the HCV life cycle, and to identify the specific step(s) of viral replication that are affected by PCBP2.

Method: We are using the HCV cell culture system (specifically the JFH-1T strain) in Huh-7.5 cells to assess how viral protein synthesis, viral RNA accumulation, and the production of infectious viral particles is affected by knockdown of endogenous PCBP2 or the overexpression of a FLAG-tagged PCBP2 construct. We are further examining the effect of PCBP2 depletion on viral IRES-mediated translation as measured using a dual-reporter luciferase assay system.

Result(s): We will show that siRNA-mediated PCBP2 knockdown inhibits HCV protein expression, RNA accumulation, and infectious particle production. We will also show preliminary results that try to tease apart whether this effect is due to a defect in viral translation, RNA replication, or both.

Conclusion(s): We anticipate that investigating PCBP2-HCV interactions will help clarify the role of this host protein in the viral life cycle, and will provide a model for the regulation of viral RNA accumulation, and/or the switch from translation to replication. These mechanisms may also be applicable to other important human pathogens related to HCV, such as the Dengue or Zika viruses.

P.08

Liver Fibrosis and Altered or Impaired CD8+ T-cell Function in Chronic HCV Infection

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Background: Chronic infection ensues in unresolved hepatitis C virus (HCV)-infections, and many experience moderate to severe liver fibrosis, cirrhosis and hepatocellular carcinoma. Disease is characterized in part by immune dysfunction, including that of HCV-specific cytotoxic $CD8^+$ T-cells (CTL) which are important for viral clearance. We previously identified a generalized immune impairment that is not limited to virus-specific T-cells, finding that bulk CD8+ T-cell signaling and survival deficits were potentially associated with liver fibrosis. The mechanisms of this immune impairment have not been determined. Since the liver filters one third of the body's blood volume every minute, its environment may influence circulating immune cells. Therefore, we hypothesized that $CD8^+$ T-cell effector functions are impaired in a generalized manner in HCV infection and that this is associated with the degree of liver fibrosis. Furthermore, this impairment will persist given the slow, if any, reversal of fibrosis following HCV cure.

Purpose: N/A

Method: Isolated circulating $CD8^+$ T cells from control subjects and untreated, HCV-infected individuals were assessed for their subset distribution, cytokine expression, and cytolytic activity. Subsets of $CD8^+$ T cells will be distinguished based on CD45RA, CCR7 and CD27 expression by flow cytometry. The ability of the $CD8^+$ T cells to kill will be assessed using a mixed lymphocyte reaction assay. Results will be tested for correlation to liver fibrotic scores. In addition, a longitudinal study of patients receiving direct-acting antiviral HCV therapy will determine the reversibility of the observed $CD8^+$ T cell impairment and potential correlation with fibrosis.

Result(s): The proportion of naïve CD8+ T-cells is reduced in untreated HCV+ individuals with high fibrosis (F3-4), reflected somewhat in increases in memory cell subsets. The percentage of anti-CD3/CD28-induced IFN-g was increasingly higher in naïve and effector memory cells in those with a high degree of fibrosis. Detection of CD107, a marker of cytolytic molecule release, suggested an inducible effect in all groups. Decreased numbers of memory cells containing perforin may confirm this, particularly in the context of high fibrosis. Whether this results in more target lysis will be determined by an innovative cytolysis assay we developed to quantify cell death by CD8+ T-cells by flow cytometry. Our ongoing study of HCV-treated individuals will indicate whether these altered effector functions are resolved following HCV cure with remaining fibrosis.

Conclusion(s): While these results do not show a reduction in CTL activity among CD8+ T-cells, a heightened response suggests the potential for widespread inappropriate cytotoxicity. Whether this reflects a lack of immunoregulation or indicates a systemic immune activation seen in chronic viral infections such as HIV, has yet to be determined. Indiscriminate CTL activity could hamper immune response specificity, thereby contributing to observed ineffective anti-HCV responses. It is imperative that these immune parameters of chronic HCV infection and liver disease be understood. Consequences of widespread CTL dysfunction with persisting fibrosis, despite HCV cure, could be ineffective responses to reinfection or novel HCV vaccines dependent on strong CD8+ T-cell activity and may predict the development of liver cancer, also best controlled with effective, specific CTL responses.

P.09

The Molecular Interplay Between Circulating MiR-24, MiR-223, and PCSK9 in Hepatitis C-Infected Patients Who Achieve a Treatment-Based Viral Cure

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Background: Hepatitis C virus (HCV) hijacks host lipid metabolic pathways as part of its replication cycle. Chronic HCV infection is associated with altered metabolism, which both contributes to disease progression and influences response to therapy.

Purpose: To help understand how HCV influences important metabolic pathways of chronic liver disease, we investigated the molecular interplay between four circulating regulators of lipid homeostasis (miR-122, miR-24, miR-223 and proprotein convertase subtilisin/kexin type 9 (PCSK9)) in HCV-infected patients who achieved viral cure with interferon-based treatment.

Method: Circulating plasma levels of microRNAs were measured at multiple time-points during antiviral therapy in

individuals achieving sustained virologic response (SVR) (n=57), relapsers (n=10), and non-responders (n=27). The concentration of plasma PCSK9 was assessed in paired samples before and after treatment in SVR (n=27) and relapsers (n=7).

Result(s): We report that miR-24 and miR-223 levels were significantly increased in HCV-infected patients who achieve SVR (miR-24, p-value < 0.0001; miR-223, p-value < 0.0001). In contrast, miR-122 decreased after HCV clearance (p-value < 0.0001), correlating with normalized liver-specific enzymes. Quantitative correlation between amounts of circulating miR-24 and miR-223 was also observed (r=0.91, p-value ≤ 0.0001) for all patients. Importantly, plasma PCSK9 concentrations were significantly upregulated in HCV-infected patients who achieve SVR (p-value=0.002). Also, miR-24 and PCSK9 levels were correlated (r=0.24, p-value ≤ 0.02) in HCV-infected patients, indicating for the first time an *in vivo* link between the two. A modulatory effect of PCSK9 on HCV infection was demonstrated using a cell-based system of viral infection employing recombinant human wild-type PCSK9 and PCSK9 gain- and loss-of-function mutants.

Conclusion(s): Together, these results provide the first insights into a novel coordinated interplay between three important molecular players in lipid homeostasis—lipoprotein-associated miR-24 and miR-223 and circulating PCSK9— whose regulation are affected by HCV infection and treatment-based viral cure.

P.10

Examination of the Molecular Mechanisms that Determine the Breadth of Cross Neutralization of HCV by Vaccine Induced Antibodies

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Background: It is estimated that 150-180 million people worldwide are infected with Hepatitis C virus (HCV) and around 20% will develop liver cirrhosis or liver cancer if left untreated. Direct acting antiviral (DAA) drugs are available for the treatment of HCV and are effective in curing the disease in over 90% of cases. But a vaccine is still urgently needed as these antiviral treatments are extremely expensive and cured patients can still be reinfected. One of the major challenges in the development of a vaccine is the genetic diversity of HCV; there 7 major genotypes with up to 30% difference in their nucleotide sequences. A global vaccine will have to be effective against all HCV isolates. Our laboratory is developing a recombinant envelope glycoprotein- based prophylactic HCV vaccine candidate. Our previous data shows that the vaccine candidate can elicit a broadly neutralizing antibody response. However, variation is seen in the neutralization sensitivity of different HCV genotypes to these vaccine induced antibodies. Additional research is needed to determine the molecular basis for this variation in neutralization sensitivity. Interestingly, we have discovered that two sub-types of HCV genotype 2a, despite being highly similar in genomic sequence, show different neutralization sensitivity to our vaccine-induced antibodies. Our preliminary data suggest the virus determinants of neutralization are located within glycoprotein E2. Another challenge to the development of an HCV vaccine is virus resistance to induced antibodies. Similar to antiviral therapy, prolonged exposure to neutralizing antibodies can select for escape mutations in the virus. Resistant mutations of HCV have been reported against effective cross-neutralizing monoclonal antibodies. We will test these HCV escape mutations for their neutralization sensitivity to vaccine-induced polyclonal antibodies. We hypothesize that vaccine-induced polyclonal antibodies involve multiple epitopes to prevent HCV infection and thus will be able to suppress virus escape. Additionally, the vaccine-induced antibodies should block infection by the HCV monoclonal antibody escape mutants. Together, our research findings will provide critical information for the design of a next generation HCV vaccine that can expand the cross genotype protection and prevent the formation of escape mutations.

P.11 – CanHepC Summer Student

HCV Core Protein Mediates CD8+ T-cell Dysfunction and This Dysfunction is Observed in Cells Exposed to HCV+ Serum

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Background: Clearance of HCV is dependent on an effective virus-specific $CD8^+$ T-cell response, which is dysfunctional in chronic HCV infection. Dysfunction in bulk or non-HCV specific $CD8^+$ T cells in HCV infection that has also been observed may contribute to observed reductions in immunity to other diseases (e.g., cancer, viral co-infections) in HCV-infected individuals. Evidence suggests that the HCV core protein (also found in blood as free protein and as non-enveloped infectious viral particles) may contribute to this impairment in terms of effector functions and survival potential.

Purpose: n/a

Method: To study this dysfunction, isolated human $CD8^+$ T cells from healthy donors were pre-incubated with recombinant HCV core protein (or serum from HCV-infected individuals) for 72 hrs and then stimulated *in vitro* to evaluate proliferation, survival potential and effector functions.

Result(s): Pre-incubation of stimulated $CD8^+$ T cells with HCV core protein significantly reduced their proliferation compared to cells not exposed to HCV core. Perforin production and degranulation were also decreased, but IFN-γ production was unchanged. Additionally, when $CD8^+$ T-cells were pre-incubated with serum from HCV-infected individuals, they produced less perforin than cells treated with control serum. Upregulation of anti-apoptotic Bcl-2 was slightly lower in cells treated with HCV core, but STAT5 activation (required for Bcl-2 production) was increased, suggesting dysregulation downstream of STAT activation.

Conclusion(s): Our study reveals that HCV core reduces the activity and target lysis-associated functions of $CD8^+$ T-cells and this dysfunction is observed in cells treated with serum from HCV-infected individuals. This may contribute to the generalized impairment of $CD8^+$ T-cells observed in HCV infection. These findings provide insight for the design of novel counteractive immune-mediated strategies including the design of effective therapeutic vaccines for use in HCV infection.

P.12

Differential Effects of Direct-acting Antivirals on Immune Phenotype in vitro

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Background: HCV is a chronic viral infection**,** and some evidence suggests that HCV proteins such as NS5A have direct immune modulatory function that contributes to persistence. Immune exhaustion markers are associated with chronic HCV infection. Previous work demonstrated restoration of immune cell function in individuals successfully treated with a direct-acting antiviral (DAA) combination containing an NS5B inhibitor and the immune modulating antiviral ribavirin. Simpler, shorter HCV treatments are a priority, and it would be helpful to understand if direct inhibition of targets such as NS5A enhance immunity and potentially facilitate shorter treatments.

Purpose: Individually and in combination, assess the effect of HCV polymerase (NS5B), and NS5A inhibitors on in vitro immune changes

Method: Peripheral blood mononuclear cell (PBMC)-derived T cell and NK cell phenotypes from HCV-infected individuals and uninfected subjects were evaluated by flow cytometry for PD-1, Tim-3, CTLA-4, CD57, CD27, and perforin within T cell subsets, and CD158b, CD158e1/e2, CD27, CD56, CD16, and perforin by NK cells at baseline and after 7 days in the absence or presence of individual DAAs *in vitro*. PBMCs were cultured in the upper chamber of transwell inserts with the bottom wells containing Huh-7.5 cells infected with the Cp7 J6/JFH1 HCV strain with inhibitors for NS5B (sofosbuvir) and NS5A (ledipasvir), or vehicle control. In separate experiments, the effects of individual DAAs on immune cell phenotype were assessed after 3 days in culture. Total cell numbers and viability were assessed on days 0, 3, 5, and 7.

Result(s): DAA alone in the absence of HCV production by Huh-7.5 cells did not impact expression of immune markers, and did not significantly affect cell growth or viability. Viral particles were undetectable in wells containing antivirals. At baseline, T cells expressing markers of immune exhaustion, including PD-1, CTLA-4, and Tim-3, were more frequent in PBMC from chronically infected HCV treatment naïve patients compared to those from uninfected individuals. Direct NS5A inhibition by ledipasvir led to reduced frequency of PD-1^+ T cells, whereas the NS5B inhibitor did not alter immune exhaustion marker expression after 7 days. There were no significant differences in NK cell phenotype between the drugs tested or vehicle alone. However, perforin$^+$ NK cells were significantly reduced in all conditions after 7 days in culture.

Conclusion(s): NS5A inhibition in vitro decreases some immune exhaustion markers after only 7 days. Studies on immune function are ongoing. These data suggest that an NS5A inhibitor may be an important immune enhancer above and beyond viral inhibition. In shortened regimens, or individuals who are difficult to treat, maintaining NS5A inhibition and enhancing host response may be an intrinsic part of the antiviral strategy, especially in those at risk for reinfection.

P.13

The Role of Micrornas in the Development of Insulin Resistance During Infection with Hepatitis C Virus

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Background: Insulin resistance is a common pathological feature of patients infected with the hepatitis C virus (HCV). Although many factors have been identified which may contribute to the development of insulin resistance, the process is not fully understood. MicroRNAs (miRNAs), small non-coding RNAs that modulate gene expression, are involved in many physiological processes. For example, we have previously identified several miRNAs that alter lipid profiles during infection with HCV. Whether they are also involved in the development of insulin resistance during infection with HCV remains unknown.

Purpose: In this study, we aimed to identify miRNAs that play a role in the development of insulin resistance during HCV infection.

Method: We performed miRNA profiling in insulin-stimulated primary human hepatocytes and the Huh7.5 hepatocellular carcinoma cell line to identify miRNAs differentially expressed during pathway activation or inhibition. We compared the miRNAs to those known to be differentially expressed during infection with HCV. We then identified putative targets of the miRNAs and monitored their expression during HCV infection and insulin signaling.

Result(s): n/a

Conclusion(s): This study will identify miRNAs that may play a role in modulating parts of the insulin pathway that are altered during HCV infection, contributing to the development of insulin resistance. This will lead to a more thorough understanding of factors contributing to metabolic alterations during viral infection.

P.14

NK Cell Exhaustion in Chronic Hepatitis C Infection is Reversible Early After Direct-acting Antiviral Treatment

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Background: HCV establishes chronic infection in at least 75% of exposed individuals, demonstrating failure of the immune system to generate sterilizing immunity. Correlates of successful (exposed uninfected persons) and failed (chronically infected persons) immunity are not clear. However, understanding immunity remains important even in the era of highly effective direct-acting antiviral (DAA) treatment and cure, as there is no vaccine. NK cells are key to antiviral activity, and several studies suggest that natural killer (NK) cell function is high in spontaneous clearers and impaired in chronic infection. Whether this impairment is the same in all HCV positive subpopulations, and if it is reversed after interferon-free HCV cure is unclear.

Purpose: Determine NK cell phenotype and function in two populations with chronic HCV infection before and after HCV DAA-induced viral cure.

Method: NK cells were enriched from peripheral blood mononuclear cells (PBMC) obtained from HCV uninfected individuals, as well as persons living with HCV. HCV viral load was measured at each time point. NK cells were assessed before, during, and after DAA treatment for expression of both activating and inhibitory markers (CD16, CD27, CD56, CD158b, CD158e1/e2, CD159a, CD314, CD337). NK cell function was measured with a lactate dehydrogenase release K562 cytotoxicity assay, and killer cell immunoglobulin-like receptor (KIR) genotype was determined for all individuals. Groups were compared by paired t test or Wilcoxon signed rank test for on treatment comparisons and by t test across infected and uninfected groups.

Result(s): NK cells from individuals with chronic HCV infection have reduced cytotoxicity compared to NK cells from healthy individuals. After seven days of DAA treatment, HCV patients have a decreased frequency of circulating $CD158b^{+}$ and $CD158e1/e2^{+}$ cells. Further data will be presented assessing NK cell function in the context of drug use and KIR genotype.

Conclusion(s): Within one week of treatment, NK cells from HCV patients continue to have an exhausted immune phenotype. However, the functional NK cell impairment observed during chronic viral infection starts to reverse early in treatment with suppression of HCV viremia. These data suggest that cells have a reversible and plastic functional impairment that is modified by treatment and viral suppression. This may have implications for vaccine development, particularly in those at high risk for reinfection after cure.

P.15

Adaptive and Innate Immune Changes Associated with Successful Interferon-free HCV Direct-acting Antiviral Cure

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Background: T cells have been well studied in chronic viral infection, whereas the roles of B cells and innate immune cells such as NK cells remain less clear, particularly in HCV-infected patients who achieve treatment-based viral cure. Moreover, studies often focus on one aspect of the immune system or another as opposed to considering cumulative immune function as a whole on a per-individual basis. This limits our ability to understand and predict what constitutes an overall effective immune response in HCV patients on interferon-free HCV direct-acting antiviral (DAA) cure.

Purpose: Determine immune cell phenotype and function in individuals with chronic HCV infection before and after HCV DAA-induced viral cure, and assess overall immunity per individual.

Method: HCV subjects were treated with DAA regimens for 12 weeks. Comprehensive peripheral blood mononuclear cell (PBMC) T cell (CD3, CD4, CD8, CD27, CD28, Tim-3, PD-1, CTLA-4, and CD57), B cell (CD10, CD19, CD20, CD21, CD27), and NK cell (CD16, CD27, CD56, CD158b, CD158e1/e2, CD159a, CD314, CD337) immunophenotyping was performed in these patients, as well as age and sex matched controls at baseline, end of treatment (EOT), and post-treatment follow-up week 24. Polychromatic flow cytometry, as well as *in vitro* Enzyme-Linked ImmunoSpot (ELISPOT) and cytotoxicity assays simultaneously assess phenotypic and functional alterations in T cell subsets, B cells, and NK cells. The relative strength of T cell, B cell and NK cell responses were ranked and the cumulative strength of the immune response was determined for each individual.

Result(s): All patients had HCV viral suppression below the level of detection on DAA therapy. Markers of T cell immune exhaustion, including PD-1, Tim-3, and CTLA-4, decrease with viral suppression. The frequency of inhibitory receptor^{+} NK cells changed with therapy within an individual and across the study population. In contrast, abnormal frequencies of multiple B cell subpopulations at baseline persisted despite viral suppression. HCV-specific T cell responses were more frequent at EOT compared with those at baseline. NK cells from some individuals had augmented cytotoxicity with viral suppression at the end of therapy compared to before treatment during chronic viral infection. Ranked cumulative measures of anti-HCV immunity will be presented per individual.

Conclusion(s): Adaptive and innate immune phenotypes become less senescent with viral suppression, however residual deficits remain. When assessed cumulatively, immune senescence, even beyond HCV-specific responses, improves with viral suppression. Chronic viral infection has an HCV-specific, as well as bystander immune exhaustion effect that seems reversible by viral cure. This may have implications for development of HCV vaccine strategies, as well as HCV treatment timing.

P.16

Removal of an Immune Masking Domain, Hypervariable Region 1 (HVR1) of HCV Glycoprotein E2, Does Not Enhance the Immunogenicity of a Glycoprotein Based HCV Vaccine

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Background: Current evidence points to a protective role for virus neutralizing antibodies[1] and virus-specific cellular immune responses[2,3] in immunity against HCV infection. Previously we have shown that a recombinant envelope glycoprotein vaccine containing the gpE1/gpE2 heterodimer derived from a single HCV strain is protective in the chimpanzee model against challenge with homologous and heterologous genotype 1a strains of HCV[4]. Vaccination of human volunteers in a phase 1 clinical trial elicited strong T-helper responses[5] and antibodies that neutralize the *in vitro* infectivity of all the major HCVcc genotypes observed around the world[6]. However, cross-neutralization appeared to favour certain genotypes with significant but lower *in vitro* neutralization against others[6]. We are optimizing the 2nd generation vaccine to broaden the immunogenicity – enabling protection against multiple HCV genotypes. In support of the protective role of neutralizing antibodies, many cross-neutralizing monoclonal antibodies have been identified. These antibodies have shown to protect[7] or clear on-going infection in animal models[8]. However, escape mutations have been reported to render these antibodies ineffective. In addition, HCV may employ mechanisms such as epitope masking and epitope decoys to avoid immunoglobulin-mediated control.

Purpose: HVR1 within the amino-terminus of glycoprotein E2 is believed to block access of many neutralizing antibodies. Consistent with this, recombinant viruses lacking the HVR1 is hypersensitive to neutralization[9]. It has been proposed E1E2 lacking this domain could be a better vaccine antigen to induce broadly neutralizing antibodies.

Method: In this study, we directly tested this hypothesis by isolating recombinant E1E2 lacking the HVR1.

Results: In mice, recombinant E1E2 lacking the HVR1 induced less neutralization activity compared to wild type E1E2. Subsequent antibody binding studies showed recombinant E1E2 lacking the HVR1 is less reactive to confirmation specific antibodies. These results are consistent with the hypothesis that the deletion of HVR1 affects the conformation of E1E2 – rendering the protein less immunogenic.

Conclusion: Based on chimpanzee protection data reported previously[4] and our current finding, we are preparing a vaccine based on a wild type recombinant gpE1/gpE2 for clinical testing in the near future.

Clinical Research

P.17

Real-Life Efficacy of Elbasvir/Grazoprevir (EBV/GZV) for the Treatment of Chronic HCV Genotype 1 and 3 Infection

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Background: The introduction of all-oral direct acting antiviral (DAA) regimens has allowed for better tolerated, shorter, and more effective courses of therapy for HCV infection. Elbasvir (EBV, NS5A inhibitor) and grazoprevir (GZV, NS3/4A protease inhibitor) is a new fixed dose combination that has demonstrated sustained virologic response (SVR) rates above 90% in a broad range of treatment-naïve and experienced populations, including people who inject drugs (PWID).

Purpose: We sought to evaluate the efficacy of EBV/GZV in a clinical setting serving HCV-infected PWID.

Method: An observational evaluation was conducted among HCV-infected patients seen at the Vancouver Infectious Diseases Centre (VIDC), where they had access to a multidisciplinary model of care to address medical, psychiatric, social and addiction-related needs prior to, during and after HCV therapy. All individuals that received EBV/GZV according to current clinical guidelines. At the time of the current analysis, the primary endpoint was defined as SVR-4, an undetectable HCV RNA four weeks post-treatment. Demographic and clinical correlates of success were also evaluated.

Result(s): To date, 13 individuals have received EBV/GZV in our program, 7 genotype 1a, 2 genotype 1b, and 4 genotype 3a (EBV/GZV administered in combination with sofosbuvir). Key demographic information includes: mean age 49.5 years, 23% female, 15% cirrhotic, 15% HIV co-infect and 85% current PWID. Adherence rates are high, with all patients having missed 0-2 doses. To date, six patients have reached the primary endpoint and 100% have achieved SVR-4, including 4/4 individuals with genotype 3a infection. Data will be presented on 20 patients with the SVR12 endpoint having been achieved.

Conclusion(s): The combination of EBV/GZV (with or without sofosbuvir) appears highly effective in clinical practice in a population similar to that enrolled in the C-EDGE CO-STAR protocol. If these preliminary data are confirmed, EBV/GZV will become another highly potent therapeutic option available for the treatment of HCV infection in diverse populations, including PWID.

P.18

Interdisciplinary Approach to Developing a Hepatitis C Testing Guide – Responding to the Needs of Local Physicians

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Background: A gap in hepatitis C testing resources was identified by local family physicians. Requests were received to create a new reference material that concisely describes hepatitis C testing and recommended follow-up care.

Purpose: To describe the process of developing a Quick Reference Guide on the testing and management of hepatitis C, that is locally relevant for family physicians and other public health personnel.

Method: Based upon environmental scans and literature searches conducted for the revision of our local Hepatitis C Guidelines, various drafts of Hepatitis C testing and care management figures and tables were created for internal review by experts from BCCDC Hepatitis program, Public Health Laboratory, and Clinical Prevention Services Surveillance and Education teams. A draft of the Hepatitis C Testing Guide was reviewed externally by the Hepatitis C Guidelines Provincial Working Group, which was comprised of front line nurses and nurse leaders working in the area of Hepatitis C and/or Communicable Disease in general. Feedback was received from several physicians working within Hepatology, Addictions, Inner City Medicine, Public Health and Family Practice. Further revisions were then reviewed by the provincial STI and Blood Borne Infections (STIBBI) working group, which is comprised of nurse and physician leaders from each health authority. Final approval was received after review by the Provincial Communicable Disease Policy Advisory group, which is comprised of representatives from the six regional Health Authorities and chaired by the Provincial Health Officer.

Result(s): A double-sided 1-page quick reference hepatitis C testing guide has been created that provides information about relevant tests, interpretation, and recommended follow-up case management. Background epidemiology information, key education points, clinical and laboratory information, and resources are also provided to help support routine testing. The rigorous review process ensured that a succinct, provincially relevant document was created that can be widely used by health care practitioners around the province.

Conclusion(s): Using an interdisciplinary collaborative process, a locally relevant provincial testing guide for hepatitis C was created to help support the daily practice of family physicians and public health personnel. Extensive consultation with external partners improved the acceptance and utility of this Quick Reference Hepatitis C Testing Guide.

P.19

Resistance-Associated Substitutions in Nonstructural Proteins 5A and 5B of the Hepatitis C Virus, Evolutionary Origins and Clinical Implications

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Background: Hepatitis C virus (HCV) contains a variety of naturally occurring polymorphisms in the non-structural protein 5A (NS5A) and non-structural protein 5B (NS5B) that reduce susceptibility to currently approved NS5A and NS5B inhibitors. Previous investigations showed the Q80K mutation in the NS3 region of HCV has a common origin in the world population around 1930 in genotype 1a strongly coupled to substitutions A915/T, S147N or V29A.

Purpose: We sought to reconstruct the evolutionary history of the NS5A and NS5B resistance-associated substitutions (RASs).

Method: We collected more than 200,000 HCV sequences from global databases. Sequences were aligned using MAFFT v.7.54b and visually inspected using AliView v.1.18. After discarding sequences from the same patient and sequences that do not cover NS5A by 75%, we were left with 1,613 NS5A sequences and 853 NS5B sequences. RASs were defined as substitutions in the NS5A gene previously identified based on literature sources. We inferred a phylogenetic tree for genotype specific datasets (1a, 1b, and 3a) under approximate maximum likelihood as implemented in FastTree2. Resulting phylogenies were rescaled to units of time using the R package ape. Next, we reconstructed the ancestral sequences at the nodes of the trees using MG94xREV codon model. Finally, NS5A/NS5B RASs were mapped onto the resulting trees to recover patterns of ancestry.

Result(s): We found, in contrast to Q80K in NS3, that most NS5A RAVs do not have a common origin, but rather each has evolved independently many times and they are widely dispersed amongst the phylogenetic trees of each genotype. In N5SB, we identified an analog of Q80K in NS3, the highly clustered RAS, C316N. We found, C316N to be highly associated with the neutral substitution, A218S.

Conclusion(s): The inferred distribution of RASs in the NS5A region and frequency of their origin suggest that, unlike Q80K, there is a low fitness barrier without the need for co-evolution of compensatory mutations. A low fitness barrier may allow rapid selection of de novo resistance to NS5A inhibitors during therapy.

P.20 - CanHepC Summer Student

AST Normalization at Week 4 is a Viable Alternative to HCV RNA Monitoring in Predicting DAA Treatment Success

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Background: Hepatitis C Virus (HCV) viral load measurements is used to monitor treatment response in HCV therapy. However, with new oral DAAs, this may not be useful for predicting treatment success. Liver enzyme levels, which are elevated in chronic HCV and tend to decline on therapy, may serve as a more logistically and economically feasible alternative for monitoring treatment response.

Purpose: N/A

Method: Retrospective analysis of 219 The Ottawa Hospital Viral Hepatitis Clinic patients receiving non-experimental oral DAA were assessed for liver enzymes and HCV RNA levels at baseline, week 4, and ≥12 weeks post treatment. Suppression cut points used for this analysis were ALT ≤ 40U/L and AST ≤ 30U/L. The primary outcome was sustained virologic response at week 12 (SVR12). Postive predictive value (PPV), negative predictive value (NPV) and area under the curve for receiver operating characteristic curves (ROC AUC) were calculated to test efficacy of predictive models. Univariate and multivariate regression models were run to identify variables associated with SVR at baseline and week 4.

Result(s): By our analysis, all week 4 indicators had strong PPV (ALT: 92.8%, AST: 97.3%, AST:ALT: 97.6%, HCV RNA: 93.4%) but limited NPV (ALT: 10.6%, AST: 20.0%, AST:ALT: 15.6%, HCV RNA: 22.2%). Week 4 HCV RNA, AST ≤ 30U/L and AST:ALT ratio (<0.9) were associated with SVR in univariate analysis. ALT, however, was not predictive of DAA outcome. In multivariate models, adjusting for cirrhosis and genotype, baseline AST:ALT ratio<0.9 (but none of the week 4 indicators) was significantly associated with SVR. ROC AUC for week 4 AST (0.75) and AST:ALT ratio (0.72) were higher than for ALT (0.54) and HCV RNA (0.58).

Conclusion(s): Our analysis suggests that AST and AST:ALT ratio demonstrate robust predictive value and provide a viable alternative to HCV RNA in determining treatment success on DAA therapies.

P.21

Telemedicine: A Model of Health Care Delivery that Can Successfully Engage Marginalized, Difficult to Cure Hepatitis C Virus-Infected Canadians

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Background: Many HCV-infected Canadians live in remote areas without access to HCV healthcare specialists. To engage and retain HCV patients residing in rural Eastern Ontario and Nunavut, The Ottawa Hospital Viral Hepatitis Program developed a multidisciplinary Telemedicine (TM) program.

Purpose: N/A

Method: To compare patient characteristics of TM patients to non-telemedicine (non-TM) hospital-based outpatient HCV clinic patients, we conducted a retrospective study of 1287 individuals (TM, n=157 and non-TM, n=1130) followed between January 2012 and August 2016. Fibrosis assessment and HCV antiviral treatment access and outcomes were analyzed and compared between groups.

Result(s): TM patients were more likely to be Indigenous (7.0% vs 2.2%), genotype 3 infected (25.9% vs 16.4%), and to have histories of injection drug use (70.1% vs 54.9%), alcohol use (69.4% vs 56.9%) and incarceration (46.5% vs 35.5%). Groups were comparable in age (mean 48.9), gender (63.7% male) and cirrhotic stage (24.0%). The length of HCV infection was greater in non-TM patients (26.7 years vs 20.7 years). TM patients were more likely to suffer material deprivation (31.8% vs 17.0%).

With regards to clinical outcomes, TM patients were less likely to have a biopsy but equally like to undergo assessment by FibroScan. TM patients were less likely to initiate interferon-based treatment, but equally likely to initiate DAA-based HCV antiviral treatment as those receiving Outpatient Clinic care. SVR rate with DAA regimens was 94.7% in the TM group and 94.8% in the non-TM group (p=0.995).

Conclusion(s): The Ottawa TM program successfully engages and retains a remote population facing barriers to treatment, and provides care leading to high SVR rates similar to those achieved by patients under traditional models of care.

P.22

Grazoprevir-Elbasvir +/-Ribavirin (+/- Sofosbuvir) is Well Tolerated and Virologically Potent in Difficult-to-Cure HCV Treatment Recipients

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Background: Cirrhosis, Black race, and renal disease have historically negatively influenced HCV antiviral efficacy. In Canada, Grazoprevir-Elbasvir (GE) (+/- ribavirin (RBV)) is approved for G1 and 4 treatment and for G3 in combination with Sofosbuvir (SOF). We assessed safety and efficacy of GE-based regimens in a non-clinical trial cohort of patients with difficult to cure characteristics.

Purpose: N/A

Method: Patient characteristics, safety and efficacy of GE-based DAA treatment were assessed utilizing The Ottawa Hospital Viral Hepatitis Program cohort database. HCV RNA and liver enzyme levels were evaluated.

Result(s): 23 GE-based therapy recipients have been assessed: mean age 61 (± 16) years, 12 (52%) female, 13 (57%) White, 9 (39%) Black, 6 (26%) G3 and 13 (57%) G4 infected. 19 (83%) had advanced fibrosis (F3/4; mean baseline fibroscan score 15.3 ± 8.2 kPa). Four (17%) were past IFN-treatment failures. Chronic co-morbid disease was common: n=5 diabetics, n=5 chronic renal disease, n=3 dialysis, n=1 kidney transplant. RBV was included in 5 regimens. All G3 patients on treatment received SOF (n=6).

Baseline HCV RNA level was $8.6 \times 10^6 \pm 2.4 \times 10^7$ IU/mL, ALT level was 114 ± 114 U/L, AST level was 75 ± 59 U/L. All patients achieved on-treatment week 4 HCV RNA decline (90.9% <15IU/mL; all <150 IU/mL). On-treatment ALT (29 ± 16 U/L) and AST (25 ± 12 U/L) decline was observed. No SAEs were detected.

Conclusion(s): These interim results corroborate that GE treatment (+/- SOF/RBV) is virologically potent and well tolerated in difficult to cure HCV patients.

P.23

Treatment Outcomes of HCV-infected Patients Identified Through the Community Pop-up Clinic

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Background: In Canada, it is estimated that over 300,000 individuals are infected with HCV, with 60,000 residing in British Columbia. The prevalence of infection on Vancouver's Downtown East Side (DTES) may exceed 70%, with relatively few individuals having been treated to date. This may relate to a lack of engagement in medical care. We developed a novel model of intervention, the Community Pop-up Clinics (CPC), as a tool to enhance access to medical care and HCV therapy in this vulnerable population

Purpose: In this study, we aim to understand factors associated with engagement in care in this vulnerable population.

Method: Participants were recruited at CPCs held at several community centres on the DTES. OraQuick® HCV Rapid Antibody and HIV Rapid Antibody point-of-care testing was offered. Participants identified as HCV positive were provided the opportunity to engage in care at a multidisciplinary clinic. A questionnaire was administered to collect demographic information, HCV disease knowledge, and data regarding barriers to receiving healthcare. A $10 gift-card incentive was provided for participants who completed the demographic questionnaire and testing.

Result(s): A total of 2378 participants (mean age 49.9 years, 93.4% male) were tested for HCV infection, with 658 (27.7%) found to carry HCV antibodies, 51 (7.7%) co-infected with HIV. Among HCV infected participants, 157 (27.6%) were linked to care (76% male, 30% First Nations, 28% homeless, 78% recent/active recreational drug use). To date, 26 (16.9%) have started treatment for HCV infection, 19 (73%) completed treatment, and 16 (84.2%) achieved sustained virologic response (SVR). Groups under-represented among those engaged in care include: females (7%), Aboriginals (15%), and those with lack of knowledge about how to access health care (9%), are homeless (9%), or perceive their health status as good (14%).

Conclusion(s): Our CPC approach in a neighborhood with HCV prevalence of 70% has successfully identified over 600 HCV-infected individuals and engaged a significant proportion of them in care. Additional efforts must be undertaken to engage certain target populations such as women, Aboriginals and those who are homeless and in ensuring that engagement leads to enhanced access to curative HCV therapies in all eligible patients.

P.24

Criteria for the Identification of Mixed HCV Infections: Implementation of an Unbiased Whole-genome Shotgun Sequencing Pipeline

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Background: Estimates of the prevalence of mixed HCV infections (infection with 2 or more distinct viral variants) and/or re-infections range from 5–39% and 1–5% per year, respectively, depending upon the study population. Higher rates of mixed HCV infections are typically observed in high-risk populations, such as people who inject drugs (PWID). Such high-risk populations also represent the majority of new HCV infections in high-income countries. How these types of infections influence key aspects of HCV pathobiology such as HCV evolutionary rate, immunologic escape, and resistance to direct acting antiviral therapies is unknown. Complicating the matter further, criteria used to identify mixed infections have not yet been established.

Purpose: To identify mixed infections using a randomly-primed whole genome sequencing (WGS) approach.

Method: Two genotypes (GT) were experimentally mixed in five different ratios: 98/2% (n=2,GT: 3/6, 1a/2), 95/5%(n=2,GT: 3/6, 1a/2), 90/10%(n=14,GT:1a/1b,2/1a,2/4,3/1a,3/6,4/3,5/6,6/1a), 75/25% (n=2, GT: 1a/2,3/6), and 50/50% (n=4, GT: 1a/1b,2/1a,3/1a,6/1a). Percent coverage and the average depth (genotype read count/total HCV reads, per region) for the NS3, NS5A, and NS5B coding regions were quantified and used as criteria to identify mixed infections. Accuracy assessment for mixed infection classification using these measures was performed with receiver operating characteristic (ROC) curves. We subsequently applied our criteria to plasma samples obtained from two chronically HCV-infected cohorts of PWID: VIDUS (n=79), and ACTIVATE (n=140).

Result(s): Optimal genotype classification was observed when at least a coverage of 90% and a minimum average depth of 2% was reached for each of the NS3, NS5A, and NS5B regions. These criteria correctly classified the experimentally mixed samples in all cases except for the 98/2% mixtures, where in each case one out of three regions was found to be below the designated thresholds. When applied to the ACTIVATE cohort, four (5.1%) potential mixed infections were identified, whereas in the VIDUS cohort 10 were identified (7.1%).

Conclusion(s): Our criteria successfully classified minor genotypes when present in at least 2% of the viral population. In agreement with previously reported rates, mixed infections were identified in 5.1% and 7.1% in two HCV cohorts.

P.25

Modulation of NK Cell Proportion and Function in Response to IIFN-free Direct-acting Antiviral Therapy in Chronic HCV Patients

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Background: Natural killer (NK) cells are involved in the pathogenesis of hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC). In patients infected with HCV, the proportion and function of NK cells are found altered, suggesting that defective NK cell immune surveillance is implicated in the development of HCC in chronic HCV patients.

Purpose: This study investigates whether NK cell proportion and function is restored after HCV eradication upon IFN-free direct-acting antivirals (DAA) therapy.

Method: Blood samples from chronically infected HCV+ individuals (i.e. > 6 months HCV RNA-positive) who were receiving IFN-free DAA therapy were collected at basal, week 4, week 12, week 24 and 3, 6 and 12 months after therapy and are analyzed for changes of NK cells during the DAA treatment. In addition, blood samples from chronically infected HCV+ individuals stratified by live pathology progression (Group 1: METAVIR score F1 or F2, Group 2: F4 without HCC development, Group 3: F4 and HCC development, Group 4: HCC and cancer treatment) are also collected to determine whether any identified change is associated with HCC development.

A written informed consent was obtained from all participants, and the study was approved by The Ottawa Health Science Network Research Ethics Board.

Multicolor flow cytometry will be performed to analyze NK cell proportions, phenotypes and functions. To evaluate NK cell functions, we will investigate natural cytotoxicity against K562, and antibody-dependent cellular cytotoxicity (ADCC) function against antibody-coated target cells. Plasma samples will be used to measure cytokine levels.

Result(s): Our study will try to determine whether HCV clearance by current efficient DAA therapy restores NK cell proportion and function during a time course up to 1 year. This finding will be extended into the identification of NK cell defect involved in HCC development.

Conclusion(s): Even though DAA is a powerful anti-HCV therapy leading to the significantly elevated sustained virological response (SVR) rate, the morbidity and incidence of HCV-induced HCC still persists. Since NK cells are a principal immune population of tumor surveillance, the role of NK cells in the development of HCC should be critical. Our result will provide an insight into prevention of HCC post DAA treatment for HCV by restoring anti-tumor activity of NK cells.

P.26

Comparing Random-priming and Target Capture-based Next-generation Sequencing Approaches for Characterization of Hepatitis C Virus Infections

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Background: New, curative, short-duration direct acting antiviral therapies are improving the health outcomes of individuals infected with hepatitis C virus (HCV). Maximizing treatment success requires accurate HCV genotyping, identification of underlying mixed infections and detection pre-existing resistance associated substitutions (RASs).

Purpose: To compare recovery of HCV sequence read depth using two methods of next-generation sequencing (NGS) library preparation using HCV infected plasma samples.

Method: NGS was performed on 16 plasma samples (Gt 3 n=14; Gt 2 n=2) drawn from participants in the ACTIVATE clinical trial of response-guided therapy in people with HCV Gt 2/3 receiving opioid substitution therapy or with a history of recent injecting drug use. The NGS methods were validated using 13 artificially mixed HCV genotype samples (Gt 1a/1b, 1a/2, 1a/3, 1a/6) in ratios of 10:90, 50:50, and 90:10. A Gt 1a/2 sample in a 95:5 ratio was also tested. HCV sequencing libraries were prepared either using a random priming (RP) approach that non-selectively amplifies sequences in a sample or using target-capture probes (TCPs) from Illumina to enrich HCV genetic material following RP amplification. Samples were barcoded with unique tags using low cycle PCR, pooled and sequenced on an Illumina MiSeq using 2 x 250 cycles. Resulting sequences were analyzed using a custom in house bioinformatics pipeline.

Result(s): Sequencing the ACTIVATE samples using the RP method yielded an average $2.2x10^5$ HCV reads/sample (16% of total reads; average read depth 5.50 $x10^3$) while the TCP approach yielded $1.1x10^6$ HCV reads/sample (66% of total reads; average read depth $4.0x10^4$). Both methods were also tested on the 13 artificially mixed HCV genotype samples. In all cases, both expected genotypes were identified using both approaches. However, on average the read depth was 4.7 fold-greater for both the most abundant and less abundant HCV genotypes in a sample using TCP compared to RP. The advantage of TCP compared to RP is most apparent with low abundance variants i.e. in the Gt 1a/2 95:5 mix, there were >10X more reads and 10x greater depth for Gt 2.

Conclusion(s): NGS offers unparalleled sensitivity for identification of low abundance HCV sequences. While both RP and TCP approaches can be used, TCP greatly increases HCV read depth and the proportion of HCV reads in the sequence library. This improves the capacity to identify mixed-HCV infections and increases the number of samples that can be processed per run, thus reducing over all sequencing cost.

P.27 - CanHepC Summer Student

Evaluation of Liver Fibrosis Scores Post-HCV SVR in People Who Inject Drugs

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Background: In the developed world, people who inject drugs (PWID) constitute the majority of prevalent and incident Hepatitis C (HCV) infections. Treatment is often withheld due to concerns surrounding reduced efficacy related to poor adherence and a higher risk of re-infection after successful treatment. Current guidelines favour increasingly widespread access to highly effective direct-acting antiviral regimens within this population, with a view to curing HCV infection but also preventing HCV transmission. An additional rationale for treatment may be to prevent the liver-related morbidity and mortality increasingly prominent among PWID. Data on the impact of HCV cure on liver fibrosis scores among PWID have not yet been generated in a systematic way.

Purpose: The purpose of this study was to evaluate liver fibrosis scores post HCV SVR, in PWID to evaluate liver damage and repair.

Method: We performed a retrospective observational study utilizing records of PWID successfully treated for HCV infection at our centre. HCV-infected PWID with ongoing recreational drug use, having achieved and maintained a sustained virologic response (SVR) and engaged in long-term medical follow-up were included. Fasting transient elastography (TE) scores post-SVR were compared to pre-treatment values. If such scores were unavailable, APRI scores were considered.

Result(s): A cohort of 57 subjects were included in this analysis. Of these, 45 (79%) actively injected drugs during treatment and 12 (21%) did so intermittently before and after HCV treatment. The median age was 53 (27-73) years, 47 (82%) were male, 52 (91%) were Caucasian, 42 (74%) were infected with HCV genotype 1, and 12 (21%) were genotype 3. In addition, 77% were HCV treatment-naïve and 10 (18%) were HIV co-infected, 9 (90%) of whom demonstrated complete virologic suppression (HIV viral load <40 copies/mL). The mean follow-up period was 472 (128-1247) days. Based on TE evaluations, the mean pre-treatment fibrosis scores of 11.9 (3-45) kPa (3-45) significantly decreased post-treatment to a mean of 9.6 (2-27) kPa (p=0.03). Mean APRI scores decreased from 0.91 to 0.40 (p=0.0001). Among 12 patients that initially suffered from cirrhosis (TE score >12.5 kPa), 11 (92%) had improved fibrosis scores after treatment, including 5 (42%) who decreased to a lower fibrosis category (F3 or less).

Conclusion(s): This data set shows significant, rapid improvement in liver fibrosis among PWID successfully treated for HCV infection. In a population where liver-related morbidity and mortality is becoming a common clinical concern, this provides additional and strong rationale for the development of strategies to increase HCV treatment uptake.

P.28

Real World Treatment of Genotype 1 Hepatitis C Using Simiprevir in Combination with Sofosbuvir: Results from a Multicentre Observational Canadian Cohort

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Background: Historically, treatments for HCV in the real world have not shown equal SVR rates to those results achieved in clinical trials. For the first all oral direct-acting antiviral regimen of simiprevir in combination with sofosbuvir (Sim/Sof), the initial Phase 2 COSMOS clinical trial reported an overall SVR rate of 95%. The recently published Phase 3 OPTIMIST-2 trial that treated cirrhotic patients with Sim/Sof reported SVR rates of 88% and 79% in treatment naïve and treatment experienced patients respectively. Real world observational cohorts have also reported SVR rates lower than those seen in the COSMOS trial.

Purpose: We wished to determine SVR rates in a multicenter real world, Canadian cohort of patients treated for genotype 1 HCV with Sim/Sof.

Method: We identified all patients treated with Sim/Sof at three different sites in Calgary between the dates of April 2014 and October 2015. We identified demographic, pre-treatment and post-treatment characteristics for each patient in a centralized database for all treatment sites in Calgary.

Result(s): A total of 22 patients were treated with Sim/Sof at the three different sites (2 from a community site, 19 from one academic site, 3 from another academic site). Patient and treatment characteristics are summarized in Table 1, with 68% being cirrhotic at baseline and 23% being treatment experienced. An overall SVR12 of 86% was achieved with only 3 virological failures. Fibroscan values after therapy were lower than those obtained before therapy (13.5 ± 8.5 vs 17.7 ± 16.3 kPa). In follow up through October 2016, one patient was lost to follow up, but all other patients were alive and none developed hepatocellular carcinoma. One of the treatment failures was treatment experienced and all were cirrhotic at baseline.

Conclusion(s): In a small cohort of Canadian patients treated at several centres with the first DAA regimen Sim/Sof, the SVR rate of 86% was comparable to that obtained in Phase 3 clinical trials and in other real world reports. The lower than expected SVR rate when compared to Phase 2 data is likely attributable to the high frequency of cirrhotic patients in our population.

P.29

An Analysis of Treatment Uptake Using All-Oral Direct-Acting Antiviral (DAA) Therapy in HCV-infected People Who Inject Drugs (PWID)

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Background: Approximately 300,000 Canadians are infected with Hepatitis C (HCV). The province of British Columbia has the highest rate of HCV infection in Canada, with an estimated 80,000 people infected with the virus. The virus is transmitted via blood-to-blood contact, and the sharing of injection equipment contributes to over 56% of HCV infection cases in Canada. Historically, many medical professionals have considered PWID poor candidates for HCV therapy due to concerns about adherence and reinfection. However, recently novel all-oral regimens have supplanted interferon-based regimens as the standard of care for HCV, consistently demonstrating higher rates of sustained virologic response (SVR) and comparatively favorable side effect profiles.

Purpose: This study seeks to assess the efficacy of all-oral therapies in PWID and provide further support for the treatment of this population.

Method: A retrospective cohort analysis was performed on all HCV-infected patients who were treated at a tertiary clinic in downtown Vancouver and had a history of injection drug use. In addition to HCV therapy, our centre provided services to address relevant medical, social and psychologic concerns. Appropriate treatment regimens were chosen and follow-up visits (at weeks 2, 4, 6, 8, 10, 12, and/or 24 weeks) were scheduled. The primary outcome of the analysis was achievement of SVR. Demographic information, along with ongoing HCV-related risk factors and co-morbidities were also collected.

Result(s): In our cohort, 50 active PWID received and completed all-oral HCV regimens. The mean age was 52.4 (range 34-75), 37 (74%) were male, 20 (40%) were on opiate substitution therapy, 33 (66%) were using cocaine, 31 (62%) were using opioids, and 23 (46%) were using other stimulants. SVR was achieved in 44 (88%) cases; 4 patients (8%) exhibited HCV relapse and 0 (0%) were re-infected. The 4 patients with virologic relapse were on Sofosbuvir-based regimens - 1 patient with genotype 2a/2c (with Ribavirin), 2 patients with genotype 3a (with NS5A Inhibitor), and 1 patient with genotype 1a (with NS5A Inhibitor).

Conclusion(s): Although barriers to care exist in PWID, they should not be excluded from treatment given the burden of HCV infection in this particular population. High SVR rates achieved with new all-oral treatment regimens can be replicated in clinical practice, at least within multidisciplinary healthcare settings. Our data provides further support for the current guidelines for the treatment of HCV-infected PWID who are not abstinent from recreational drug use.

Health Services Research

P.30

The Disproportionate Burden of HCV Infection in Ontario by Gender and Incarceration Status

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Background: Hepatitis C infection (HCV) is the most burdensome infectious disease in Ontario; however, there are inconsistencies in the rigor of testing practices across the province. HCV testing includes a preliminary screening test, following by confirmatory testing. Confirmatory testing following an anti-HCV positive result is important to determine infection activity, viral load and genotype. Little research has been conducted on HCV testing patterns in the incarcerated population.

Purpose: The purpose of this research is to determine if there is a difference between confirmatory testing practices in males and females in an "ever incarcerated" population in comparison to those who have never been incarcerated.

Method: A Public Health Ontario dataset of the hepatitis C testing results of 1055073 unique Ontarians between 1999 and 2014 was examined. Patients were stratified based on incarceration status, with "ever incarcerated" defined as having been tested at least once in a provincial or federal correctional facility. Confirmatory testing was defined as having completed quantitative or qualitative RNA testing following a positive or inconclusive anti-HCV result. Groups were then divided by sero-positivity to determine if the proportion that had confirmatory testing differed among each group. A chi-square analysis of categorical variables was used to determine relationships between gender, incarceration status and testing completion.

Result(s): Among those ever incarcerated, 30.1% were sero-positive for HCV, whereas 8.9% of never incarcerated Ontarians tested positive. Incarcerated females carried a disproportionate burden of disease with 45.7% sero-positivity and only 60.3% testing confirmation ($p<0.0001$). All other subgroups displayed a 70.0% or higher proportion of testing confirmation.

Conclusion(s): The next step is to determine if the diagnostic efficiency, or time to completion of testing, differs between the strata. This is particularly important in women given approximately one-third of recently admitted women offenders are sentenced to 25 months or less, meaning they may resume high risk drug use and sexual behaviours in the community, without having the advantage of knowing their full HCV status.

P.31

Physician Knowledge, Attitudes, and Behaviour Associated with HCV Care in the Direct-Acting Antiviral (DAA) Treatment Era: a National Canadian Survey

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Background: The advent of DAA therapy for HCV presents an opportunity to decrease the burden of HCV in Canada. However, treatment uptake is suboptimal, and in 2013, only 3600 HCV cases were treated. Practice guidelines call for increased treatment capacity for HCV to prevent progression of liver disease.

Practice patterns vary across Canada. A national survey of family physicians found that physicians who practise in rural settings were more likely to provide HCV care. A survey of ID specialists found that while most felt they should manage HCV infections, 61% felt inadequately trained.[4] These data suggest that suboptimal training and regional variability in practice may present barriers to delivering optimal HCV care. Limitations of these studies include lack of transdisciplinary sampling, and data that reflects the interferon era. Our study addresses these limitations.

Purpose: Our aim is to assess knowledge, attitudes, practice patterns, and perceived barriers to care surrounding HCV care in Canada in the era of DAA therapies. We seek to identify areas where we can intervene to improve HCV care delivery.

Method: We will administer a national cross-sectional survey to physicians who may be involved in HCV care: general internists, ID specialists, gastroenterologists, hepatologists, and addiction medicine specialists.

A web-based survey was developed based on conceptual frameworks on physician adherence to practice guidelines. Questions from existing surveys were adapted. Physician experts provided feedback on the survey. Information on the following attributes will be collected:

1) Physician and practice characteristics

2) Knowledge about screening, natural history, and treatment

3) Attitudes toward HCV care and people who inject drugs (PWID)

4) HCV practice patterns and barriers to care

5) Preferred knowledge resources for HCV

The survey will be piloted (N=15) to test the survey platform and to improve face validity of the survey. We will work with professional societies to access physician members and encourage participation. Each participant receives CDN$50 compensation. We will use multivariable regression analysis to identify physician and practice characteristics associated with barriers to HCV care. Based on prior data, we hypothesize that physicians in rural areas who treat PWID are more engaged in HCV care.

Result(s): The first phase of data will be reported. We have partnered with AMMI Canada to survey ID specialists.

Conclusion(s): These interim results elucidate practice patterns and barriers to care experienced by Canadian ID specialists regarding HCV care. The next phase will survey other relevant specialties, starting by partnering with CASL to reach hepatologists. These combined data will allow us to work toward improving efficiency of screening, linkage to care, and treatment with novel DAA therapies.

P.32

Estimation of Fibrosis Progression Rates for Chronic Hepatitis C: Updated Meta-analysis and Meta-regression

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Background: Chronic Hepatitis C viral infection (HCV) is a leading cause of cirrhosis, liver failure, and transplantation. The accurate estimation of HCV-disease progression is essential for evaluating the cost effectiveness of treatment and determining treatment prioritization.

Purpose: The purpose of this study was to obtain updated progression rate estimates (FPRs; i.e., pooled annual transition probabilities) of hepatic fibrosis in individuals with chronic HCV infection and to evaluate the impact of covariates on disease progression though an updated systematic review of the evidence, meta-analysis and meta-regression.

Method: A literature search was conducted using MEDLINE, EMBASE, and PubMed databases. The search covered a period of January 1990 to August 2014 with no language limit and was supplemented by reference and citation searches. In general, the review included peer-reviewed studies which examine hepatic fibrosis progression in HCV-infected individuals. Stage-specific annual transition probabilities ($F_{0\rightarrow1}$, $F_{1\rightarrow2}$ $F_{2\rightarrow3,}$ $F_{3\rightarrow4}$) were estimated using the Markov Maximum Likelihood estimation method. Random-effects meta-analyses were use to pool FPRs. The impact of covariates on FPRs was explored through random effects meta-regression analyses. Time-to-cirrhosis was estimated using the pooled FPRs.

Result(s): Overall, the systematic review included a total of 130 studies involving 160 groups of HCV-infected individuals (N=55,581). The update contributed more subjects from non-clinical settings, injection drug users (IDUs), blood donor populations and genotype-1 and -3 infected groups. The pooled stage-specific FPRs were $F_{0\rightarrow1}$: 0.113 (95%CI, 0.103-0.123); $F_{1\rightarrow2}$: 0.087 (95%CI, 0.079-0.096); $F_{2\rightarrow3}$:0.120 (95%CI, 0.110-0.131); $F_{3\rightarrow4}$: 0.116 (95%CI, 0.105-0.128). Based on meta-regression analyses, a longer duration of infection, and genotype-1 infection were independently associated with a slower progression, whereas male gender and blood transfusion were associated with faster progression with at least one transition rate. Relative to liver clinic populations, pediatric and IDU populations also displayed a faster rate of progression for at least one FPR. The estimated unadjusted time-to-cirrhosis was 37 years for all groups, 36 for patients identified in a clinical setting, 48 for non-clinical settings, 59 for genotype-1 and 30 years for genotype-3 groups.

Conclusion(s): The current study provides updated estimates of FPRs associated with chronic HCV, explores covariates associated with fibrosis progression and provides more precise progression estimates for specific patient populations. These estimates should allow for more accurate estimation of the cost-effectiveness of new HCV antivirals and alternative prevention strategies targeting different groups of patients.

P.33

Using a Blended Learning Approach to Increase Capacity in Hepatitis C

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Background: CATIE's Hep C Basics blended learning course provides foundational knowledge of hepatitis C, covering topics such as prevention, transmission, testing, treatment and health literacy. Using a blended learning approach, the course is delivered over six weeks through a combination of interactive e-Learning units, discussion board assignments, self-directed readings and face-to-face instruction (five weeks of online sessions, followed by a one day in-person workshop).

In February 2015, we piloted our first course on Hep C Basics in Halifax, NS, followed by an additional three pilots in Newfoundland and PEI in July 2015. Since the pilot, demand for the course has continued to increase, particularly in B.C., the Prairies, and Atlantic Canada. During the 2015-16 fiscal year, we ran 10 courses across 6 provinces reaching 221 people.

Purpose: CATIE's blended learning program has three primary objectives:

1. Deliver core knowledge training in HIV and hepatitis C that is adaptable to local contexts using a customizable approach to learning

2. Increase access to CATIE educational programming by offering a flexible learning option for participants

3. Increase knowledge transfer through the use of a multimedia approach that addresses a variety of learning styles

Method: Evaluation forms were completed online through CATIE's learning management system upon completion of the course.

Data was entered into Excel and analyzed. Frequency descriptives were produced to summarize the outcome of the workshops. Paired t-tests were used to assess changes in knowledge of hepatitis C.

Result(s): Responses to the evaluations were very positive and pointed to the effectiveness and relevance of the blended learning approach and the Hep C Basics curriculum:

- 98% would recommend the blended learning course to others
- 94% reported an increased capacity to respond to hepatitis C within their community
- 96% reported an increased knowledge of hepatitis C
- 90% reported the course was useful for the work that they do
- 95% were satisfied with the course
- The average score on the pre-test knowledge test was 12.7 out of 20. This increased to 18.6 after the course. This increase was statistically significant.

Qualitative responses supported the shift to Blended Learning, both for its flexibility and the quality of the content offered.

Conclusion(s): CATIE's blended learning program has been very successful in delivering engaging and effective hepatitis C core education since its launch in 2015. It has made CATIE trainings more accessible, allowing us to expand our reach to new audiences such as public health nurses, health care providers working on and off reserve and Indigenous service providers. Many of these new audiences work in rural/remote areas of Canada and blended learning makes training more accessible by allowing learning to occur at a time and place that is convenient for participants. With the success of this approach in delivering core hepatitis C training, CATIE is expanding its catalogue to offer more blended learning courses.

P.34

Professionalization of Harm Reduction in an Unexpected Place: HIV and HCV Prevention in the Communal Spaces Where People Use Drugs

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Background: HCV rates among people who inject drugs remain high in Canada. Expanding the reach of existing harm reduction programs to ensure that sterile injection equipment is available when and where needed is key to preventing transmission of HCV among people who inject drugs. Secondary distribution of harm reduction equipment, where people who are active drug users provide sterile equipment for injecting and smoking/snorting drugs, as well as condoms to their peers outside of formal public health programs, is common. However, innovations in practice may improve prevention efforts.

Purpose: We examine the role of a formalized intervention that transforms secondary distribution points, run by people who use drugs in the spaces where people congregate to use and buy drugs, into satellite harm reduction programs that aim to prevent HIV and HCV transmission.

Method: Qualitative interviews and ethnographic methods are privileged in this study. Semi-structured interviews with Satellite Site Operators (SSO) & clients, as well as program staff and managers in the parent organization were conducted. Interviews are complemented by participant observation of program functioning within the satellite sites, using direct observation of harm reduction equipment distribution, education, and drug use, as well as analysis of program statistics. Thematic analysis is used to examine key themes. We identify factors that contribute to and impede the ability of Satellite Sites to function as an effective public health intervention to reduce transmission of HCV, as well as programmatic factors influencing long term viability.

Result(s): Satellite Sites are effective as high volume locations for the distribution and disposal of harm reduction supplies, expanding the geographic and temporal reach of the parent harm reduction program. The use of people who use drugs as operators of the Satellite Sites gives them credibility when performing education with peers, and provides a unique opportunity to reach hidden drug users who are not accessing traditional harm reduction programs. Factors that impede their ability to be effective include SSO's own precarious housing, the need to find a balance between their own drug use and their work as SSOs, and fear of police intervention. Clients report that they are convenient, comfortable locations to receive harm reduction equipment and information. Training and salary for SSOs contribute to a sense of pride in their work, and ensure consistency across site locations. Key factors contributing to program viability are regular, high volume delivery of supplies; flexible and supportive management from the parent harm reduction program; and supervision as SSOs negotiate their new role as paid public health workers. Ensuring adequate and stable program funding is the main threat to program viability.

Conclusion(s): The formalization of Satellite Sites allows for HCV prevention to be extended directly into the spaces where people congregate to use and buy drugs, an environment typically outside the reach of traditional public health interventions. As harm reduction programs seek new methods to expand the reach and the impact of their HCV prevention efforts, the Satellite Site program provides a potential model for scaling up service provision and addressing barriers to program access.

P.35

A Treatment Model for Bringing Standardised Care for Hepatitis C in Big River First Nation Community

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Background: Hepatitis C is a chronic disease that disproportionately affects Indigenous people living on-reserve. Inadequate access to timely screening, diagnosis and appropriate treatment leads to increased morbidity and poor health outcomes. Implementing another intervention that has shown to yield positive results elsewhere is not enough to address the unique healthcare needs of hepatitis C patients residing in Indigenous communities.

Purpose: The purpose of the study was to engage community members in developing and implementing a care model that can address the unique needs of the hepatitis C patients residing in a rural and remote Indigenous community in northern Saskatchewan.

Method: Through continuous improvement and consultation with elders, nursing staff, administrative staff and community members a care model adequate to deliver screening, diagnosis and treatment of hepatitis C patients residing in Big River First Nation community was implemented.

Result(s): Consultation revealed that access to adequate and timely screening, diagnosis and treatment continues to be major barriers for hepatitis C patients residing in the community. Many patients struggle with addiction, making them vulnerable to hepatitis C infection and interfering with treatment adherence. Patients need access to healthcare that is supportive, confidential and culturally appropriate. Hepatitis C screening and FibroScan uptake can be improved by providing these services at a mobile clinic operating out of the local healthcare center. Treatment delivery can be led by the nursing staff already providing other healthcare programs in the community healthcare center. The nursing staff is supported by a visiting infectious disease specialist from an urban tertiary care centre. On-site nursing staff shares pertinent patient health information with the infectious disease specialist for hepatitis C case management through usage of technologies, including tele-health and electronic health records. Directly observed therapy, in which patients are observed while they take their medication, will help support eligible patients better adhere to treatment. Patients currently ineligible for treatment are connected to appropriate healthcare services to monitor disease progression. Elders and community members can assist with mental health, addictions and ensure treatment delivery is confidential and culturally appropriate. With support from the chief and council the delivery of the program through the mobile clinic will be promoted among the residents of the community.

Conclusion(s): Access to standardised care for hepatitis C can be improved through meaningful engagement of the community members and usage of technology. Consultation with community members helped conceptualize a nursing led hepatitis C treatment model which can be delivered through a mobile clinic. With support of an off-site infectious disease specialist, technology can be used to support on-site nursing staff in rural communities in Saskatchewan and build capacity, knowledge and expertise in infectious disease case management. Support from Chief and Council is integral to promoting screening and testing among residents. Involvement of elders and community members ensures delivery of care is culturally appropriate further encouraging patients to access and adhere to treatment.

Social, Cultural, Environmental, and Population Health Research

P.36

A Novel Investigation of Long-term Trajectories of Injection Patterns in Relation to HCV Risk Among People Who Inject Drugs in Montreal

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Background: People who inject drugs (PWID) are the population most at risk of infection with hepatitis C virus (HCV). With drug addiction being recognized as a chronic condition, studies have increasingly attempted to characterize its long-term course. Yet, up until now, few have investigated patterns of injection drug use over long periods of time, partly due to a more recent development of statistical approaches needed to address this topic. Moreover, little research has been done to characterize the distinct courses of injection patterns among PWID over time and to determine if specific trajectories are predictive of greater HCV risk.

Purpose: The overall aim of this study is to characterize trajectories of injection patterns over a 20-year period in a community-based sample of PWID in Montreal. Specifically, we will: i) examine whether there are distinct trajectory groups over time with respect to injection frequency, and ii) compare HCV incidences among groups. This presentation will focus on the development of the methods and analytical strategy to address these objectives, and preliminary results.

Method: This project will be conducted using data collected in St. Luc/HEPCO, a CIHR/FRQS-funded ongoing prospective open cohort of PWID (1992-). A total of 4235 PWID have been enrolled in the study (3078 and 2549 completed 2 and 3 visits, respectively). To be eligible for enrolment, participants must have injected drugs in the past 6 months and be at least 18 years old. At each bi-annual interview, blood samples are collected for HCV testing and an interviewer-administered questionnaire collects data on socio-demographic characteristics and detailed information on patterns of injection drug use, including frequency of daily injection within the past six months. Trajectories of injection frequency will be examined using semi-parametric latent class growth modelling, an extension of conventional maximum likelihood models. Up to six patterns of injection frequency will be examined and the final number of latent classes will be determined based on several criteria, including average posterior probabilities of groups, the Bayesian Information Criterion, and their clinical relevance. Cumulative HCV incidences in each trajectory group will be examined using Kaplan-Meier survival analyses.

Result(s): We hypothesize that: i) there will be between three and six distinct groups of PWID with similar patterns of injecting frequency [e.g., stable (high, moderate, low), decreasing (early, late), fluctuating], and ii) HCV incidences will be highest among those with stable high injecting frequency and those experiencing frequent episodes of cessation and relapse.

Conclusion(s): Given the ongoing transmission of HCV among PWID, it is imperative to develop more tailored prevention strategies in this high-risk group. Findings derived from this study have the potential to better characterize the long-term course of injection patterns among PWID, and to identify sub-groups who have the highest risk of infection with HCV, and thus, are most in need of prevention efforts. In the long run, this project can potentially inform the development of tailored harm reduction and prevention strategies, adapted to PWID's course of injection patterns over time.

P.37

A Cure for All: Promoting Universal Access to HCV Treatment

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Background: Prior to 2014, the standard treatment for HCV was a 24-48 week regimen of injections of pegylated interferon administered weekly combined with twice daily tablets of ribavirin. This therapy was associated with significant toxicity and side-effects and had a low cure rate (or Sustained Virologic Response) of 40%-50%. New treatments are now available. These new Direct-Acting Antiviral (DAA) medicines are highly tolerable, are taken for a shorter duration and result in a cure rate of more than 90%.

Purpose: Many provincial governments in Canada have placed strict restrictions on access to DAA treatments, limiting eligibility for public reimbursement of treatment costs to people whose virus has progressed to cause significant fibrosis and damage to their liver. These restrictive criteria are not based in best practice or medical evidence and are inconsistent with recommendations made by expert bodies in the field of Hepatology, including the Canadian Agency for Drugs and Technologies in Health, the Canadian Association for the Study of the Liver and the American Association for the Study of Liver Diseases. Requiring the virus to progress to advanced liver disease before treatment denies early access to a cure and raises the risk of future medical complications caused by HCV.

Method: N/A

Result(s): There is an abundance of evidence demonstrating the benefits of treating HCV as early as possible before the development of severe liver disease or other preventable complications. Early treatment results in:

- a higher likelihood of successfully curing the virus through the attainment of a Sustained Virologic Response;
- the prevention of the development of liver disease and a decrease in liver inflammation;
- a reduction in liver-related conditions, including end-stage liver disease and liver cancer;
- a reduction in the risk of liver-related mortality and liver transplantation;
- a reduction in all-cause mortality;
- lesser likelihood of transmission of HCV to others;
- less required follow-up care; and
- substantial improvements to the quality of patients' physical, emotional and social health.

Without early treatment, the incidence of these complications and the prevalence of chronic HCV will increase significantly in the coming years.

Conclusion(s): HCV is curable. Early intervention and treatment is highly cost-effective and crucial to reducing morbidity and mortality levels. Direct-Acting Antiviral medications should be accessible to all Canadians who are living with chronic HCV regardless of their stage of disease progression. Public reimbursement restrictions based either on fibrosis level or presence of cirrhosis should be eliminated. Reimbursement policies should be based on clinical evidence, ensuring early access to treatment for all people living with HCV.

The provinces of Quebec and Prince Edward Island have been able to implement province-wide programs that ensure access to treatment for all people living with HCV. With enough will, other Canadian provinces can do the same.

P.38

Age-cohort Screening: a Crucial Step to HCV Elimination in Canada

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Background: As of 2011, at least 250,000 Canadians were living with HCV, with thousands of new infections occurring every year. In recent years, a growing number of people in Canada have been accessing health care with advanced cases of HCV infection, many of whom have been living with the virus for several decades and are now in need of extensive health care due to symptoms related to advanced liver disease, including liver failure and liver cancer.

Purpose: Canada's current screening guidelines recommend HCV testing for people with known risk factors for the infection including people who use drugs; people in prison; those who were born, traveled or lived in a region with high HCV prevalence; people who received health care where there is a lack of universal precautions; and people who received blood or blood products in Canada prior to 1992.

Method: N/A

Result(s): More than 75% of chronic HCV infections in Canada are among people who were born between the years 1945 and 1975 and it is estimated that at least 100,000 people living with chronic HCV infection are unaware that they are infected. A risk-based approach to screening has had limited success because it relies heavily on memory and disclosure of past potential exposure to HCV. Under this policy, it is estimated that nearly half of all cases of chronic HCV in Canada remain undiagnosed.

Treatment is less effective when HCV is diagnosed and treated late. Late diagnosis also contributes to increased health care costs as a result of expensive treatment for liver failure and liver cancer such as liver transplantation. Without improved rates of screening among people born between 1945 and 1975, the burden of infection and costs to our health and social systems will continue to increase as thousands of chronically infected individuals develop severe illness, jeopardizing their capacity for employment and requiring significant support from health and social assistance systems.

Conclusion(s): Action Hepatitis Canada (AHC) believes that current risk-based screening recommendations need to be complemented with a recommendation for one-time screening for those born between 1945 and 1975. This recommendation has also been made by the Canadian Liver Foundation, as well as the Centres for Disease Control and Prevention and Preventative Services Task Force in the U.S. Targeted testing of this age cohort would facilitate the identification of chronic cases of HCV infection before the onset of severe symptoms, thus enabling individuals to learn about the virus and its progression, ways to promote their own health, and their options for treatment, care and support. Awareness of individuals' viral status is a crucial first step in the prevention of infection to others, the promotion of self-health and the eventual elimination of HCV in Canada.

P.39

From Client to Co-worker: a Case Study of Peer Work Within a Harm Reduction Hepatitis C Treatment Program in Toronto

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Background: In Canada, 70% of new Hepatitis C (HCV) infections are related to injection drug use (IDU) and yet only 1-3% of HCV positive substance users receive treatment. The Toronto Community Hep C Program (TCHCP) began 10 years ago to improve access to HCV treatment for this group and is a partnership between 3 community-based health agencies. Key to the program's success at engaging people who use drugs in HCV treatment has been the meaningful involvement of peers in program design and delivery. Peer involvement is integrated in several ways: group support, a patient advisory board and integrated, paid, permanent community support worker (CSW) positions filled by current or former clients. CSW responsibilities include: group facilitation, public speaking, training, accompaniments, and informal counselling. In depth analysis of peer work in health care overall and of the TCHCP's unique form of peer involvement is lacking. In particular, little is known about the factors that contribute to, or limit, one's trajectory from client to worker.

Purpose: The purpose of this study was to gain an in-depth understanding of the facilitators and challenges in the transition from client to support worker from the perspective of two individuals had undergone this transition within the TCHCP.

Method: This case study employed a collaborative approach whereby the study subjects (authors JB, MB) have had input into the study design and data analysis. Study cases (n=2) were purposefully selected from the group of Community Support Workers (CSW) to represent the diversity of CSW backgrounds and trajectories. In-depth interviews were conducted and audio recordings transcribed verbatim. Data collected from the interviews was coded and analyzed using an inductive approach to identify emergent themes. Study authors PT, KM, JB and MB met multiple times over a period of 3 months to compare, review and discuss findings with a focus on uncovering both unique and common features of each transition.

Result(s): Five main themes emerged: (1) personal qualities, (2) boundaries, (3) substance use, (4) structural factors, (5) journeys. Under each theme both facilitators and challenges emerged. Common personal qualities that contributed to success included identifying as being 'natural helpers'. Being able to identify and maintain boundaries and to learn from boundary breaches was a key facilitator in both cases. A change in substance use, although not necessarily abstinence, was also cited by both as key to ongoing success. Structural factors such as stable housing, income and flexible job parameters were also key facilitators. Both CSW have made substantial life changes since becoming involved with the program that were enabled and further supported by their work as CSW.

Conclusion(s): This study provides insight into a lesser explored aspect of peer work and suggests that the transition from client to co-worker is a gradual process and one that is supported by and in turn helps to support a number of other personal transitions. The cases examined here suggest that a model of peer employment with flexible qualification criteria, transition timelines, job responsibilities and a harm reduction framework can support integration of former clients into health care teams.

P.40

Study of the Interplay Between Access to Services for Mental Health Problems and Receptive Sharing of Material Injection Among People Who Inject Drugs

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Background: In Canada, the population of people who inject drugs (PWID) is estimated between 80,000 and 125,000. This is a major public health concern given that injection drug use, through injection material sharing, is the main source of HCV transmission. Studies have reported a high prevalence of mental health disorders within this population, which in turn have been shown to compromise PWID's ability to adopt safe consumption behaviours. A recent study has suggested that another marker of mental health, psychological distress, is associated with high-risk injection behaviours. Moreover, we know that service utilization, especially for mental health problems, is low among PWID. However, little is known about the services that are provided and their impacts on injection material sharing.

Purpose: The main objectives of the present study were to 1) assess the association between access to services related to a mental health problem and receptive sharing of injection material and 2) to evaluate the impact of psychological distress on this previous association by examining interaction.

Method: The study was conducted using the existing database from the HEPCO study, which is a prospective open cohort of active PWID based in Montréal. At 3-month intervals, between March 2011 and December 2015, participants were tested for HCV and answered an interviewer-administered questionnaire eliciting information on socio-demographic characteristics, substance use and related behaviours, utilization of services (general practitioner, psychiatrist, psychologist, social worker, street/outreach worker, nurse, other) and mental health indicators [Kessler Psychological scale (K10)]. Access to services related to mental health problems, the exposure, was characterized as a dichotomous variable (yes vs. no). The outcome, receptive sharing, described as using injection material previously used by someone else in the past 3 months, was also characterized as a dichotomous variable (yes vs. no). Psychological distress was characterized as a dichotomous variable (severe distress vs. low or no distress). General estimating equation (GEE) analyses were performed.

Result(s): 358 participants contributed to 2,537 visits (median age 40.3, 82% male). Access to services for mental health concerns was reported in 631 visits (24.9%) and receptive sharing in 321 visits (13%). Severe psychological distress was reported in 359 visits (14%). After controlling for age at baseline, gender, and confounders, multivariate GEE analyses have shown that having access to services related to mental health problems was associated with a reduced risk of receptive sharing (adjusted odd ratio of 0.69, 95% confidence interval of 0.50-0.94). No interaction was found with psychological distress.

Conclusion(s): Among PWID, access to services for mental health problems was associated with a lower likelihood of receptive sharing, regardless of the level of psychological distress. Public health interventions should be implemented to increase PWID's engagement in mental health services that could potentially decrease receptive sharing of injection material. Future work should evaluate the impact of mental health services on the acquisition of HCV or other blood-borne infections.

P.41

Ongoing Incident Hepatitis C Virus Infection Among People with a History of Injecting Drug Use in an Australian Prison Setting, 2005-2014: the HITS-p Study

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Background: Hepatitis C virus (HCV) transmission is high in prisons. Understanding trends in incidence and factors associated with infection in prisons is crucial for developing HCV prevention and treatment programs.

Purpose: This study investigated trends in HCV incidence and associated factors among a cohort of prisoners in New South Wales (NSW), Australia.

Method: Data were available from the Hepatitis C Incidence and Transmission Study in prisons (HITS-p) from 2005-2014. Temporal trends in HCV incidence were evaluated. Factors associated with time to HCV seroconversion were assessed using Cox proportional hazards regression.

Result(s): Among 590 participants enrolled, 320 were eligible for inclusion (≥1 follow-up visit, lifetime history of injecting drugs, and HCV antibody/RNA negative at enrolment). Mean age was 26 years, 72% (n=229) were male, 33% (n=104) reported recent injecting drug use, and 25% (n=81) reported syringe sharing during follow-up. Overall, 93 infections were observed [815 person-years (p-yrs) of follow up], with a median time to infection of 553 days (IQR: 228-1024). HCV incidence was 11.4/100 p-yrs (95% CI: 9.3-14.0/100 p-yrs) in the overall population and 6.3/100 p-yrs (95% CI: 4.5-8.9/100 p-yrs) among the continually imprisoned population. A stable trend in incidence was observed over the study period. Overall, time to incident HCV infection was independently associated with older age [adjusted hazard ratio (aHR): 0.66; 95% CI: 0.45-0.98], receiving opioid substitution therapy (OST) (aHR: 1.77; 95% CI: 1.10-2.85), recent methamphetamine injecting (aHR: 2.00; 95% CI: 1.15-3.46), and recent heroin injecting (aHR: 2.52; 95% CI: 1.62-3.91).

Conclusion(s): In Australia, HCV incidence in prisons among people with a history of injecting drug use is high and is associated with older age, injecting methamphetamine, and injecting heroin, with no protective effect of OST. These findings highlight the need for improved harm reduction strategies and evaluation of interferon-free HCV treatment as prevention strategies in prisons.

P.42

Impact of Treatment Induced vs. Spontaneous HCV Clearance on the Long-term Risk of Hepatocellular Carcinoma: BC Hepatitis Testers Cohort

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Background: Chronic hepatitis C is a major cause of hepatocellular carcinoma (HCC). Although interferon-based HCV treatment was associated with reduced HCC risk, low uptake and effectiveness, as well as delay in treatment up until the more advanced stage of the disease, has limited the population level impact of these therapies. Highly effective and well-tolerated direct acting antiviral (DAA) agents are expected to reduce the burden of end stage liver disease including HCC. However, since similar to the interferon-based treatments most people are being treated with DAAs at advanced stage of the disease, their impact could partly be hampered by delay in treatment initiation. As the long-term outcomes of DAAs will take years to accrue, evidence on the effect of early interferon-based treatments on HCC could likely inform the same impact for DAAs.

Purpose: We compared HCC risk among patients who spontaneously cleared the infection with those who achieved sustained virologic response (SVR) to assess likely impact of early treatment on prevention of HCC.

Method: The BC-HTC includes ~1.5 million individuals tested for HCV, HIV or reported as a case of HBV, HCV, HIV or active TB between 1990–2013, linked with medical visits, hospitalizations, cancers, prescription drugs and mortality. Interferon-based HCV treated patients (SVR vs. No SVR) and not treated patients (cleared vs. active infection) were followed to HCC diagnosis, death, or December 31, 2012. We examined the risk HCC across treated vs. not treated groups using multivariable Cox proportional hazards model. Population attributable risk (PAR) was computed to estimate the proportional reduction in HCC incidence that would be achieved by treating people closer to their infection acquisition.

Result(s): Of 46,666 eligible HCV infected individuals: 12,527 were spontaneously cleared; 9,345 were treated of whom 5,355 (57%) achieved SVR and 3,990 (43%) did not; and 24,794 were not treated and had chronic HCV (active infection). The annual HCC incidence rate per 1,000 person-yr (PY) was 0.26 (HCC/PY:34/129,382) for spontaneously cleared; 1.19 (35/29,304) for SVR; 7.7 (170/ 22,169) for No SVR; and 1.24 (381/307,828) for active infection. In the multivariable model, compared to spontaneously cleared group, No SVR group had the highest risk of HCC (hazard ration HR: 14.41, 95%CI 9.68-21.45), followed by active infection (HR: 4.11; 95% CI 2.83-5.96), and SVR (HR: 2.45; 95% CI 1.49-4.01). Cirrhosis, older age (50+), male sex, genotype 3 vs. 1 infection, diabetes, and problematic alcohol use were associated with increased risk of HCC. Compared to the spontaneously cleared group, active infection had the highest PAR (46%) for HCC, followed by No SVR (25%), and SVR (3%).

Conclusion(s): As expected, the HCC risk for spontaneously cleared patients was low. The No SVR group had the highest HCC risk, likely reflecting a poorer prognostic profile at treatment initiation. This highlights the limited HCC prevention benefits of treating the disease at the later stage, even if SVR is achieved. The higher PAR among SVR compared to spontaneously cleared group suggest that earlier HCV treatment will be required to achieve the same risk reduction observed for spontaneously cleared patients.

P.43

Qualitative Evaluation of the Decisions and Experiences of People Who Inject Drugs Who Received a Liver Disease Assessment as Part of a Health Promotion Campaign

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Background: A liver health promotional campaign took place in New South Wales, Australia (May to October 2014), with 235 people who inject drugs (PWID) receiving FibroScan®-based disease assessment. Participant follow-up occurred 2-16 weeks post-enrolment.

Purpose: The aim of this qualitative sub-study was to evaluate the decisions and experiences of participants who received a liver disease assessment, including interpretation of FibroScan® score and subsequent health behaviours.

Method: Participants were recruited from two opioid substitution treatment clinics and one medically supervised injecting centre between November 2015 and February 2016. The four recruitment categories were: a) high FibroScan® score (≥9.5 kPa)/ attended LiveRLife follow-up; b) high score/did not attend follow-up; c) low score (≤9.4 kPa)/attended follow-up; and d) low score/did not attend follow-up. Participants were not reminded of their category during recruitment. Inclusion criteria were: participation in the LiveRLife campaign, received a FibroScan® score, and informed written consent.

Result(s): Of 33 semi-structured interviews [category a (12 participants); category b (2); category c (11); category d (8); 21% female], reasons for wanting to receive a FibroScan® were varied. Most participants interpreted their level of liver disease correctly based on their recalled FibroScan® score. Persons with higher scores frequently recalled feeling shocked by their score (e.g. 'wake-up call') whereas participants with lower scores were typically pleasantly surprised (e.g. incentive to keep liver healthy). Some positive health changes were stated with several relating their score to hepatitis C treatment. However, confusion regarding causes of liver disease persisted with participants linking histories of drug use to advanced liver disease, potentially impeding health literacy and health-seeking behaviours.

Conclusion(s): Results provide greater insight into targeted liver health educational strategies and 'linkage to care' for PWID with, and at-risk of, advanced liver disease. Findings also underscore how healthcare practitioners can help to minimise assessment and treatment barriers for PWID.

P.44

Hepatitis C: The Basics - An Online Course to Address Hepatitis C Knowledge Gaps and Encourage Engagement in Hepatitis C Care

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BACKGROUND: Low levels of linkage and retention in care along the Hepatitis C Illness and Care Journey (HCV ICJ) contribute to HCV-related morbidity and mortality. Knowledge and support gaps, poor patient-provider communication, and stigma are associated with low HCV-ICJ engagement. Existing gaps/barriers which contribute to low HCV ICJ engagement may be compounded by new factors arising from rapid changes in HCV care and treatment (e.g., new drugs, evolving screening guidelines, laboratory testing and primary care involvement). Efficient, timely and easy-to-implement education is needed to address these factors and to foster engagement along the HCV-ICJ. With this in view, we and our partners developed *Hepatitis C: The Basics*, an online course on HCV for people affected by and at risk of the virus.

METHODS: *Hepatitis C: The Basics* is a 30-60 minute self-paced, narrated online course to address key knowledge gaps along the HCV ICJ in a non-stigmatizing and easy-to-understand format. People affected by hepatitis C as well as front line health care providers have taken the course, either online only or via a facilitated event. Two studies were conducted with Time 1 (Aug-2014 to Mar-2016) participants (Online T1, n=85; Facilitated T1, n=38) and two studies for Time 2 (May-2016 to Dec-2016) participants (Online T2, n=201 and Facilitated T2, n=89). All studies included participants that could be matched on pre- and post-course data. Outcome measures included: actual knowledge gains (pre- and post-course tests: 6 questions at T1 and same 6 questions + 4 new questions at T2), perceived knowledge gains, and increased capacity to educate clients about HCV and to encourage client engagement in HCV care.

RESULTS: Average post-test scores for Online T1, Facilitated T1, Online T2, and Facilitated T2 (99%, 88%, 98%, and 69%, respectively) were significantly higher than pre-test scores (79%, 60%, 73%, and 46%, p<.001) across all four studies. As a result of taking the course, the percent of participants reporting their knowledge to have increased 'some' or greater were: Online T1, 85%; Facilitated T1 81%; Online T2, 76.7%; and Facilitated T2, 90.8%. Reported capacity to educate clients increased 'A lot' or 'Double' for 79.6% and 48.2%* of Online T1 and T2 providers, respectively. Provider capacity to engage clients increased 'A lot' or 'Double" for 71.4% and 53.3%* of Online T1 and T2 providers, respectively.

CONCLUSIONS: *Hepatitis C: The Basics* significantly improved participant HCV knowledge and increased provider capacity to educate and encourage client engagement in HCV care. Given the rapidly changing landscape of HCV, e-learning tools could be employed in a variety of settings to efficiently and effectively address significant HCV knowledge gaps among providers and people at-risk or affected by HCV.
*58% (n=117) of T2 Online participants were health care or support workers who received in –clinic training about hepatitis C **before** taking the online course.

P.45

Direct Acting Antiviral Uptake Disparities in HIV-HCV Co-infected Populations in Canada

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Background: Direct acting antivirals (DAAs) have revolutionized hepatitis C (HCV) treatment with nearly 100% cure rates even in real-world studies, giving hope that HCV can be eliminated. Historically, HCV treatment initiation rates have been low, particularly among people who inject drugs (PWID) an important group to target if the goal is to reduce incident HCV infections.

Purpose: In a publically funded health care setting, we investigated DAA treatment uptake disparities among HIV-HCV co-infected subpopulations.

Method: The Canadian Co-Infection Cohort Study prospectively follows 1625 HIV/HCV co-infected participants from 19 centers, representing approximately a quarter of the total Canadian co-infected population in care. Among HCV RNA+ participants, we determined the incidence of HCV treatment initiation per year and stratified by different risk profiles (Aboriginals, women, PWID and men who have sex with men (MSM)). Multivariate Cox models were used to estimate adjusted hazard ratios (aHR, 95% CI) for DAA initiation accounting for age, sex, Aboriginal status, active (within 6 months) and past PWID, MSM, alcohol use, advanced fibrosis, HCV genotype, undetectable HIV RNA, province and income (a priori predictors of treatment initiation).

Result(s): Overall, HCV treatment initiations rose more than three times between 2013 and 2015, from 7 (95% CI: 5-9) to 25 (95% CI: 21-29) per 100 person-years. After stratifying initiation by risk profiles, uptake was markedly lower among Aboriginals, women and active PWID. Among 812 HCV RNA+ participants, 195 initiated DAAs from November 22nd 2013 until December 31st 2015. The vast majority of HCV regimens were interferon free (181/195). Specifically, 127 initiations were regimens including, ledipasvir/ sofosbuvir; 29 initiations were sofosbuvir/ ribavirin; 18 sofosbuvir/ simeprevir +/- ribavirin; 13 sofosbuvir / ribavirin/ peg-interferon; 6 ombitasvir/ paritaprevir/ ritonavir/ ribavirin; 3 sofosbuvir/ daclatasvir and 1 simeprevir/ ribavirin/ peg-interferon.. After adjustment (aHR, 95% CI), Aboriginals (0.51, 0.31-0.85), active PWID (0.58, 0.35-0.98)remained less likely to initiate HCV treatment. Women and past PWID tended to have lower treatment rates (0.86, 0.57, 1.29) and (0.80, 0.53, 1.22). Conversely, MSM were more likely to initiate DAAs (1.75, 1.20-2.55). Despite low treatment uptake, SVR rates were high, 100% among Aboriginals (15/15) and Women (33/33), 86% in active PWID (25/29) and 89% among MSM (63/71) compared to 91% for the cohort overall.

Conclusion(s): Treatment uptake has increased with the availability of all oral DAAs, but marginalized populations are still failing to access treatment. Barriers to treating these subgroups, who can obtain high SVR rates, need to be addressed if DAAs are to impact HCV incidence and the overall burden of chronic liver disease.

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Impact of Availability of Direct-Acting Antivirals for Hepatitis C on Canadian Hospitalization Rates 2012-14

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Background: Hepatitis C has been associated with a substantial and increasing disease burden. Hospitalizations associated with hepatitis C and liver disease increased an average of 6.0% per year from 2004 to 2010 in Canada. As of 2010, rates were highest for persons born between 1950 and 1959. The increase in hospitalization rates has been attributed to the relatively higher HCV prevalence in the baby-boomer birth cohort, the aging of this cohort and limited uptake of HCV treatment options between 2004 and 2010. New direct-acting antivirals (DAA) were available and prescribed starting in 2012 (Boceprevir, Telaprevir) and 2014 (Sofosbuvir and Ledipasvir). These new antivirals have been shown to be effective in eliminating chronic HCV infections and are well tolerated. According to IMS Health, the number of DAA prescriptions peaked in late 2015.

Purpose: We aimed to assess the impact of the availability of the new DAA on hospitalizations associated with hepatitis C and liver disease over the 3 year period of the initial rollout of the new DAA.

Method: The hospital records of inpatients with a diagnosis of chronic hepatitis C and liver disease, including liver cancer, were extracted from the Canadian Discharge Abstract Database (DAD) for four additional fiscal years: April 2011 to March 2015, three of which cover the initial rollout period of treatment with DAAs. Quebec does not participate in the DAD. Rates for this period were compared with those predicted for a status quo scenario from a published study with the predictions based on rates for the 2004-2010 period as the status quo.

Result(s): In the 2014/15 fiscal year there were 3100 hospitalizations with chronic HCV and liver disease compared to a predicted 3400. The expected 4% increase per year from 2011 to 2014 declined to 2% per year. Hospitalization rates for patients under the age of 55 showed no evidence of improvement and were actually slightly higher than expected for the 3 years of the rollout period. Hospitalizations for patients over the age of 70 declined noticeably and were also 25% below expected. Hospitalizations for patients born between 1950 and 1954 were lower than expected and potentially accounted for the largest reduction in the number of hospitalizations as a result of DDA treatment.

Conclusion(s): The liver disease burden associated with chronic HCV is still high and the potential impact of new DDA treatments on hospitalization rates appears to have been modest at best. Reasons for continued increases in hospitalization rates in younger birth-cohorts (patients currently 40-50 years of age) should be explored further. Linked health administrative databases created to monitor the disease burden in the new treatment era will greatly facilitate post treatment surveillance and provide insight not available from the hospital discharge records alone.

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The Effect of Homelessness on HCV Treatment Outcomes Among People Who Inject Drugs

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Background: Recent European guidelines have identified people who inject drugs (PWID) as a priority population to receive HCV treatment. Achievement and maintenance of a sustained virologic response (SVR) may be influenced by a number of factors, including the social determinants of health in such vulnerable populations. One such variable may be unstable housing.

Purpose: We sought to evaluate the impact of homelessness on the achievement and maintenance of SVR in both HCV mono-infected and hepatitis C/human immunodeficiency virus (HCV/HIV) co-infected PWID receiving HCV therapy at a tertiary clinic located in downtown Vancouver.

Method: The target population consisted of HCV-infected PWID receiving HCV therapy according to contemporary clinical guidelines within the multidisciplinary program at the Vancouver Infectious Diseases Center (VIDC), providing care to address medical, psychological, social and addiction-related needs. Demographic information was collected including patterns of recreational drug use. Self-declared homelessness was ascertained by a self-administered questionnaire. The initial endpoint of the study was achievement and maintenance of SVR, with patients followed every 6 months after SVR, more frequently in the setting of suspected HCV re-infection, with such re-infection post-SVR considered a failure of treatment.

Result(s): The study population included 38 individuals of whom 7 (12.5%) women, 20 (53%) HIV co-infected, 24 (63%) genotype 1, 20 (53%), on opiate substitution therapy, with mixed patterns of recreational drug use (39% opiates, 17% cocaine, 47% amphetamines). Homelessness was present in 38 (100%). The crude SVR rate was 79% (30/38), higher in HCV mono-infected individuals (89% vs. 70%). In addition, 2 cases of HCV re-infection were documented, all among HIV co-infected individuals, leading to an effective SVR rate of 60% in this sub-group. Overall, homelessness was associated with a 30% increase in risk of not achieving and maintaining SVR. Type of recreational drug use (opiates vs. stimulants) was not associated with the likelihood of HCV treatment success.

Conclusion(s): High rates of response to HCV treatment can be achieved and maintained among active PWID. However, in this vulnerable population, attention must be paid to non-traditional factors that may influence outcomes, including homelessness, especially among those who are co-infected with HIV. As more PWID are offered HCV therapy, programs must be developed to address short and long-term housing to maximize the impact of these interventions.

P.49

Establishing the ON-HBC Cohort: A Validated Population-Based Linkage of Laboratory and Health Administrative Data for Understanding Hepatitis B and C Epidemiology in Ontario, Canada

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Background: Viral Hepatitis B and C (HBV/HCV) are among the most burdensome infectious diseases in Ontario, with current prevalence of chronic infection estimated at 1.6% for HBV and 0.9% for HCV. These estimates are based on serological or mathematical modeling studies among the general Canadian population, and do not reflect disparities across at-risk groups. In addition, prevalence may be over- or underestimated by serological studies due to selection biases, and mathematical models may be inaccurate if not properly validated with empirical data. Therefore, better population-level estimates are needed for more informed policy and clinical decision making, and hence better facilitated patient care. In this abstract, we describe a proposal for establishing a cohort of individuals living with HBV/HCV in Ontario, and present preliminary findings.

Design/Methods: We previously linked 18 years (2007-2014) of HBV/HCV laboratory tests performed by Public Health Ontario (PHO) laboratories to health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES). This linkage includes all individuals with a valid health insurance number tested for HBV/HCV in the province of Ontario, excluding private or hospital labs. PHO laboratories collect information on HBV/HCV antigen, antibody, and nucleic acid tests conducted as a part of routine screens, treatment follow-up, or confirmatory testing within the province. We use a modified provincial case definition, designed to make full use of available serology, to determine infection/immunity status. These categories are then linked to an extensive array of administrative data, including databases with information on demographics, mortality, hospitalizations, emergency department visits, physician services, medications, chronic conditions (cancer, diabetes, HIV), and immigration status. With this information, Random Forest Classification and Regression Tree (RF-CART) models will be used to develop and validate case-finding algorithms for identifying HBV/HCV. These algorithms will then be used to identify additional HBV/HCV cases not captured by PHO laboratories, in order to establish the Ontario-Hepatitis B and C (ON-HBC) cohort.

Results: Our cohort includes 5,006,263 records of tests performed on 2,541,358 individuals. We observe 119,411 (3.2%), 677,282 (49.4%), and 142,234 (79.2%) detections of HBV surface antigen, antibody (Ab), and DNA, respectively; as well as 171,068 (87.9%) and 53,526 (50.1%) detections of anti-HCV Ab and HCV RNA, respectively. A number of combinations of HBV serology are currently being classified (by two gastroenterologists) into six infection and six immunity groups, which represent our modified case definition categories. The inter-rater reliability will be reported, and discrepancies will resolved by consensus. This process will then be repeated for HCV serology. The next steps are to compare these infection/immunity categories with the administrative data and develop case-finding algorithms. These algorithms will then be applied to health administrative data, independent of laboratory results, to identify cases not present in the PHO database. Once established, the ON-HBC cohort can be used to address a multitude of research questions to better facilitate clinical and public health initiatives aimed at reducing the burden of HBV/HCV.

Conclusion: The ON-HBC cohort will equip decision makers with improved epidemiological estimates needed to guide evidence-informed public health and health care interventions in Ontario.

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Type I Interferon-Associated Impairment of the Humoral Immune Response against HCV

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

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The Effect of Short Injection Remission Episodes on the frequency of Injection During Relapses, Among People who Inject Drugs in Montréal, Canada

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Background: People who inject drug (PWID) are at increased risk of contracting hepatitis C (HCV). Drug injection usually follows a non linear trajectory, and is often characterized by multiple remissions and relapses. Injection frequency is an important risk factor for HCV infection. Whether short injection remission episodes are associated with a reduction of the injection frequency when resuming injection is not well studied.

Purpose: The objective was to assess the association between injection frequency and short injection remission episodes.

Methods: Between March 2011 and December 2014, people who inject drugs recruited in HEPCO, a Montréal-based observational cohort study, were tested for HCV and completed a baseline questionnaire administered by an interviewer and eliciting information on sociodemographics and drug use behaviours in the past 3 months. For this investigation, all participants had injected in the month prior to baseline interview. The outcome of interest, i.e. injection frequency in the past month, was categorized as either lower frequency (1 to 30 injections) or higher frequency (>30 injections). The independent variable of interest, having a short injection remission episode, was assessed by asking whether participants injected in each of the first two months of the past 3-month period, and was dichotomized as follows: having a short injection remission episode (no drug injection in one or both months) vs. not (drug injection in both months). Univariate and multivariate logistic regression analyses were performed.

Results: 479 participants followed-up between March 2011 and December 2014 injected drugs in the month prior to baseline (mean age 39.6, 82% male). One hundred ten (23%) participants had a short injection remission episode. Participants with an injection remission episode were more likely to be male (P=0.028) and to have been incarcerated in the past 3 months (P<0.001) compared to those who did not. In univariate logistic regression analyses, having a short injection remission episode was significantly associated with a reduced likelihood of having a higher injection frequency [odds ratio (OR) 0.24, 95% confidence interval (CI) 0.15-0.38). After adjusting for all covariates, the association remained statistically significant (adjusted OR 0.21, 95% CI 0.12-0.35).

Conclusion: Having a short episode of injection remission was associated with a lower injection frequency when relapsing. Short episodes of injection remission could potentially be associated with reduced likelihoods of harms related to drug injection, such as the transmission of HCV.

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Activity-based Protein Profiling of the Role of 25-hydroxycholesterol and miRNA-185 in the Immunometabolic Response to Hepatitis C Infection

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Emerging evidence has attributed a pivotal role to microRNAs in the arms-race between viral proliferation and the host immune response. It has recently been shown that microRNA 185 (miR-185) inhibits proliferation of hepatitis C virus (HCV) via the down-regulation of genes involved in the synthesis of lipids required by the virus. To counteract these effects, HCV induces a decrease in miR-185 levels during infection. The host innate immune system is capable of increasing the expression of miR-185, and therefore inhibiting cellular lipid synthesis and viral replication, via the small molecule 25-hydroxycholesterol (25-HC). MicroRNAs exert their cellular effects by interacting with messenger RNAs using components of the RNA silencing pathway and thus ultimately affect protein abundance and function. A modern tool for proteomic profiling of enzyme function is activity-based protein profiling. This approach makes use of small molecule probes to covalently label families of active enzymes at their active site, and profile their function. We have used an activity-based probe based on an inhibitor scaffold containing a fluorophosphonate to profile changes to host serine hydrolase enzymes caused by HCV and 25-HC regulation of miR-185, with the goal of identifying enzymes whose activities are modified via viral and/or host immunometabolic systems. Using stable isotope labelling and mass-spectrometry analysis to quantify changes in activity, a number of serine hydrolases were identified with altered activity during infection and immunometabolism regulated by 25-HC and miR-185.

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Use of Oncolytic Measles Vector for Targeted Treatment of HCV-Induced Liver Cancer

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Without a preventive vaccine, hepatitis C virus (HCV) remains an important pathogen and a medical burden worldwide. About 170-300 million HCV carriers are predisposed to risks of end-stage liver diseases including cirrhosis and hepatocellular carcinoma (HCC). While direct-acting antivirals (DAAs) have been developed for the antiviral treatment of HCV infection, options for late stage liver cancer induced by the virus remain limited, with liver transplantation often being the only treatment available. Oncolytic measles virus (MV) represents a novel therapy for the management of cancers. Recent identification of the tumor marker nectin-4 as one of its receptors underscores its potential for treatment against carcinomas that highly express this adhesion molecule, including HCC. Furthermore, host cell innate immunity is suppressed in HCV-infected liver owing to HCV NS3/4A protease-mediated suppression of interferon (IFN) production. Such a diminished antiviral response could facilitate the infectivity of oncolytic MV vector. To explore this possibility, we examined the use of MV oncolytic vectors expressing the viral H glycoprotein which targets and attaches to nectin-4 in HCV replicating-hepatoma cells. Results indicate that HCC cell lines including Huh-7, HepG2, and Hep3B express nectin-4 and are susceptible to oncolytic MV infection. In addition, Huh-7 cells harboring replicating HCV subgenomes exhibit better MV infectivity compared to the HCV-negative parental cells. We propose to generate xenograft (immune deficient) and syngeneic (immune competent) liver tumor models in mice and determine the effect of MV-derived vectors on tumor growth. Further studies are underway and results from these studies will help develop MV-based oncolytic vectors as a highly targeted treatment against HCV-induced liver cancer.

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Hemoglobin-conjugated Ribavirin Preferentially Targets M2-type Primary Human Kupffer Cells.

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Background/Aims: Macrophages are key contributors to the immunopathogenesis of liver disease. For example, "regulatory" M2-like tumor macrophages have been linked to worse outcomes in hepatocellular carcinoma. Therapeutic targeting of liver macrophages is an attractive method to treat macrophage-influenced diseases; targeting individual macrophage subtypes might shift the local immune environment. M2 and "inflammatory" M1 macrophages express different levels of CD163, a scavenger receptor that binds haptoglobin-hemoglobin conjugates (HDC). The aim of the current study was to examine whether HDC could be targeted to particular macrophage subtypes and to subpopulations of primary human liver Kupffer cells.

Methods: Peripheral blood monocytes were polarized to macrophages using different stimulation cocktails that induce varying levels of CD163 expression (higher in M2-type cells). Macrophages were exposed to 10 µg/mL of AF750-labeled haptoglobin-hemoglobin (Hp-Hb) and AF750-labeled haptoglobin-hemoglobin-ribavirin (Hp-Hb-RBV) and stained with CD68 (macrophages), CD3 (T cells), CD19 (B cells), and anti-human CD163. HDC uptake was measured by flow cytometry and correlated to CD163 expression. Anti-CD163 antibodies were used to block HDC uptake. To show human liver relevance, fresh primary human Kupffer cells were isolated from healthy liver tissue obtained during transplantation. Kupffer cells were exposed to 100 µg/mL of Hp-Hb-RBV for 1 h or left untreated. Kupffer cell Hp-Hb-RBV uptake was measured by flow cytometry as above.

Results: Hp-Hb-RBV was avidly ingested by primary human monocyte-derived macrophages and human Kupffer cells. Uptake correlated positively with surface expression of CD163, a prototypical M2 scavenger receptor. Specificity of Hp-Hb-RBV for CD163 was demonstrated by blocking using anti-CD163 antibodies. Kupffer cells showed heterogeneous CD163 expression. Flow cytometric analysis revealed that CD163-positive Kupffer cells took up Hp-Hb-RBV more avidly than CD163-negative Kupffer cells.

Conclusions: In summary, our data demonstrated that Hp-Hb-RBV was sequestered by both primary human Kupffer cells and monocyte-derived macrophages, but in a differential manner that correlates with macrophage phenotype. Hp-Hb-RBV was preferentially taken up by CD163+ M2-like Kupffer cells and the degree of sequestration by monocyte-derived macrophages was determined by the level of CD163 expression. Taken together these results suggest that Hp-Hb-RBV directly targets subpopulations of human Kupffer cells and macrophages demonstrating the potential for differential macrophage targeting.

You will also find the following abstracts/posters from CanHepC Summer Students in:

P.11 and P.20: Khan, Sarwat T.

P.27: Rycraft, Tyler

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