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

5th Canadian Symposium on Hepatitis C Virus

5ème Symposium canadien sur le virus de l'hépatite C

Institut de recherche
Centre universitaire de santé McGill

Research Institute
McGill University Health Centre

February 26, 2016 – 26 février 2016

The Fairmont Queen Elizabeth,
Montréal, QC

Saint-François Banquet Room

McGill UNIVERSITY

CRCHUM
CENTRE DE RECHERCHE

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Welcome Message

Dear Colleagues,

We are pleased to welcome you to the 5th Canadian Symposium on Hepatitis C Virus (HCV). Over the past 12 years, Canadian researchers have contributed to major discoveries in the field of Hepatitis C. Such discoveries include: the first proof of concept antiviral against HCV, the development of the first humanized mouse model for HCV infection, identification of novel biomarkers for HCV disease progression and treatment outcome and research assessing access to treatment in marginalized populations, in particular people with HIV, people who inject drugs, and First Nations people.

With revolutionary advances in HCV treatment we are now at a cross roads. Many have declared the HCV epidemic already over in anticipation of the widespread use of these highly effective therapies. HCV research and care paradigms are rapidly changing. With optimism comes the need to re-evaluate priorities and find better ways to effectively use research to change policy so that all can benefit. Despite our internationally recognized successes, it is evident that interactions between Canadian scientists, clinicians and the affected communities need to be strengthened in order to effectively respond to current and future challenges in the management of hepatitis C. We believe that the Canadian HCV Symposium provides an ideal forum to exchange research findings, promote collaboration, and create synergy among Canadian researchers, practitioners and people living with HCV. We hope that this fifth annual symposium will build on the success of the first 4 meetings and continue to foster knowledge translation for researchers, healthcare practitioners and community-based groups working in the field, It is indeed an exciting moment but we are not done yet!

The National Canadian Research Training Program in Hepatitis C (NCRTP-HepC) that is now the Canadian Network on Hepatitis C (CanHepC) has significantly contributed to advancing research training and knowledge translation in the field of hepatitis C. It has been very successful in its goal to improve research capacity by developing a network of collaborative investigators whose work encompasses the social, behavioural, clinical and basic sciences, crucial to develop, study and implement effective prevention and care programs to eradicate HCV-related diseases in Canada and worldwide. We are pleased that we are able to continue to contribute to the organization of this important meeting.

We would like to welcome you to the beautiful city of Montreal. We look forward to finding out about your exciting research and to discussing together how we can shape the future of Hepatitis C research in Canada.

On behalf of the organizing committee,

Marina Klein, MD, MSc, FRCP(C), Chair

Selena M. Sagan, Ph.D., Co-Chair

Message d'accueil

Chers Collègues,

Nous vous souhaitons la bienvenue au 5ème Symposium canadien sur l'hépatite C. Au cours des 12 dernières années, des chercheurs de partout au Canada ont contribué à certaines des découvertes majeures dans le domaine de l'hépatite C. Ces découvertes incluent la première démonstration clinique de l'efficacité de molécules antivirales ciblées contre le virus de l'hépatite C (VHC), le développement du premier modèle de souris humanisée permettant l'infection par le VHC, l'identification de nouveaux biomarqueurs de la progression de la maladie et prédisant le résultat du traitement et l'identification de déterminants de l'accès au traitement antiviral chez les populations marginalisées, notamment les individus infectés par le VIH, les utilisateurs de drogues illicites et les citoyens faisant partie des Premières Nations.

Suite aux avancées révolutionnaires dans le domaine des traitements contre le VHC nous sommes à une croisée des chemins. Plusieurs affirment déjà que l'épidémie du VHC est terminée, en anticipation de l'utilisation généralisée des nouveaux traitements hautement efficaces. La recherche dans le domaine de l'hépatite C et les paradigmes de traitement changent rapidement. Cet optimisme nous pousse à réévaluer les priorités et à trouver de nouvelles façons d'utiliser efficacement la recherche pour changer les mentalités afin que tous en profite. Malgré nos succès reconnus internationalement, il est apparu évident que les interactions entre les scientifiques, les cliniciens et les communautés cibles partout au Canada avaient besoin d'être renforcées afin de répondre efficacement aux défis présents et futurs que soulèvent l'infection par le VHC. Nous sommes convaincus que le Symposium canadien sur le virus de l'hépatite C est un excellent forum pour échanger résultats de la recherche, promouvoir les collaborations, et créer une synergie globale. Nous espérons que ce cinquième symposium annuel nous permettra de bâtir sur les succès engendrés par nos 4 premiers symposiums, et qu'il continuera à promouvoir le transfert des connaissances entre les chercheurs, les cliniciens et les groupes travaillant sur le terrain. C'est définitivement une période excitante, mais plusieurs défis demeurent!

Le Programme de subvention nationale de formation des Instituts de recherche en santé du Canada sur l'hépatite C (NCRTP-HepC) qui est devenu le réseau canadien sur l'hépatite C (CanHepC) a contribué de façon significative à la formation de nouveaux étudiants et chercheurs ainsi qu'à la diffusion des connaissances dans le domaine de l'hépatite C. Ce programme a particulièrement permis d'accroître l'étendue des travaux de recherche en développant un réseau de chercheurs dont les thèmes englobent les sciences sociales et du comportement ainsi que la recherche clinique et fondamentale. Les objectifs du programme sont, entre autres, de développer, étudier et mettre en œuvre des moyens efficaces de prévention et des programmes de soins dans le but d'éradiquer à long terme l'infection par le VHC au Canada et dans le reste du monde. Nous sommes donc très heureux d'organiser encore une fois cette année cet important symposium.

Nous tenons à vous souhaiter la bienvenue à Montréal. Espérons que nous pourrons découvrir les problématiques importantes que soulèvent encore l'infection par le VHC, l'étendue des travaux de recherche qui sont actuellement effectués sur le VHC au Canada et en profiter afin de discuter ensemble des moyens à prendre afin de façonner l'avenir de la recherche sur l'hépatite C au Canada.

De la part du comité d'organisation,

Marina Klein, MD, MSc, FRCP(C), Présidente

Selena M. Sagan, Ph.D., Coprésidente

Program – Programme

"We're not Done Yet: Remaining Challenges in Hepatitis C"

07h00 - 08h00 Registration, Breakfast. Poster Area Opens at 14h00: Saint-Laurent and Gatineau, Convention Floor
Inscription, déjeuner. Ouverture de la salle des affiches à 14h00: Saint-Laurent et Gatineau, étage des congrès

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

Biomedical Sciences
Co-Chairs: Dr. Hugo Soudeyns and Dr. Sonya MacParland

08:15 - 08h45 Opening Keynote: How Close Are we to Realizing an HCV Vaccine?
Dr. Andrea Cox, Johns Hopkins University, Baltimore, USA

08h45 - 09h05 Is it Time to Move on from HCV? A Basic Science Perspective
Dr. Daniel Lamarre, Université de Montréal, Montréal, Canada

Oral Presentations – Présentations orales

09h05 - 09h15 Transcriptomic Characterization of the Immune Response to Acute Hepatitis C Virus Infection
Dr. Naglaa Shoukry, Université de Montréal, Montréal, Canada

09h15 - 09h25 Investigating the Mechanisms of Action of Neutralizing Antibody Responses Elicited by a Recombinant Hepatitis C Virus Envelope Glycoprotein E1E2 Vaccine
Jason A. Wong, University of Alberta, Edmonton, Canada

Clinical Sciences
Co-Chairs: Dr. Marc Bilodeau and Dr. Lisa Barrett

09h25 - 09h55 Targeting HCV: What Have we Learned from Real World Roll Out of DAAs?
Dr. David Nelson, University of Florida, Gainesville, USA

09h55 - 10h10 Coffee Break – Pause café

10h10 - 10h30 Will HCV Antiviral Resistance Matter?
Dr. Richard Harrigan, University of British Columbia, Vancouver, Canada

Oral Presentations - Présentations orales

10h30 - 10h40 Real Life Clinical Experience with Second Generation Directly Acting Antiviral (DAA) Drugs for the Treatment of Chronic Hepatitis C in Calgary, Alberta, Canada
Dr. Golasa Samadi Kochaksaraei, University of Calgary, Calgary, Canada

10h40 - 10h50 Real Life Experience of Hepatitis C Management with Interferon-Free DAA Treatments in Montreal
Dr. Emmanuelle Huchet, Clinique Médicale l'Actuel, Montréal, Canada

Epidemiology and Public Health
Co-Chairs: Dr. Julie Bruneau and Sahar Saeed

10h50 - 11h20 HCV Prevention: Modeling the Impact of Expanding HCV Treatment
Dr. Matthew Hickman, University of Bristol, Bristol, UK

11h20 - 11h40 Harm Reduction Along the HCV Prevention and Care Continuum
Dr. Joseph Cox, McGill University Health Centre, Montréal, Canada

Oral Presentations - Présentations orales

11h40 - 11h50	Correctional Facilities As HCV Treatment Access Point: a Framework for Corrections Research and HCV Treatment **Dr. Lisa Barrett, Dalhousie University, Halifax, Canada**
11h50 - 12h00	Risk of Hepatitis C Virus Re-Infection or Late Relapse after Sustained Virologic Response to Interferon-based Therapy in HIV Co-infected Canadians **Carmine Rossi, McGill University, Montréal, Canada**
12h00 - 13h15	Lunch and Exhibition – Diner et exposition: Saint-Laurent and Gatineau, Convention Floor

Behavioural Sciences
Co-Chairs: Dr. Benedikt Fischer and Emmanuel Fortier

13h15 - 13h45	Challenges in Implementing HCV Therapy Broadly in Low and Middle Income Countries **Dr. Manal El-Sayed, Ain Shams University, Cairo, Egypt**
13h45 - 14h05	How Indigenous Methodologies can Inform our Response to the HCV Epidemic in Canada **Dr. Alexandra King, Simon Fraser University, Burnaby, Canada**
	Oral Presentations - Présentations orales
14h05 - 14h15	Community-Directed Research Priorities for Those with Indigenous Lived Hepatitis C Experience **Chris Macklin, Simon Fraser University, Burnaby, Canada**
14h15 - 14h25	CACTUS Montreal: Initiatives to Identify Needs of PWID to Provide a Support and Increase Their Hep C Treatment Access **Julie Bouchard, CACTUS Montréal, Montréal, Canada**
14H25 - 14h40	Coffee Break – Pause café
14h40 - 14h50	The Evolving Role of Nurses in the Hepatitis C Care **Geri Hirsch, Nova Scotia Health Authority, Halifax, Canada**
14h50 - 15h00	Patient Advocate **Marsha Lecour, Toronto, Canada**
15h00 - 15h40	Debate: 'Is an HCV Vaccine Really Needed?' **Pro: Dr. Andrea Cox, Johns Hopkins University, Baltimore, USA** **Con: Dr. David Wong, University Health Network, Toronto, Canada** Moderator: Dr. Jason Grebely, University of New South Wales, Sydney, Australia
15h40 - 15h50	Update on Restriction of Reimbursement of Treatments/Drugs in Canada **Alison Marshall, University of New South Wales, Sydney, Australia**
15h50 - 16h55	Panel and Audience Discussion – Table ronde et discussion avec l'audience **From Research to Action: How to Translate Research into Policy Change** Moderator: Dr. Mel Krajden, University of British Columbia, Vancouver, Canada Panelists: Glenn Betteridge, CTAC, Dr. Howard Njoo, PHAC, Dr. Dan Werb, University of San Diego
16h55 – 17h00	Closing Remarks – Mot de la fin **Dr. Marina Klein, McGill University, Montréal, Canada**
17h00 - 18h30	Cocktail and Poster Session – Cocktail et présentation des affiches: Saint-Laurent and Gatineau, Convention Floor

Committees – Comités

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Marina Klein, McGill University, Chair
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Naglaa Shoukry, Université de Montréal
Hugo Soudeyns, Université de Montréal
Nicholas van Buuren, Stanford University
Joyce Wilson, University of Saskatchewan

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Sonya MacParland, University of Toronto

Clinical Sciences
Marc Bilodeau, Université de Montréal
Lisa Barrett, Dalhousie University

Epidemiology and Public Health
Julie Bruneau, Université de Montréal
Sahar Saeed, McGill University

Behavioural Sciences
Benedikt Fischer, University of Toronto
Emmanuel Fortier, Université de Montréal

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Jason Grebely, University of New South Wales
Mel Krajden, University of British Columbia
Marina Klein, McGill University
Jeff Kwong, University of Toronto
Evan Cunningham, University of New South Wales
Rosie Thein, University of Toronto

Speaker Biographies and Abstracts – Biographies des conférenciers et résumés

Biomedical Sciences

Dr. Andrea Cox, Johns Hopkins University, Baltimore, USA

Biography

Andrea Cox is currently an Associate Professor at the Johns Hopkins School of Medicine. She earned her Ph.D. studying T cell immunology at The University of Virginia. She subsequently completed an M.D. and Internal Medicine and Infectious Disease training at Johns Hopkins. Clinically, she specializes in the treatment of patients with hepatitis virus infections. Her laboratory investigates human immune responses to chronic viral infections, including mechanisms through which these infections stimulate and evade immune responses, vaccine development, and immunotherapy. Dr. Cox has managed a longitudinal cohort of injection drug users since 2003 to permit detailed molecular analysis of HCV transmission, host immune responses, and virus sequence evolution. She is also a principal investigator on the first prophylactic HCV vaccine trial in at-risk people.

Abstract

How Close are we to Realizing an HCV Vaccine?

HCV therapy has improved dramatically with the advent of potent directly acting antivirals. However, numerous aspects of HCV disease make significant control of HCV a substantial challenge. An estimated 5% of HCV-infected persons are diagnosed globally. The proportion of patients who access and complete treatment remains low. HCV therapy does not provide immunity against subsequent infection or reverse severe liver disease in all. HCV transmission persists in areas with limited access to antiviral drugs and poor needle injection and blood product hygiene. Successful control of HCV infection will likely require a combination of mass screening to identify those with infection, treatment, and harm reduction strategies for uninfected people at risk, including prophylactic HCV vaccination. A prophylactic vaccine would likely prevent liver damage associated with infection and lessen the need for engagement of at-risk populations at the time of greatest risk, such as during active injection drug use. Barriers to development of a vaccine include the marked genetic diversity of HCV, the lack of immunologically competent and convenient model systems, the numerous mechanisms through which HCV evades the immune response, and the infeasibility of using live attenuated and inactivated whole virus as HCV vaccines due to limited culture capacity and risk of reversion to virulence. This talk will discuss the need for a vaccine, evidence that a vaccine to prevent chronic infection is possible, challenges to immunologic control of HCV, and the vaccine strategies tested to date.

Dr. Daniel Lamarre, Université de Montréal, Montréal, Canada

Biography

Dr. Daniel Lamarre began his academic career at the Université de Montréal in 2003 as full professor at the department of Medicine and Chairman (2003-2013) of the Novartis/Canadian Liver Foundation Hepatology Research Chair. He leads the Molecular Immunovirology Laboratory at CRCHUM/Université de Montréal. Previously, he completed his doctoral studies in biochemistry at the Université de Sherbrooke with Dr.. Guy G. Poirier, and his postdoctoral training in immunology at the Institut de Recherches Cliniques de Montréal and Genentech with Dr. Rafick P. Sekaly. He subsequently joined Boehringer Ingelheim R&D Canada (1990-2013), where he contributed to research programs in the areas of HIV and HCV infectious diseases. Dr Lamarre's major research contributions are in the field of virology/immunovirology and therapeutic area of infectious diseases. Over the last 25 years, he has focused his activities in deciphering molecular aspects of virus infection that are causing serious human diseases, with a major impact into hepatitis C medicines. As the HCV Research Therapeutic Area Head at Boehringer Ingelheim, he established a leading position within the pharmaceutical industry world-wide with the discovery of HCV protease inhibitor BILN 2061 (ciluprevir; Nature 2003) leading to the first and robust proof-of-concept in human infected with HCV. He oversaw the discovery of several HCV drug candidates. Dr. Lamarre is now focusing his research towards the discovery of broad-spectrum therapies for infectious diseases. Using proteomic and functional genomics approaches for the identification of therapeutic targets, his overall objective is to identify antivirals and immunodulators of innate responses for the treatment of viral infection and cancer cells.

Abstract

Is it Time to Move on from HCV? A Basic Science Perspective

Hepatitis C virus (HCV) infection is a substantial health problem worldwide associated to different outcomes of liver diseases and several extrahepatic manifestations. The discovery of HCV in 1989 (Choo et al. Science 1989) had provided fundamental molecular insights for initiating antiviral drug discovery, which rapidly led to the discovery of the first NS3 protease inhibitor to establish a robust proof-of-concept in human (Lamarre et al. Nature 2003). As of 2014, the treatment of patients with chronic HCV infection has been revolutionized by the approval of a number of direct acting antivirals (DAAs), which yield spectacular cure rate when used in combination. The last 25 years have also been full of discoveries opening up new avenues for studying HCV biology. Our lab focuses on discovery of target-based broad spectrum therapies for infectious diseases, based on novel biology exploiting virus-host protein interactions and regulators of innate immunity. Our virus-host interactome research program led to the identification of hundred of human proteins as specific HCV-interacting partners (JVI 2011, JVI 2013; MCP 2014) for which the interaction network analysis emphasizes a high interconnectivity of these human proteins involved in viral replication and pathogenesis. We found that majority of targeted human proteins are also known interactors of other virus proteins, suggesting that a restricted number of host factors are critical to multiple virus life cycles. Such findings open an innovative drug discovery paradigm into the validation of critical host targets for broad-spectrum first-in-class antivirals against family of RNA viruses.

Clinical Sciences

Dr. David Nelson, University of Florida, Gainesville, USA

Biography

Dr. David Nelson is Professor of Medicine and Assistant Vice President for Research at the University of Florida where he serves as the Director of the Clinical and Translational Science Institute. The mission of this NIH funded institute is to improve how biomedical research is conducted and to enable scientists to work together to accelerate the translation of laboratory discoveries into clinical treatments. Dr. Nelson's area of clinical expertise is Hepatology with an emphasis on the management of viral hepatitis. In 2013, he was recognized as one of the Clinical Research Forum's Top 10 Clinical Research Achievements and in 2014 received the AAMC Learning Health System Champion Research Award. He currently oversees more than 15 active clinical trials and has a 20 year track record of NIH funding. He serves as Principal Investigator on both basic science and clinical research grants and has an impressive record of academic achievement with more than $40 million in research funding and over 200 publications.

Abstract

Targeting HCV: What Have we Learned from Real-World Roll-Out of DAAs

Background: Since the translation of novel HCV therapeutics from clinical trials to clinical practice has traditionally been associated with significantly lower SVR rates and higher rates of adverse events than observed in phase 3 trials, the objective of many ongoing registries is to evaluate the safety, tolerability and effectiveness of new therapies in a large cohort of patients undergoing treatment in real-world clinical practice settings.

Methods: HCV-TARGET (HCVT) is a multicenter, prospective, observational cohort where patients who initiated HCV treatment in clinical practice were enrolled and treated according to the regional standards of care at academic (n=38) and community medical centers (n=13) in North America (n=47) and Europe (n=4). Information is collected from the medical records and abstracted into a unique centralized data core. Independent data monitors systematically review data entries for completeness and accuracy. Demographic, clinical, adverse events (AEs) and virological data are collected throughout treatment and post-treatment follow-up.

Results/Conclusions: To date, over 3,000 patients have been treated with all-oral, direct acting antiviral regimens in HCVT. Multiple other registries are ongoing and the comparative results of these real world registries will be presented. Overall, the genotype 1, 2, and 4 populations (including transplant) have responded with a similar efficacy and safety pattern as predicted in phase III trials. High percentages of patients with decompensated cirrhosis have also undergone successful therapy and many have shown improvement in liver disease markers. However, genotype 3 patients, especially those who are treatment experienced and have cirrhosis show suboptimal response rates from phase III trials.

Dr. Richard Harrigan, University of British Columbia, Vancouver, Canada

Biography

Dr. Richard Harrigan is the Director of Research Laboratories at the BC Centre for Excellence in HIV/AIDS. For more than a decade, Dr. Harrigan has been a local, national, and international leader in the development of cutting-edge translational research with important implications for the clinical management of HIV. He has contributed extensively to our understanding of HIV drug efficacy and resistance, as well as the human and viral parameters that influence HIV disease progression. His lab has developed and distributed software for improved automated analysis of drug resistance ("ReCall"), which is now being used worldwide, and is expanding his focus to HCV. His work primarily focuses on drug efficacy, drug resistance, and the human and viral parameters that influence disease progression. As well as the Glen Hillson Professor in Clinical HIV Virology, Dr. Harrigan also holds the CIHR-GSK Research Chair in HIV/AIDS at the University of British Columbia, and is a Professor in the Division of AIDS (Faculty of Medicine) at the University of British Columbia.

Abstract

Will HCV Antiviral Resistance Matter?

Our experience with chemotherapy for infectious diseases is that sooner or later there will be issues with drug resistance. Despite remarkable progress, treatment of Hepatitis C is no exception. This presentation will describe the basis for the emergence of resistance upon treatment failure, and our experience with HCV treatments in Canada (past, current, and best guesses for the future). I will argue that the time to consider HCV drug resistance is now, before there are widespread problems with high level resistance, and that the NS5a drug class is particularly vulnerable to problems with resistance. The potential issues have likely been underestimated in data obtained in clinical trials.

Epidemiology and Public Health

Dr. Matthew Hickman, University of Bristol, Bristol, UK

Biography

Matt Hickman is a Professor in Public Health and Epidemiology at Bristol, and Honorary Public Health Consultant at Bristol City Council and Public Health England. He is the director of NIHR Health Protection Research Unit on Evaluation of Interventions, and a member and co-investigator of UK CRC Public Health Centre of Excellence (DECIPHer: Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement) and NIHR School of Public Health Research. His research programme focuses on epidemiology and public health consequences of drug misuse – including adolescent substance use, and epidemiology and prevention of HCV and drug related mortality. MH is deputy regional editor of Addiction, and is a member of the Scientific Committee of European Monitoring Centre on Drugs and Drug Addiction and WHO Technical Advisory Group on alcohol and drug epidemiology.

Abstract

HCV Prevention: Modeling the Impact of Expanding HCV Treatment

Background New HCV direct-acting antivirals (DAAs) will dramatically improve cure rates but are associated with high costs. HCV treatment, however, may be critical to HCV prevention among people who inject drugs (PWID) and in the population in many developed countries. We consider epidemiological and model evidence on the impact of HCV treatment and other interventions on HCV transmission and consider who should be prioritized for HCV treatment.

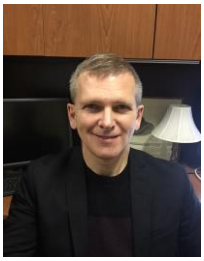
Methods: A) Pooled surveillance data and systematic reviews of the effect of opioid substitution treatment (OST) and needle and syringe programmes (NSP) on HCV transmission. B) Dynamic HCV transmission and disease progression cost-effectiveness models to compare the impact of different HCV interventions on HCV prevalence among PWID and the prioritization of HCV treatment using interferon-free DAAs.

Results: There is good evidence emerging that OST and high coverage NSP can reduce HCV transmission by 50% or more. OST and NSP avert HCV infections but in the UK and many other settings the coverage required to achieve substantial reductions in HCV prevalence are unsustainable and unlikely to be achieved. In contrast model evidence suggests that scaling up HCV treatment can reduce HCV prevalence substantially – especially in settings where chronic HCV prevalence is <20% or <40% - with each PWID treated averting an additional 1-2 HCV infections. The prevention benefit also makes treating PWID highly cost-effective and in many settings PWID would be prioritized for treatment at earlier disease stages. Current treatment rates in many settings, however, are insufficient to lead to observable changes in HCV prevalence over the next 5-10 years.

Conclusions: There is an important distinction in the quality of the evidence. The effect of OST and NSP is based on empirical, albeit observational, studies. HCV treatment as prevention is likely to be cost-effective but lacks empirical data – primarily because current treatment rates are too low. Our model estimates need to be tested in well planned studies of the impact of scaling up HCV treatment in well characterized PWID populations.

Dr. Joseph Cox, McGill University Health Centre, Montréal, Canada

Biography



Joseph Cox graduated in Medicine from Dalhousie University. He completed Public Health and Prevention Medicine training at McGill University, during which he completed an MSc in Epidemiology. He is also certified in Addiction Medicine by the American Board of Addiction Medicine. He is currently an attending physician in the STI-Bloodborne Infections & Harm Reduction Team, Infectious Disease Prevention & Control Sector, Montreal Public Health Department, and the Medical Director of the Chronic Viral Illness Service at the McGill University Health Centre – Glen Site. Dr. Cox is an Associate Professor in the Department of Epidemiology, Biostatistics and Occupational Health at McGill University.

Dr. Cox's research activities focus on HIV- and HCV-at-risk populations, evaluating risks for infection and related outcomes for the purpose of improving prevention and care. He has undertaken research on HCV-related knowledge, attitudes and behaviours of PWID and examined HCV care practices of family physicians. He is an investigator on several current initiatives, including the identification of drivers of food insecurity among HIV-HCV co-infected persons in Canada and examining HIV & STI prevention uptake and impact on HIV and STI occurrence among gbMSM (ENGAGE Study) in Vancouver, Toronto and Montreal. In these and past works, substance misuse in understanding risk and poor health outcomes, has been an important focus. He is funded by the Canadian Institutes for Health Research (CIHR).

Abstract

Harm Reduction along the HCV Prevention and Care Continuum

People who inject drugs (PWID) represent a key population for HCV-related surveillance, prevention and care. Preventing HCV infection and caring for people living with HCV, in the context of substance use, represents an important challenge for health professionals working in public health and in clinical settings. The harm reduction framework is useful for conceptualizing strategies to control the HCV epidemic among PWID. Initiatives related to and informed by harm reduction have the potential to decrease HCV transmission and contribute to a sustainable cure in this population. The presentation will highlight several examples along the HCV prevention and care continuum.

Behavioural Sciences

Dr. Manal El-Sayed, Ain Shams University, Cairo, Egypt

Biography

Manal El-Sayed, MD, is Professor of Pediatrics at Ain Shams University, Cairo, Egypt, where she trained in medicine and subsequently completed her masters and doctorate in Pediatrics. Since 1990 she has worked in pediatric hematology and oncology teams developing a program for the management of liver disease in children with hematological disorders, malignancies and recipients of bone marrow transplantation at Ain Shams University, National Cancer Institute and 57357 Children's Cancer Hospital. She is a member of the Egyptian National Committee for Control of Viral Hepatitis since 2006 charged with planning and implementing the nationwide program for prevention and management of viral hepatitis. Professor El-Sayed authored and co-authored numerous journal articles on hepatitis and liver diseases. She is an active board member and secretary general of the Egyptian Liver Care Society, a non-governmental organisation supporting needy patients undergoing liver transplantation or treatment of hepatitis. She is also the clinical director of the national HCV Pediatric treatment program. Since 2011 Professor El-Sayed has been appointed as Vice Chair of the WHO's Technical Advisory Group for Prevention and Control of Viral Hepatitis in Egypt 2012 through 2018 and by the Minister of Health as the supervisor of the Egyptian national program for control of viral hepatitis at Ministry of Health.

Abstract

Challenges in Implementing HCV Therapy Broadly in Low and Middle Income Countries

According to the World Bank, Egypt is considered a low middle income country and has one of the highest global burdens of HCV infection, with an estimated 7%, over 6 million people between 15-59 years, being chronically infected. In recognition of the enormity of the problem, in 2006, the Ministry of Health (MOH) established a National Committee for Control of Viral Hepatitis (NCCVH), who established a nationwide treatment program in 26 specialized viral hepatitis units treating 350,000 patients with peg-interferon and ribavirin. In 2014, the NCCVH introduced the first approved DAA (Sofosbuvir) for nationwide treatment of HCV infection at 1% of its international price. Other approved medications were introduced consecutively during 2015, in addition to encouraging the local manufacturers to produce highly effective generics to implement a cost-effective elimination program. A web-based registration system has been established to schedule patient's appointments to receive treatment. So far, more than one million patients with known HCV infection have registered and are being evaluated for eligibility to receive treatment according to the national guidelines. Currently, more than 140,000 patients have received treatment with DAAs in 45 treatment centers with a further 300,000 anticipated to receive treatment by the end of 2016. Despite a well-structured program there are many challenges namely access to prevention, screening and point of care testing as well as treatment in remote areas. In addition to quality assurance of generics, management of special populations and advanced liver disease. The success of the Egyptian endeavor in collaboration with national and international partners would provide an exemplary model that can be replicated in other resource-limited countries.

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

Biography

Dr. Alexandra King, MD, FRCPC, is a member of the Nipissing First Nation (Ontario). She is an Internal Medicine Specialist with an interest in HIV and HCV. She continues to develop her clinical practice, with a focus on those inadequately served by the existing system. She also leads a shared care model to provide hepatitis C care to Williams Lake and surrounding communities. Alexandra is an active researcher in HIV and HCV, focused on the impact of these diseases on the First Nations, Inuit and Métis; she also is involved with other Indigenous health research projects. She serves on many local and national initiatives, including *Canadian National Aboriginal Working Group on HIV & AIDS*, the *Interagency Coalition on AIDS and Development*, *CanHepC* and is a co-lead for the *CIHR Canadian HIV Trials Network* (CTN) Working Group for *Health for People Who Use Drugs*. Throughout her medical training, she received numerous awards for her activism. She has started her PhD at Simon Fraser University, focusing on intervention research at the nexus of health determinants, mental health and addictions, blood-born and sexually transmitted infections, and incarceration in Indigenous people in Canada.

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.

Abstract

How Indigenous Methodologies can Inform our Response to the HCV Epidemic in Canada

Alexandra King and Renée Masching

Indigeneity is a central consideration in the HCV Epidemic in Canada, linking to questions and issues of access to care and treatment; approaches to health and healing and risk factors for infection. The Meaningful Engagement of First Peoples in all aspects of health and wellbeing is clearly addressed in high level documents such as the United Nations Declaration on the Rights of Indigenous Peoples and the more recent Truth and Reconciliation Report and Recommendations in Canada. Within this context, HCV research with First Peoples in Canada is an exciting and demanding process.

The introduction of concepts such as Two-Eyed Seeing and renewed attention to Indigenous Methodologies in research have changed the research landscape. Excellence in research is grounded in ceremony and core values such as respect, humility, honesty, truth and wisdom. Reciprocal learning opportunities between academic and community researchers, First Peoples and members of the general population can be exciting exchanges that influence the very spirit of the research. Research itself has been shown to be a vehicle for healing when conducted with attention to creating and maintaining a culturally safe environment. There are also complexities regarding respectful engagement such as clear language that is relatable and respectful to research team members as a whole.

Our response to HCV in Canada will be enhanced by engaging with Indigenous leaders and stakeholders in research that is grounded in Indigenous worldview, methodology and ceremony. In a time of great transition and hope in the response to the HCV epidemic, creativity and inclusivity will be central to addressing remaining challenges with solutions that are relevant, meaningful and effective.

Debate

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

Biography

Jason Grebely is an Associate Professor in the Viral Hepatitis Clinical Program at the Kirby Institute in the Faculty of Medicine at UNSW Australia in Sydney. Jason completed his BSc in Biochemistry and Molecular Biology and his PhD in Pharmacology at the University of British Columbia in Vancouver, Canada. He then moved to Australia where he completed a Post Doctoral Fellowship in Clinical Epidemiology at the Kirby Institute, University of New South Wales.

Associate Professor Grebely's research focuses on the epidemiology, natural history and therapeutic strategies for acute and chronic HCV infection in people who inject drugs. He has published 110 peer-reviewed publications and has current research funding from the Canadian Institutes of Health Research, Australia's National Health and Medical Research Council (NHMRC) and the US National Institutes of Health.

He is an Associate Editor for the International Journal of Drug Policy, PLOS One and BMC Infectious Diseases. In recent years, he has been awarded a NHMRC Career Development Fellowship. Associate Professor Grebely is also the President of the International Network for Hepatitis in Substance Users, an international body for improving knowledge translation, education and advocacy for HCV among people who inject drugs.

Dr. David Wong, University Health Network, Toronto, Canada

Biography

Dr. David Wong is the Education Director for Hepatology Education at the University of Toronto. Dr. Wong was trained at the University of Toronto. After completing his Gastroenterology training at McMaster University, Dr. Wong worked as post-doctoral research fellow at Harvard University 1994-1999, under the supervision of Dr. Bruce Walker, studying the cellular immune responses to hepatitis C infection. Dr. Wong's other interests include liver disease in HIV, the development of electronic clinical notes. He is the recipient of many teaching awards including the Lou Cole teaching award for Gastroenterology, the Wightman-Berris Academy award for teaching excellence, and the University Health Network Award for excellence in clinical teaching.

Panel Discussion

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

Biography

Mel Krajden MD, FRCPC is the Acting 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 serves on numerous organizations and is the author of 270 peer-reviewed publications.

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 – Hepatitis C Program (now known as CanHepC) and a Co-PI on the CIHR Hepatitis Team grant.

He also spearheads the BC-Hepatitis C Tester's Cohort (BC-HTC). BC-HTC contains de-identified health information for 1.5 million British Columbians tested for HCV, HIV, HBV & TB. It includes almost all: lab tests/results, medical visits, hospitalizations, prescriptions, cancer outcomes, and mortality outcomes. With 25 years of information, the BC-HTC is able to determine net costs of services and health outcomes by different groups & 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.

Mr. Glenn Betteridge, CTAC, Toronto, Canada

Biography

Glenn Betteridge is a Policy Researcher with the Canadian Treatment Action Council (CTAC). CTAC is Canada's national, non-governmental organization led by and for people living with HIV and viral hepatitis co-infection, working to strengthening access to treatment. Glenn first became involved in HIV/AIDS as a member of ACT UP Montreal in the late 1980s. Since completing university he has worked at the HIV & AIDS Legal Clinic Ontario, the Canadian HIV/AIDS Legal Network, and as a consultant to various local, provincial, national and international organizations focusing on HIV/AIDS, health and human rights. Glenn has volunteered at with HIV/AIDS, LGBT community, social justice and performing arts organizations in Toronto, as a board or collective member.

Dr. Howard Njoo, PHAC, Ottawa, Canada

Biography

Dr. Howard Njoo is the Associate Deputy Chief Public Health Officer for the Public Health Agency of Canada and directly supports the Chief Public Health Officer (CPHO) in providing public health advice, speaking to Canadians and representing the Agency in a variety of domestic and international fora. In addition, Dr. Njoo supports the CPHO in developing the CPHO Report and talent management and provides technical expertise and support to the Branch Heads of the Agency.

Since joining the Federal Government in 1996, Dr. Njoo has held a variety of positions in the areas of both infectious and chronic diseases as well as emergency preparedness and response within the Public Health Agency of Canada, including being the Interim Chief Science Officer, the Director General of the Centre for Communicable Diseases and Infection Control and the Acting Director General of the Centre for Emergency Preparedness and Response.

Dr. Njoo earned his medical degree and a Master's in Health Science, specializing in community health and epidemiology, from the University of Toronto, and subsequently completed a fellowship and certification with the Royal College of Physicians and Surgeons of Canada in community medicine.

Prior to joining the federal government, Dr. Njoo was the Associate Medical Officer of Health for the City of Toronto Department of Public Health and also worked at the Ontario Ministry of Health.

Dr. Njoo's extensive domestic and international public health experience include being deployed to Guinea in 2015 as Technical Deputy for Program Coordination on the U.S. Centers for Disease Control and Prevention (CDC) Guinea Ebola Response Team, being deployed to Haiti in 2010 post earthquake to assist the United Nations Office for the Coordination of Humanitarian Affairs in conducting public health needs assessments, being the technical lead on the Canadian delegation for the revision of the International Health Regulations, being part of Government of Canada's senior level management of the SARS and H1N1 outbreaks in Canada and being the Vice-Chair of NATO's Joint Medical Committee.

Dr. Njoo is a consultant physician at the Ottawa Hospital Tuberculosis Clinic. He is an Assistant Professor, Department of Medicine, Division of Infectious Diseases at the University of Ottawa and also has an adjunct appointment in the Department of Epidemiology and Community Medicine.

Dr. Dan Werb, University of California San Diego / St. Michael's Hospital, Toronto, Canada

Biography

Dan Werb, PhD, is an epidemiologist and policy analyst with expertise working in the fields of HIV, addictions, and drug policy. Dr. Werb defended his PhD at the School of Population and Public Health at the University of British Columbia in Vancouver. Dr. Werb is an inaugural recipient of the US National Institute on Drug Abuse's Avenir Award, which funds highly innovative and potentially high impact research projects at the nexus of HIV and drug use. Dr. Werb's Avenir Award funds the PRIMER project (PReventing Injecting by Modifying Existing Responses), a multi-site, international study seeking to test the potential impact of existing structural interventions on reducing the risk that people who inject drugs initiate others into injecting.

Dr. Werb is also the Director of the International Centre for Science in Drug Policy, a Toronto-based research institute focused on systematic assessments of the evidence on the effectiveness of illicit drug policy. His research interests are wide ranging and include preventing injection drug use, the effect of drug law enforcement on public health, global drug supply reduction, discretionary policing, identifying determinants of illicit drug market participation, and drug market violence. He is a researcher with the BC Centre for Excellence in HIV/AIDS and a Visiting Scientist at the Li Ka Shing Knowledge Institute at St. Michael's Hospital in Toronto

Dr. Werb is a 2012 Trudeau Foundation Scholar, a Canadian Institutes of Health Research Fellow, and the recipient of a 2014 National Magazine Award in Canada for his general interest science journalism.

Oral Abstracts – résumés oraux

Biomedical Sciences

Oral presentation at 09h05

TRANSCRIPTOMIC CHARACTERIZATION OF THE IMMUNE RESPONSE TO ACUTE HEPATITIS C VIRUS INFECTION

Brad R. Rosenberg[1, 2] Marion Depla[3] Catherine A. Freije[1] Denis Gaucher[3] Nathalie Bédard[3] Julie Bruneau[3, 4] Charles M. Rice[1, 6, 7] Naglaa H. Shoukry[3, 5]

1. The Rockefeller University, New York, NY, USA; 2. Whitehead Presidential Fellows Program, New York, NY, USA; 3. Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC; 4. Département de médecine familiale et de médecine d'urgence, Université de Montréal, Montreal, QC; 5. Département de médecine, Université de Montréal, Montreal, QC; 6. Laboratory of Virology and Infectious Disease, New York, NY, USA; 7. Center for the Study of Hepatitis C, New York, NY, USA

Background: Most individuals exposed to hepatitis C virus (HCV) become persistently infected while 25% spontaneously clear the virus. This resolution is mediated by an early and effective immune response. However, the underlying molecular and cellular networks, including the cross-talk between innate and adaptive mechanisms, remain incompletely understood.

Purpose: The goal of this study was to perform in-depth transcriptome analysis of the immune response to acute hepatitis C infection in the peripheraly blood.

Method: We utilized RNA-Seq and modular transcriptomic analysis methods to extensively characterize immune function in peripheral blood mononuclear cells (PBMCs) collected from high risk people who inject drugs (PWID) participating in the Montreal Acute Hepatitis C Cohort (HEPCO) before, during, and after acute HCV infection. Our study includes 12 patients, of which six spontaneously cleared the virus and six progressed to chronic infection.

Result(s): Our results provide a detailed description of the innate antiviral gene programs active in PBMC during acute HCV infection, which include a prominent type I interferon signature. Elevated interferon-stimulated gene expression returns to pre-infection levels by approximately 16 weeks post-infection in spontaneous resolution, but persists in chronic infection. Blood transcriptome module analysis and flow cytometry revealed dynamic changes of several immune cell populations. $CD14^{+}CD16^{+}$ intermediate monocyte subsets expand and peripheral B cell frequencies decrease during acute infection, but normalize upon spontaneous viral clearance. In addition, comparative analysis with peripheral blood gene expression profiles from vaccine recipients suggests notable similarities in the response to acute HCV and yellow fever 17D, a live-attenuated flavivirus.

Conclusion(s): These results represent the first longitudinal transcriptomic characterization of the human immune response to acute HCV infection and define the diverse host defense mechanisms active shortly after exposure to this important hepatotropic pathogen.

Oral presentation at 09h15, Poster 55

INVESTIGATING THE MECHANISMS OF ACTION OF NEUTRALIZING ANTIBODY RESPONSES ELICITED BY A RECOMBINANT HEPATITIS C VIRUS ENVELOPE GLYCOPROTEIN E1E2 VACCINE

Jason A. Wong[1] Michael Logan[1] Darren Hockman[1] Rakesh Bhat[1] Chao Chen[1] Aviad Levin[1] Abdul Khan[2] Jillian Whidby[2] Joseph Marcotrigiano[2] Sharon E. Frey[3] Robert B. Belshe[3] D. Lorne Tyrrell[1] John L. Law[1] Michael Houghton[1]

1. Li Ka Shing Institute of Virology, Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, AB; 2. Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, USA; 3. Department of Internal Medicine, Saint Louis University School of Medicine, Saint Louis, MO, USA

Background: A global prophylactic vaccine for Hepatitis C Virus (HCV) remains elusive. The diversity of the virus is a major hurdle; a successful vaccine will need to protect against all 7 major genotypes of HCV. Our lab is developing a vaccine comprising the two envelope glycoproteins of HCV (E1E2). A broadly effective vaccine based around E1E2 would likely work through generating cross-genotype neutralizing antibodies (nAbs) binding conserved regions on E1E2 critical for entry. A vaccine comprising recombinant envelope glycoproteins (E1E2) derived from the genotype 1a (gt1a) HCV-1 strain has been shown to be capable of eliciting cross-neutralizing antibodies in guinea pigs, chimpanzees, goats, and healthy human volunteers.

Purpose: N/A

Method: N/A

Result(s): In order to investigate the basis for this cross-neutralization, epitope mapping of anti-E1E2 antibodies present within antisera from goats and humans immunized with HCV-1 E1E2 was conducted through competition studies with a panel of cross-neutralizing mAbs targeting various epitopes within E1E2. Immunized goat and human antisera was shown to compete with the binding of all mAbs tested, and competed especially well with mAbs known to block the interaction between E2 and the major cell entry receptor CD81. Neutralizing antisera from goats immunized with HCV-1 (gt1a) E1E2 and J6 (gt2a) E2 were investigated to determine the mechanisms of neutralization. Synchronized time-of-addition experiments revealed that both vaccines elicited nAbs that neutralize entry prior to or at the CD81 binding step. Further experiments showed that these goat antisera directly blocked the interaction between E1E2 and CD81.

Conclusion(s): Together with previous data demonstrating that these antisera could compete with the binding of cross-neutralizing monoclonal antibodies binding disparate sites on E2 that are responsible for interactions with CD81, these results suggest that immunizing with HCV envelope glycoproteins elicits nAbs that act at early binding steps in viral entry such as CD81 interactions and possibly HSPG and SR-B1 interactions (work in progress). These results support the use of such a vaccine antigen to induce cross-genotype neutralization.

Clinical Sciences

Oral presentation at 10h30

REAL LIFE CLINICAL EXPERIENCE WITH SECOND GENERATION DIRECTLY ACTING ANTIVIRAL (DAA) DRUGS FOR THE TREATMENT OF CHRONIC HEPATITIS C IN CALGARY, ALBERTA, CANADA

Golasa Samadi Kochaksaraei[1] Alexander I. Aspinall[1] Samuel S. Lee[1] Gisela Macphail[2] Lynda Watson[2] Kelly W. Burak[1] Meredith A. Borman[1] Stephen E. Congly[1] Bertus Eksteen[1] John Gill[3] Saumya Jayakumar[1] Jeff Kapler[3] Martin Labrie[3] Oscar Ernesto Larios[3] Jacqueline Pinto[1] Laura Stinton[1] Mark G. Swain[1] Carla S. Coffin[1, 3]

1. Calgary Liver Unit, Division of Gastroenterology and Hepatology, Cumming School of Medicine, University of Calgary, CANADA, Calgary, AB; 2. CUPS | Health/Education/Housing Medical Clinic, Alberta Health Services, Calgary, Alberta, CANADA, Calgary, AB; 3. Southern Alberta HIV Clinic, Alberta Health Services, Calgary, Alberta, CANADA, Calgary, AB

Background: There has been great progress in hepatitis C virus (HCV) antiviral therapy allowing achievement of a sustained virological response (SVR) in previously difficult-to-treat patients (i.e., cirrhosis, liver transplant, HIV co-infected, and vulnerable populations).

Purpose: Our objective was to assess treatment outcomes in a real life clinical setting with the second-generation anti-HCV directly acting antiviral's (DAA) in HCV patients seen in outpatient hepatology / infectious disease clinics in Calgary, Alberta, Canada.

Method: All patients with chronic hepatitis C infection who were known to undergo treatment in Calgary with second generation DAA (i.e., excluding telaprevir and boceprevir-based treatment) from March 2014 - November 2015 were included. Demographic, clinical, and laboratory data were retrospectively collected including age, sex, HCV genotype, fibrosis stage, and (in HIV co-infected) antiretroviral regimen. Outcomes included SVR or relapse rate at 12 weeks after the completion of treatment (SVR-12) and treatment related adverse events, including change in estimated glomerular filtration rate (eGFR) from baseline were determined.

Result(s): In total, 362 patients were known to be treated to date (349 HCV-monoinfected, 12 HIV/HCV-coinfected and 1 HCV/HBV-coinfected). DAA treatment regimens included sofosbuvir/ledipasvir or Harvoni® (58%, 211/362), sofosbuvir/ribavirin (21%, 77/362), sofosbuvir/simeprevir (6% 23/362), sofosbuvir/pegylated interferon/ribavirin (Peg-RBV; 6%, 22/362), Harvoni®/ribavirin (4%, 16/362), dasabuvir/ombitasvir/paritaprevir/ritonavir (Holkira-Pak®) + Ribavirin (2%, 8/362) or Holkira-Pak® (0.8% 3/362), and simeprevir/Peg-RBV (0.5%, 2/362). Overall 75% (272/362) were GT1, 7% (26/362) GT2, 15% (54/362) GT3, 2% (8/362) GT4, and 0.5% (2/362) GT6. In data available to date, the median age was 57 years (IQR 50-62), 62% male, 33% cirrhotic, 6% with hepatocellular carcinoma, 4% were liver transplant recipients, and 3% were HIV coinfected. The median liver stiffness assessed by Fibroscan® at baseline was 9.6 Kpa (IQR 6.3-19.30) and the median HCV RNA at baseline was 5.83 log IU/ml (IQR 5.1-6.21). All HIV/HCV co-infected patients were on a stable HIV antiretroviral regimen with restoration of immunity and undetectable HIV RNA. In 57% (207/362) with SVR-12 data, 92.2% (191/207) of them achieved SVR. In the 7% who relapsed, DAA therapy included Harvoni® (5.3%, 6/113), sofosbuvir/ribavirin (18%, 6/33), simeprevir/sofosbuvir (13 %, 3/23) and sofosbuvir/Peg-RBV (5%, 1/19). In patients with available eGFR data to date (54%,196/362), 1 developed worsening renal function ~16 weeks after starting Harvoni® treatment.

Conclusion(s): In this large Canadian cohort study, we report real-life clinical outcomes in 362 hepatitis C positive patients treated with second generation DAA's. Similar to clinical trial reports, therapy was well tolerated and highly effective, and over 92% of patients treated achieved an SVR.

Oral presentation at 10h40

REAL LIFE EXPERIENCE OF HEPATITIS C MANAGEMENT WITH INTERFERON-FREE DAA TREATMENTS IN MONTREAL

Emmanuelle Huchet; Benoit Trottier; Chrissi Galanakis; Marc Poliquin; Sylvie Vézina; Danièle Longpré; Stephane Lavoie; Caroline Bedard; Nima Machouf; Réjean Thomas

Clinique médicale l'Actuel, Montreal, QC

Background: The advent of new interferon-free direct-acting antiviral (DAA) treatments and their promising efficacy rates in randomised clinical trials (RCT) have prompted changes to the Canadian guidelines for Hepatitis C management. However, few studies have examined the impact of these treatments in clinical practice.

Purpose: The aim of this study is to evaluate the efficacy of DAA regimens in real life settings.

Method: We prospectively assessed all HCV infected patients attending our clinic receiving DAA treatments without pegylated interferon. Patients were followed every two weeks by a multidisciplinary team of nurses, physicians and pharmacists. Patients enrolled in RCTs were excluded. The primary outcome was sustained virologic response (SVR) at 12 weeks post-treatment by intent-to-treat analysis. Comparisons among groups were assessed by chi-square.

Result(s): 249 DAA treatments were included. Patients were mainly male (70%) with a mean age of 53 years (IQR 48-59). The majority of patients were infected by HCV genotype 1 (74%) and were treatment naïve (64%). 99 (40%) of patients were cirrhotic at baseline, 61 (25%) were co-infected with HIV and 39 (20%) were active injection drug users. Patients received: SOF/LDV (32%), followed by SIM + SOF (26%), SOF + RBV (26%), SOF/LDV+ RBV (8%) and OBV/PTV/r +DSV ±RBV (8%). 156 patients had available follow-up at 12 weeks post-treatment. 149/156 (96%) patients completed treatment, while 7/156 (4%) discontinued due to death (n=3), patient/physician preference (n=3) and loss to follow-up during treatment (n=1). Overall, 133/156 patients (85%) achieved SVR, 8 (5%) relapsed and 6 (4%) failed to respond to treatment. Nine patients (6%) were lost to follow-up and were considered treatment failures. The SVR rates for each regimen were: SOF/LDV (32/38, 84%), SIM+SOF (55/65, 85%), SOF+RBV (34/40, 85%), SOF/LDV+ RBV (8/8, 100%), OBV/PTV/r +DSV ±RBV (4/5, 80%). No difference was observed in the SVR rate among treatment regimens (p=0.82). Though 6 patients on SOF/LDV failed treatment, 4 were lost to follow-up and 2 died during treatment from unrelated causes. The SVR rate did not vary according to treatment history, injection drug use or genotype. Cirrhotic patients were less likely to achieve SVR (78% for cirrhosis vs. 91% for non-cirrhotic patients, p=0.02). Moreover, in the absence of cirrhosis, there was no effect of HIV co-infection on SVR (91% for HCV-infected vs. 90% for HIV-HCV, p=0.75). In the presence of cirrhosis, however, co-infected patients had significantly lower SVR rates (85% for HCV-infected vs. 64% for HIV-HCV, p=0.04). Sixty-eight percent of patients experienced side effects; namely fatigue (42%), insomnia (31%), headache (25%) and rash (21%). Four patients discontinued RBV due to side effects, yet still completed treatment.

Conclusion(s): DAAs offer high SVR rates in clinical settings, though lower than those described in RCTs. Nevertheless, all of the recommended DAAs achieve equally successful SVR rates. The treatment of cirrhotic patients remains a challenge in clinical practice as SVR rates are lower than anticipated. Thorough follow-up of patients is needed to ensure they are cured from HCV and continue post-treatment counseling to prevent re-infection.

Epidemiology and Public Health

Oral presentation at 11h40

CORRECTIONAL FACILITIES AS HCV TREATMENT ACCESS POINT: A FRAMEWORK FOR CORRECTIONS RESEARCH AND HCV TREATMENT

Karen MacDonald[3] Kimberly Kempton[3] Donna Myers[3] Daniel Smyth[4] Sharon Oldford[1] Lisa Barrett[1, 2]

1. Dalhousie University, Halifax, NS; 2. Nove Scotia Health Authority, Halifax, NS; 3. Department of Justice and Public Safety, Charlottetown, PE; 4. Horizon Health Authority, Moncton, NB

Background: Incarcerated individuals have generally been excluded from interventional medical research for many years; however, there is increasing recognition that this may be discriminatory to individual offenders. There is no consensus on the best design to ensure ethical implementation of an interventional drug trial in a dedicated incarcerated population. We define a framework for ethical design and implementation of interventional research in an incarcerated population.

Purpose: Define a framework for ethical design and implementation of interventional research in an incarcerated population

Method: A phase 4 study to treat hepatitis C virus (HCV) infection in an incarcerated population was used as a model. A literature review was performed to identify international experts in prison research, as well as identify existing best practices in prisoner health research. A broad range of community, academic, government and industry experts provided iterative feedback that was incorporated into study design. The framework was implemented at the PEI provincial correctional facility in July 2015 with the start of an HCV treatment study.

Result(s): The literature review and expert consultation identified several key features for ethical research in incarcerated populations. The principles of equity (to research opportunities) and justice were recognized as key guiding ethical principles. A mechanism to assess informed consent and coercion was integral to ethical study implementation, and an independent study advisory board would be necessary to provide frequent review of participant feedback. Advisory board members are separate from government custodians and the study team, reporting directly to the institutional study board. Additionally, all participants have access to an independent advocate at all study visits, if so desired. This framework was positively reviewed and approved by multiple institutional review boards (IRB). Initial implementation included IRB selection of an advisory board chair who will subsequently populate the advisory board. A health provider in the circle of care initially approaches all offenders, and importantly, offenders are offered education and advice on harm reduction throughout the study. Individuals from HCV positive and offender advocate groups were involved in the design and implementation of the model and have fully endorsed each stage. Ongoing analyses monitor participant feedback for negative effects (either from other offenders or facility staff) through an anonymous feedback mechanism.

Since implementation, HCV screening rates and standard of care vaccination rates at the correctional facility have increased. 16 offenders were identified as HCV positive, and all wanted to talk with the coordinator about the HCV treatment study. All eligible individuals decided to enroll in the study after extensive discussion with the study team.

Conclusion(s): The framework developed through extensive community consultation and literature review has been approved by multiple IRBs, and provides guidance and precedent for one of the first Phase 4 intervention studies in a dedicated incarcerated population in 60 years. This framework facilitates access to research opportunities, as well as state of the art HCV care and treatment, for a traditionally marginalized population.

Oral presentation at 11h50

RISK OF HEPATITIS C VIRUS RE-INFECTION OR LATE RELAPSE AFTER SUSTAINED VIROLOGIC RESPONSE TO INTERFERON-BASED THERAPY IN HIV CO-INFECTED CANADIANS

Carmine Rossi[1] Mark Hull[2] Joseph Cox[1] Curtis Cooper[3] Valérie Martel-Laferrière[4] Neora Pick[5] Sharon L. Walmsley[6] Julio S. Montaner[2] Marina B. Klein[1]

1. McGill University, Montreal, QC; 2. BC Centre for Excellence in HIV/AIDS, Vancouver, BC; 3. Ottawa Hospital Research Institute, Ottawa, ON; 4. Centre Hospitalier de l'Université de Montréal, Montreal, QC; 5. Oak Tree Clinic, Vancouver, BC; 6. Toronto General Research Institute, Toronto, ON

Background: Direct-acting antiviral (DAA) therapy is effective for the treatment of hepatitis C virus (HCV) infection in HCV-HIV co-infected patients but benefits of these costly therapies may be mitigated by HCV re-infection.[1]

Purpose: We describe rates and predictors of re-infection or late relapse after sustained virologic response (SVR) in co-infected patients mostly treated with interferon-based therapy.

Method: We included patients from the Canadian Co-Infection Cohort who were enrolled from 2003-2014 and had a confirmed SVR and at least one follow-up HCV RNA measurement. Patients were followed from the time they achieved SVR until re-infection, which was defined as a single detectable HCV RNA measurement. Deep-gene sequencing was not currently available to distinguish re-infection from relapse. However, as late relapse is rare we assumed these to be re-infections for this analysis. Subjects were censored at their last HCV RNA measurement. Demographic, substance abuse, and behavioral risk factors for re-infection were self-reported semi-annually. HCV RNA testing was performed, on average, every six months post-SVR. The five-year cumulative risk of re-infection was calculated using the Kaplan-Meier method. Time-updated Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for re-infection.

Result(s): One-hundred and fifty-seven co-infected patients who acheived SVR were followed for a total of 383 person-years (PYs; interquartile range [IQR]: 1.0-3.3 years). The median age was 46 years (IQR: 39-51), 84% were male, and 6% were aboriginal. The median time from estimated HCV infection to SVR was 17 years (IQR: 9-27). Genotype 1 was the most common treated infection (54%). 8% were treated with first-generation DAAs. Most patients (90%) were on stable antiretroviral therapy (ART) and the median $CD4^+$ count at SVR was 459 cells/μL (IQR: 360–660). We identified 20 re-infections or possible late relapses, yielding an incidence rate of 5.2 per 100 PYs (95% CI: 3.4–8.1). Eight infections resolved spontaneously. The cumulative five-year risk of re-infection was 24% (95% CI: 14%–38%). Overall, 29% reported injection drug use (IDU), 13% shared needles or other drug equipment and 51% reported unprotected sex post-SVR. In univariate analysis, IDU, sharing IDU equipment, snorting/sniffing drugs, and sharing snorting equipment significantly increased the risk of re-infection. Patients on ART had a significantly lower risk of re-infection. Unprotected sex or recently having a sexually transmitted infection were not associated with re-infection. After adjustment, the relative hazard of re-infection was 3.4 times higher among injection drug users (95% CI: 1.2-9.2). Among MSM, IDU appeared to be the principal risk factor for re-infection (HR 4.6, 95% CI: 0.9-23), although inference was limited because of few subjects.

Conclusion(s): HCV re-infection post-SVR was common. IDU is an important driver of HCV re-acquisition, even among MSM. While needle sharing was relatively infrequent, sharing of other equipment associated with injections and/or snorting drugs was associated with elevated re-infection risk. To realize the potential of new HCV therapies for cure, DAAs will need to be paired with broader harm reduction programs to reduce the risk of re-infection.

References:

[1] Pineda, J. Hepatitis C virus reinfection after sustained virological response in HIV-infected patients. *J Infect*; 71:571-577..

Behavioral Sciences

Oral presentation at 14h05

COMMUNITY-DIRECTED RESEARCH PRIORITIES FOR THOSE WITH INDIGENOUS LIVED HEPATITIS C EXPERIENCE

Chris Macklin[1] Alecia Kallos[1] Sharon Jinkerson-Brass[2] Sandy-Leo Laframboise[2] Malcolm King[1] Renée Masching[3] Sherri Pooyak[3] Alexandra King[1]

1. Simon Fraser University, Vancouver, BC; 2. Indigenous Elder, Vancouver, BC; 3. Canadian Aboriginal AIDS Network, Vancouver, BC

Background: With prevalence rates estimated at up to 10 times that of the non-Indigenous population, available evidence suggests that Indigenous peoples in Canada bear a disproportionately high hepatitis C disease burden. This issue must be framed within the context of historical and ongoing trauma. Having Indigenous ancestry - First Nations, Inuit or Métis - is a foundational risk factor for hepatitis C. Moreover, the landscape for hepatitis C is dramatically changing: newly available therapeutics have resulted in significantly shorter treatment courses with fewer toxicities and huge improvements in cure rates. Yet, these new treatments come at substantially increased financial costs. In the wake of this changing landscape, there is a pressing need for a hepatitis C research agenda developed *by* and *for* Indigenous peoples.

Purpose: To develop and inform a larger exploratory study concerning the unique lived experience of First Nations, Inuit and Métis peoples living with hepatitis C. The study aimed to use a decolonizing and community-based methodology to elucidate and explore culturally resonant approaches for Indigenous peoples across Canada in a wholistic care cascade for this population.

Method: Indigenous people with diverse lived hepatitis C experience participated in sharing circles as a modality to discuss hepatitis C research priorities. We conducted four concurrent sharing circles (one male, two female and one two-spirit). Discourse within the sharing circles was guided by an Indigenous Elder. The discussions in the sharing circles were audio recorded and transcribed verbatim. Sharing circle transcripts were then analyzed qualitatively through content analysis. Relevant themes and sub-themes were systematically identified using qualitative data analysis software to gain a comprehensive picture of the sharing circle discourse that was grounded in the lived experience of the participants.

Result(s): The lived experiences shared by the women, men and two-spirit participants point to several cross-cutting themes. Participants discussed both individual and systems-level factors which impacted their life course with hepatitis C. The results from the sharing circles highlighted strength and resiliency among Indigenous people living with hepatitis C and presented opportunities for ways forward that honour Indigenous Knowledges and Ways of Knowing. Additional key themes identified included the intersection of multiple hepatitis C risk factors, issues related to the continuum of care, the priority of hepatitis C in one's life, reduced health literacy and the importance of transformation and finding purpose along one's healing journey with hepatitis C.

Conclusion(s): This project highlights the criticality of involving Indigenous peoples and communities in the process of deciding program and research priorities. Within this, there must be a focus on innovation, self-determination, integration of services, cultural safety, wholism, traditional values and the application of strengths-based approaches. Furthermore, if gains are to be made in reducing rates of hepatitis C in Indigenous populations, the themes identified by the sharing circle participants must be taken into consideration across the realms of research, policy, prevention programs and the continuum of hepatitis C care.

Oral presentation at 14h15

CACTUS MONTREAL: INITIATIVES TO IDENTIFY NEEDS OF PWID TO PROVIDE A SUPPORT AND INCREASE THEIR HEP C TREATMENT ACCESS

Julie Bouchard; Amélie Goyette

CACTUS Montréal, Montréal, QC

Background: The Fixed Site of CACTUS Montreal, a distribution and recovery centre of injection, inhalation and prevention equipment, is open 7 evenings/nights a week. We receive between 120 and 225 daily visits. Our intervention team is available to listen, support, and give information about safer drug use, safe sexual practices and blood-borne and sexually transmitted infections.

Purpose: Several studies suggest that «the HCV treatments for people who inject drugs (PWID) combined with other harm reduction interventions (like Fixed Site) can decrease prevalence and transmission. » (Martin, Hickman, et al., 2013). In 2014, CACTUS Montreal began a new initiative to identify the needs of PWID to provide a real support and increase their Hep C treatment access.

Method: *First Step:*

Fall 2014: To understand the reality of PWID- their story, their needs and the supportive services provided by the organizations-we organised focus groups (3 sessions- 2 hours each), with PWID who live with Hep C.

Recommendations were made:

- *Development of new educational tools adapted to the reality of PWID about hepatitis C and treatments*
- *Creation of a new position in our organization: worker with the mandate of following the person after the diagnosis*
- *Development of partnerships with organizations and clinics*

Result(s): *Second Step* **:**

Implementation of recommendations

Recommendation 1: Development of new educational tools adapted to the reality of PWID about hepatitis C and treatments

Summer 2015: we organised new focus-groups with PWID who live with Hep C to explore their perceptions concerning appropriate and available information about Hep C to create a new information tool. Those groups (2 sessions-2 hours each) were the place to discuss about:

Existing brochures: format, content, images.

What they want to learn/to know about Hep C before and after the diagnosis

Results: Our new brochure will be ready and available in November 2015. It will be also distributed in other provinces of Canada.

Recommendation 2: Creation of a new position in our organization: a worker who's mandate is to follow the person after the diagnosis (a lot of people are lost after the diagnosis)

Fall 2015: a Hep C service worker joined our intervention team. She was already a member of the Fixed Site for the past ten years. Her role is to provide and create, with PWID who live with Hep C, the best conditions for a successful treatment:

- Support by a worker with whom a trusting relationship is established
- Medication supervision
- Drug use planning and support
- Promotion of good practices concerning drug injection to prevent Hep C transmission and reinfection
- Promotion of health habits
- Housing support

Results: We referred many people for HCV screenings. A service worker made individual meetings to provide information about Hep C, good practices about injection and to prevent reinfection.

The **third recommendation**- *Development of partnerships between organizations and clinics or hospitals* – is also effective as of now since the Hep C worker is part of our team. This is a perfect leverage to meet our partners in order to present our initiative and establish better collaborations to optimize treatment access.

Posters - Affiches

Biomedical Sciences

Poster Presentation: P.03

EXAMINATION OF GENETIC VARIATION WITHIN THE HEPATITIS C VIRUS NS3 HELICASE USING DEEP SEQUENCING

Christopher Ablenas[1] Natan Bensoussan[1] Megan Powdrill[2] Laura Mayrthaler[3] John Pezacki[2] Matthias Gotte[4]

1. McGill University, Montreal, QC; 2. University of Ottawa, Ottawa, ON; 3. Ludwig-Maximilians-Universität München, Munich, Germany; 4. University Of Alberta, Edmonton, AB

Background: Hepatitis C virus (HCV) subgenomic replicons are extremely useful for the study of viral replication. Replication enhancing mutations (REMs)[1], also referred to as cell culture adaptive mutations, have been identified that result in efficient RNA amplification in the highly permissive Huh-7 hepatoma cell line. Within the HCV replicon REMs cluster to NS5a, as well as to the amino terminus of the NS3 helicase (NS3h), and at two positions in NS4b[2]. In the context of NS3h, the majority of REMs map to domain 1, with few REMs in domains 2 and 3. Domains 1 and 2 are highly structurally related, containing the ATP binding site and the majority of the contacts with the RNA substrate, while domain 3 is primarily structural.

Purpose: To use a deep sequencing approach to investigate genetic variation in the NS3 helicase using the replicon system. We compared genetic variation in domain 1, which contains the majority of NS3h REMs reported in the literature, to that in domain 3 where few REMs have been reported.

Method: Deep sequencing of amplicons covering the different domains of NS3h was performed to detect minor variants arising during replication. Briefly, RNA was extracted from Huh7 cells harbouring the 1b replicon and reverse transcribed into cDNA. PCR amplicons were then amplified using barcoded PCR primers with 454 adaptor sequences and subjected to pyrosequencing on a GS Junior sequencer (Roche). The raw reads were processed, and minor variants calculated using Roche amplicon variant software. Select mutants were introduced back into the replicon by site-directed mutagenesis, and the replication capacity was measured using a luciferase reporter.

Result(s): The error rate calculated from variants sequenced in a region of domain 1 in NS3h was approximately 2-fold higher than that for a region in domain 3. This suggests a higher tolerance for variation in domain 1 as compared to domain 3, consistent with the greater number of REMs previously reported in domain 1. In agreement with previous reports from our group, the majority of the variants consisted of transitions due to the high bias by the NS5b polymerase to form G/U or U/G mismatches[3], with only a small number of transversions. At the level of the individual variants, we noted five mutations in domain 1 and one mutation in domain 3 that were detected repeatedly over 2 to 3 independent RNA transfections. When the replication capacities of select mutants were tested, four mutants were found to replicate ~4-9 fold higher than WT.

Conclusion(s): We found that genetic variation was better tolerated in domain 1 as compared to the more structural domain 3. In addition, certain nucleotide positions were identified as hot spots for specific mutations.

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Poster Presentation: P.04

GENERATION OF AGO2 KNOCKOUT HUH 7.5 CELLS FOR THE STUDY OF AGO2 AND MIR-122 PROMOTION OF HCV REPLICATION

Yalena Amador-Canizares; Joyce Wilson

University of Saskatchewan, Saskatoon, SK

Background: miR-122, a liver-specific microRNA promotes HCV replication by an as yet unknown mechanism. Previous work in the Wilson laboratory identified that Argonaute 2 (Ago2), a host protein involved in the cellular activity of miRNAs, is required for the miR-122-induced promotion of HCV replication. Ago2 is a multifunctional protein with regions (motifs) of the protein having different functions. In our laboratory, we aim at identifying key Ago2 functions required for miR-122 promotion of HCV replication. We plan to do so, by generating a complementation system in which we will test the ability of Ago2 mutants to promote HCV replication.

Purpose: In order to have a cell line, both HCV replication permissive and devoid of Ago2 expression, we aimed at generating an Ago2 knockout Huh 7.5-derived cell line.

Method: We used the recently developed CRISPR/Cas9 system technology for genome editing. The selected single guide RNAs (sgRNAs) were delivered by a sgRNA expression plasmid (pSpCas9(BB)-2A-GFP) bearing both Cas9 and the remainder of the sgRNA as an invariant scaffold immediately following the oligo cloning site. Transfection of the GFP-expressing plasmid allowed selection of transfected cells by cell sorting. Sorted cells were clonally isolated by serial dilutions, followed by an expansion period to establish new clonal cell lines. Insertion/deletion (indel) mutations were screened by heteroduplex mobility assay (HMA) and the SURVEYOR nuclease assay and confirmed by Sanger sequencing. Ago2 protein expression was assessed by Western blot and Ago2 messenger RNA (mRNA) levels were determined by quantitative real-time PCR (qPCR).

Result(s): Twenty-six cell clones were initially screened by the HMA. Only 3 of them showed heteroduplexes with reduced mobility in neutral polyacrylamide gels. Four out of 6 of the clones that were negative by the HMA yielded detectable cleavage products as a result of the SURVEYOR nuclease assay. Anti-Ago2 Western blot exhibited a variable degree of Ago2 protein expression in 13 out of 21 screened clones. Two cell lines that were positive by at least one of the indel screening assays (HMA or SURVEYOR) and which also showed undetectable levels of Ago2 expression by Western blot, were chosen to confirm the presence of indel mutations in both alleles by sequencing. A significant reduction in the Ago2 mRNA levels was detected by qPCR in both of them as well. Data on the ability of the Ago2 knockout cells to support HCV replication will be presented.

Conclusion(s): We successfully generated two Ago2 knockout Huh 7.5-derived cell lines using the CRISPR/Cas9 system. These cell lines will be valuable tools to perform complementation assays in which the effect of the expression of different Ago2 mutant variants on HCV replication can be measured.

Poster Presentation: P.05

INVESTIGATING THE ROLE OF MICRORNA-122-ASSOCIATED COMPLEXES IN HEPATITIS C VIRUS INFECTION

Annie Bernier; Selena Sagan

McGill University, Montreal, QC

Background: Approximately 200 million individuals worldwide are infected by hepatitis C virus (HCV), including more than 300 000 Canadians. HCV-infected individuals typically develop a persistent infection that leads to chronic hepatitis, cirrhosis and liver cancer. MicroRNA-122 (miR-122) is a highly abundant liver-specific microRNA shown to interact at two "tandem" microRNA-binding sites in the 5' UTR of the HCV genome. This unusual interaction promotes HCV RNA accumulation in both HCV-infected cells, and the livers of infected patients. Mutation, truncation, or exchange of the 3' terminal ribonucleotides of miR-122 for deoxynucleotides reduces HCV RNA accumulation. However, these nucleotides are not required for canonical miRNA activities (i.e. target cleavage and translational inhibition). This suggests that sequences in the 3' tail of miR-122 may mediate important interactions with viral or cellular factors involved in HCV RNA accumulation.

Purpose: We hypothesize that miR-122 forms a distinct complex with host and/or viral proteins that together mediate HCV RNA accumulation in infected cells. Hence, we aim at identifying and characterizing host and viral factors associated with non-canonical miR-122 complexes in HCV-infected cells to identify novel antiviral targets that can be targeted with small molecules.

Method: Alkyne-tagged miR-122 molecules are transfected into HCV RNA-harboring Huh-7 or Hep3B cells. Following miR-122 biotinylation by a click reaction, miR-122 ribonucleoprotein complexes from naïve and HCV-infected cells are isolated by streptavidin affinity purification. MiR-122-associated proteins are then analyzed by SDS-PAGE, liquid chromatography tandem mass spectrometry (LC-MS/MS) and multidimensional protein identification technology (MudPIT). Comparison of miR-122 complexes from naïve and cells infected with HCV RNA with mutations in either site 1 or site 2 of the miR-122 binding sites will allow the identification of proteins acting specifically at site 1 or site 2 of the HCV genome.

Result(s): Here, we demonstrate that alkyne-tagged miR-122 molecules are functional in mediating HCV RNA accumulation in Huh-7 cells. We show that the click reaction is stable under physiological conditions and permits efficient labeling and affinity purification of miR-122 molecules in cell lysates. Western blot of affinity purified miR-122 complexes show enrichment in the RNA-induced silencing complex (RISC) protein Argonaute 2.

Conclusion(s): We expect that the results will provide insight into a novel microRNA *'capping complex'* as well as a non-canonical *'microRNA enhancing complex'*. We anticipate that we will identify novel host-virus interactions important for viral replication that will provide new targets for therapeutic intervention.

Poster Presentation: P.06

LONGITUDINAL ANALYSIS OF FOLLICULAR T HELPER (TFH) AND B CELL RESPONSES IN HEPATITIS C VIRUS INFECTION

Maude Boisvert[1] Nathalie Bédard[1] Julie Bruneau[1, 2] Naglaa Shoukry[1, 3]

1. Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC; 2. Département de médecine familiale et de médecine d'urgence, Université de Montréal, Montréal, QC; 3. Département de médecine, Université de Montréal, Montréal, QC

Background: Primary acute hepatitis C virus (HCV) infection becomes chronic in nearly 75% of exposed individuals. CD4 and CD8 T cell responses are essential to achieve spontaneous clearance. The role of B cell responses remains controversial and no clear correlation could be established between efficient B cell response and viral clearance. Antibody response is usually delayed, of low titer, and decline rapidly after viral clearance. Neutralizing antibodies often appear after establishment of chronic infection, without control of virus replication. More recent data have reported that cross-reactive antibody responses were associated with protection upon reinfection. Furthermore, broadly neutralizing antibodies were reported in several settings, suggesting that a first successful B cell immune response, even of low magnitude can be protective. Follicular helper T cells (Tfh) are a subset of CD4 cells that mediate help for B cells and antibody production but their role during acute HCV remains understudied.

Purpose: We hypothesized that early induction of a functional Tfh response will correlate with induction of B cell responses in HCV resolvers.

Method: We optimized the analysis of Tfh and B cell responses by developing 4 different flow cytometry panels. The first two panels focus on Tfh (phenotypic panel and functional panel). The third panel analyses the dynamics of the B cell response (B cell subsets panel). The fourth panel enables us to evaluate markers of activation / inhibition / proliferation / apoptosis in both total B cells and Tfh subsets.

Result(s): Using these 4 panels we are currently analysing longitudinal blood samples from HCV resolvers, from individuals that developed a chronic HCV infection and from a healthy donor group.

Conclusion(s): The results that we will obtain will provide a first global analysis of both Tfh and B cell responses during acute primary HCV infection and their role in mediating viral clearance.

Poster Presentation: P.07

LIVE CELL SHAPE TO INVESTIGATE THE STRUCTURE OF HCV RNA

Jasmin K. Chahal; Selena M. Sagan

McGill University, Montreal, QC

Background: Hepatitis C virus (HCV) is a positive-sense single-stranded RNA virus and, as such, the genomic RNA itself must act as a template for viral translation, replication, and packaging. To accommodate this, the 5' and 3' non-coding regions (NCRs), as well as some of the coding region, contain *cis*-acting RNA elements (CREs) that play fundamental roles in the different stages of the viral life cycle. These CREs are also involved in interactions with RNA and proteins. One of these interactions is with the highly abundant, liver-specific microRNA, miR-122 and the 5'NCR of the HCV genome. miR-122 binds to two sites in the 5'NCR and *Promotes* HCV RNA accumulation. Previous studies have demonstrated that viral RNA accumulation is impaired in the absence of miR-122, though it is unclear how miR-122 modulates viral RNA accumulation. Recent studies suggest that there might be crosstalk occurring between the miR-122 molecules (or the binding sites) and the IRES region (specifically SLIV) of the HCV genome. These results suggest that miR-122 could modulate the interactions between the 5' terminus and SLIV of the HCV IRES. *Hence, we hypothesize that miR-122 binding to HCV genomic RNA alters the structure of 5'NCR.*

Purpose: The purpose of this project is to determine the structural changes that occur in the 5'NCR as a result of miR-122 interactions.

Method: To test this, we will perform **Selective 2' Hydroxyl Acylation analyzed by Primer Extension (SHAPE)** on the HCV 5' NCR +/- miR-122 in live cells. SHAPE reagents are able to modify flexible (mostly unpaired) ribonucleotides and subsequent primer extension analysis using an end-labeled gene-specific primer allows one to infer the structure of a given RNA.

Result(s): We have synthesized *in vivo* SHAPE reagents in house and optimized SHAPE *in vitro* and in *live cells* on the human 5S ribosomal RNA as well as HCV RNA templates. Using *in vitro* SHAPE, we have mapped the structure of the 5' NCR of the HCV genome.

Conclusion(s): We are currently working on generating SHAPE profiles in live cells +/- miR-122. We anticipate that these studies will uncover how miR-122 alters the structure of the HCV genome in live cells. Moreover, we hope to further clarify the role of miR-122 in HCV RNA accumulation, identify novel modes of RNA regulation, and identify novel RNA-based targets for antiviral intervention.

Poster Presentation: P.08

SODIUM TAUROCHOLATE CO-TRANSPORTING POLYPEPTIDE (NTCP) FACILITATES HCV ENTRY BY MODULATING BILE ACID TRANSPORT AND EXPRESSION OF INTERFERON-STIMULATED GENES

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

1. University of Strasbourg, Strasbourg, France; 2. Inserm U1110, Strasbourg, France; 3. INTS, Laboratoire de Virologie Moléculaire, Paris, France; 4. Icahn School of Medicine at Mount Sinai, New York, NY, USA; 5. Institut Hospitalo-Universitaire, Pôle Hépato-digestif, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Background: Chronic hepatitis B and C virus (HBV and HCV) infections are leading causes of progressive liver disease and hepatocellular carcinoma. Although HBV and HCV differ in their replication strategies, both exclusively infect hepatocytes, suggesting that liver-specific factors are likely important in the entry processes of both viruses. The sodium taurocholate co-transporting polypeptide (NTCP), a bile acid transporter, was recently identified as the first receptor for HBV.[1] However, although bile acids have been shown to affect HCV replication steps,[2] the potential role of NTCP in HCV infection is still unknown.

Purpose: In this study, we aimed to explore and characterize the potential role of NTCP in HCV infection.

Method: n/a

Result(s): Exogenous NTCP expression in Huh7.5.1 cells enhanced HCV entry, whereas siRNA- or shRNA-mediated knockdown of NTCP inhibited HCV infection in cell lines and primary human hepatocytes. Mechanistic studies revealed that NTCP facilitates HCV entry at a post-binding step without affecting expression of other entry factors. Treatment of cells with a peptide (preS1) that blocks NTCP-mediated bile acid uptake inhibited HBV and HCV entry by distinct mechanisms. For HCV, microarray analyses and validation studies revealed that preS1 blockage of bile acid transport not only modulates bile acid metabolism, but also induces expression of interferon-stimulated genes (ISGs). One such gene was interferon-induced transmembrane protein 3 (IFITM3), which was recently implicated as a restriction factor for HCV entry.[3] Conversely, treatment of NTCP-expressing Huh7.5.1 cells with bile acid decreased the expression of IFITM3 and enhanced HCV entry. In contrast, preS1 or bile acid treatment inhibited hepatitis D virus infection (a surrogate model for HBV entry) by directly interfering with viral binding.

Conclusion(s): We propose a model in which NTCP-mediated bile acid uptake suppresses the expression of ISGs such as IFITM3, thereby enhancing HCV entry. Our study highlights NTCP as a novel player linking bile acid metabolism to the interferon response in hepatocytes and establishes a role for NTCP in the entry process of multiple hepatotropic viruses, via distinct mechanisms. Collectively, these findings enhance our understanding of hepatitis virus-host interactions and suggest NTCP as an attractive antiviral target for HBV/HCV co-infection.

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Poster Presentation: P.09

DISSECTING THE ROLE OF THE POLY(C)-BINDING PROTEIN 2 IN THE HEPATITIS C VIRUS LIFE CYCLE

Sophie Cousineau; Selena M. Sagan

McGill University, Montréal, QC

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. However, the exact molecular mechanisms behind many of these effects are still unknown. 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 picornaviruses to promote their replication [1-3]. Six PCBP2 binding sites have been identified on the HCV genome, including in areas of the 5' and 3' untranslated regions with annotated roles in HCV translation and RNA replication [4]. 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-1 strain) in Huh-7 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 by the overexpression of a FLAG-tagged PCBP2 construct. We are further examining the effect of PCBP2 depletion or abundance on viral IRES-mediated translation as measured using a dual-reporter luciferase assay system. To assess PCBP2's effect on viral RNA accumulation and stability, we will conduct HCV RNA stability assays by inhibiting the viral RNA polymerase under conditions of PCBP2 depletion or overexpression.

Result(s): Previous studies show that siRNA-mediated PCBP2 knockdown inhibits HCV RNA accumulation and infectious particle production, although it is unclear if this effect is due to a defect in viral translation, RNA replication, or both [5]. We will show preliminary results that try to tease apart whether PCBP2 plays a role on viral translation or replication.

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.

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Poster Presentation: P.10

THE AUTOPHAGY ELONGATION COMPLEX (ATG5-12/16L1) POSITIVELY REGULATES HCV REPLICATION AND IS REQUIRED FOR WILDTYPE MEMBRANOUS REPLICATION FACTORIES FORMATION

Ahmed M. Fahmy; Patrick Labonté

INRS-IAF, Laval, QC

Background: Hepatitis C virus (HCV) infection is known to induce autophagosome accumulation as observed by the typical punctate cytoplasmic distribution of LC3-II in infected cells. In a previous study, we showed that viral RNA-dependent RNA polymerase (NS5B) interacts with ATG5, a major component of autophagy initiation. In this study, we evaluate the involvement of the autophagy elongation complex (ATG5-12/16L1) in HCV replication.

Purpose: In this study, we evaluate the involvement of the autophagy elongation complex (ATG5-12/16L1) in HCV replication

Method: we utilized indirect immunofluorescence and proximity ligation assay (PLA) to investigate colocalization and interaction of ATG5-12/16L1 with viral replicase components (NS3, NS4B, NS5A and NS5B) respectively. The recruitment of ATG5-12/16L1 complex to the replication site was assessed by studying its colocalization with the replicative intermediate double stranded RNA (dsRNA) and further confirmed by purification of HCV membranous web using co-immuoprecipitation and analysing its morphology using transmission electronic microscopy.The implication of ATG5-12/16L1 complex in HCV replication was studied using overexpression of a dominant negative forms of ATG5, ATG12 and siRNA approach.

Result(s): We demonstrate that the elongation complex is recruited at the site of viral replication and is required for efficient replication. Using *in situ* proximity ligation assay, we show that ATG5 interacts with several replicase components. Furthermore, purification of HCV membranous web revealed the presence of ATG5-12 and ATG16L1 along with HCV nonstructural proteins. Interestingly, LC3 is not recruited along with the elongation complex to the site of viral replication. Using dominant negative forms of ATG proteins and siRNA approach, we demonstrate that ATG5-12 conjugate is critical for viral replication but not LC3-II formation. Finally, we showed that inhibition of the elongation complex but not LC3 highly impaired the formation of the wildtype membranous web phenotype.

Conclusion(s): Together, these findings suggest that the autophagy elongation complex acts as a proviral factor and is important for the formation of wildtype membranous web.

Poster Presentation: P.11

ELEVATED PLASMA PCSK9 AND CIRCULATING MICRORNAS MIR-24 AND MIR-223 LEVELS IN HEPATITIS C-INFECTED PATIENTS WHO ACHIEVE A TREATMENT-BASED VIRAL CURE

Anastasia Hyrina[1] Paul Steven[2] Mel Krajden[3] Edward Tam[4] François Jean[1]

1. University of British Columbia, Vancouver, BC; 2. QIAGEN, Manchester, United Kingdom; 3. BCCDC Public Health Microbiology and Reference Laboratory, Vancouver, BC; 4. LAIR Centre, Vancouver, BC

Background: Hepatitis C virus (HCV) hijacks host lipid metabolic pathways as part of its replication cycle and this likely plays a role in viral pathogenesis. MicroRNAs (miRNAs) are small non-coding RNAs that silence gene expression by binding to mRNA transcripts; they act as regulators of cellular processes. However, the function of miRNAs in lipid homeostasis during HCV infection and after viral clearance and their association with progressive liver disease are poorly understood. To help clarify the role circulating miRNAs play in hepatic lipid metabolism during chronic HCV infection, we determined plasma levels of three candidate miRNAs (i.e., miR-122, miR-24, and miR-223) and the abundance of one of the predicted targets of miR-24, proprotein convertase subtilisin/kexin type 9 (PCSK9), from HCV-infected patients undergoing interferon-based treatment. Human PCSK9 has an important role in lipoprotein metabolism and is viewed as a new therapeutic target for the treatment of lipid disorders.

Purpose: In this study, we investigated how circulating levels of miR-122, miR-24, and miR-223 change during chronic HCV infection and after interferon/ribavirin-based viral cure.

Method: Circulating levels of miR-122, miR-24, and miR-223 from 94 patients with HCV were measured using qRT-PCR assays at multiple time-points before, during, and after interferon therapy. The concentration of plasma PCSK9 was determined by ELISA in patients before and after anti-HCV therapy. Serum HCV RNA levels and routine blood parameters were measured at each sample collection.

Result(s): We demonstrated that circulating miR-122 decreased after HCV viral clearance, correlating with the normalization of liver-specific enzymes (AST, $r=0.544$, $p\leq0.0001$; ALT, $r=0.618$, $p\leq0.0001$) and with a linear relationship to the baseline liver injury APRI score, while miR-24 and miR-223 levels significantly increased after viral clearance ($p\leq0.01$). Interestingly, we found that plasma PCSK9 concentrations are significantly upregulated in HCV-infected patients who achieve a treatment-based viral cure ($p=0.002$) but are not in patients who relapse. In contrast, circulating levels of miR-24 and miR-223 in patients who underwent an HCV treatment-based relapse remained unchanged, while miR-122 levels demonstrated a statistically significant increase ($p\leq0.001$). Quantitative correlation in amounts of circulating miR-24 and miR-223 was also detected ($r=0.91$, $p\leq0.0001$) for all patients.

Conclusion(s): Our findings provide the first experimental evidence of upregulation of circulating miR-24 and miR-223 in the plasma of HCV-infected patients who achieve an interferon-based viral cure. These results reveal that miRNAs known to act as regulators of lipid metabolism may be correlated with interferon-based therapeutic outcomes in patients with HCV infection. This suggests dynamic changes in the human lipidome following viral cure as assessed by circulating miRNAs and by PCSK9 abundance, and those changes may be correlated with the risk of progressive liver disease. Future lipidomics studies could help elucidate the precise molecular mechanisms of action of human miR-24, miR-223, and PCSK9 in HCV-infected patients who achieve a treatment-based viral cure.

Poster Presentation: P.12

DACLATASVIR CAN AFFECT THE MULTIMERIZATION STATE OF NS5A DOMAIN I

Moheshwarnath Issur[1] Hsaio-Wei Liu[2, 1] Marianne Ngure[1] Cosa Gonzalo[1] Matthias Götte[2, 1]

1. McGill University, Montreal, QC; 2. University of Alberta, Edmonton, AB

Background: HCV NS5A is an essential viral protein and therefore serves as a prime target in current drug development efforts. The RNA-binding protein is subdivided into three domains (DI, DII, and DII). Crystal structures of DI derived from genotype 1a and 1b are available. These previous studies reveal a similar fold of monomeric NS5A DI. Despite the structural resemblance at the tertiary level, each structure assembles in unique dimeric and possibly multimeric conformations. The biological roles of these structures remain to be determined.

Purpose: Previously, we established distinct conditions for the preparation of species competent and deficient for RNA-binding. FRET-based assays allowed us to distinguish between these populations. Moreover, our data further suggested the existence of a barrier to a free inter-conversion between the functionally distinct conformations. We hypothesized that stable multimeric forms may help to 'freeze' a given population.

Method: To address this issue, we diluted fluorescently labeled NS5A DI encompassing residues 26-216 to low nanomolar levels and utilized fluorescence polarization spectroscopy to monitor the state of the protein over time following the addition of increasing concentrations of 'cold' NS5A DI.

Result(s): We observed an increase in the fluorescence polarization under these conditions, which is indicative of the formation of a larger species of the protein complex in solution. When cy3-labeled NS5A DI is incubated with daclatasvir the observed increase in the fluorescence polarization signal was markedly reduced. This reduction was dependent on the concentration of daclatasvir. The presence of the Y93H mutation in NS5A DI alleviated this reduction although.

Conclusion(s): Taken together, our data reveals a multimeric state of NS5A DI that can be affected by daclatasvir.

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Poster Presentation: P.13

HEPATITIS C VIRUS CORE PROTEIN REDUCES CD8+ T-CELL PROLIFERATION AND PERFORIN PRODUCTION

Sarwat T. Khan[1, 2] Angela M. Crawley[1, 2]

1. Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, ON; 2. Chronic Diseases, Ottawa Hospital Research Institute, Ottawa, ON

Background: Clearance of HCV is dependent on an effective $CD8^+$ T-cell response and dysfunction of HCV-specific $CD8^+$ T-cells has been widely observed in chronic infection. We and others have also observed impaired functionality of bulk or non-HCV specific $CD8^+$ T-cells in chronic HCV mono- and HIV-HCV co-infection. This may contribute to observed reductions in immunity to other pathogens and the increased prevalence or accelerated disease progression of extra-hepatic diseases dependent on effective $CD8^+$ T-cell responses (e.g. cancer, viral co-infections) in HCV-infected individuals. Evidence suggests that HCV core protein may contribute to this dysfunction, and its circulating levels are elevated in chronic disease.

Purpose: n/a

Method: To study this dysfunction, isolated human $CD8^+$ T-cells from healthy donors were pre-incubated with recombinant HCV core protein for 72 hours and then stimulated *in vitro* to evaluate proliferation, cytokine signaling, and the production of Bcl-2, perforin and IFN-γ by flow cytometry.

Result(s): Pre-incubation with HCV core significantly reduced the proliferation of anti-CD3/28-stimulated $CD8^+$ T-cells. Perforin production was also decreased in cells pre-treated with HCV core. Decreases in target cell lysis are also expected. The effect of HCV core on IFN- γ production was variable and further study is warranted. Bcl-2 production in response to IL-7 in cells pre-incubated with core was similar to cells treated with IL-7 only, but pSTAT5 production (required for Bcl-2 production) was increased.

Conclusion(s): Our study reveals that HCV core reduces the activity and target lysis-associated functions of $CD8^+$ T-cells, suggesting a functional anergy. This may contribute to the generalized impairment of $CD8^+$ T-cells observed in chronic HCV mono- and HIV-HCV co-infection, providing insight for the design of novel counteractive immune-mediated strategies including the design of effective therapeutic vaccines.

Poster Presentation: P.28

HCV INFECTION CAUSES MULTIPLE FORMS OF PROGRAMMED CELL DEATH IN INFECTED AND NEIGHBOURING UNINFECTED CELLS

Hassan Kofahi; Nathan Tylor; Michael Grant; Rodney Russell

Memorial University Of Newfoundland, St John's, NL

Background: Chronic infection with HCV increases the risk of developing cirrhosis and hepatocellular carcinoma. Induction of programmed cell death (PCD) in the infected liver plays a role in the pathogenesis and studying it will help to understand the mechanism of development of these liver diseases.

Purpose: To study the effect of HCV infection on inducing different forms of PCD in infected and neighbouring cells, and to analyze the mechanism by which it is induced.

Method: Huh-7.5 cells were infected with the JFH1T strain of HCV. Cell viability was measured by MTT assay. DNA fragmentation was tested by staining with propidium iodide (PI) and detecting hypodiploid cells. Apoptosis was tested by detecting cPARP-positive cells and by inhibiting caspase-3. Bystander apoptosis was detected by co-culturing infected Huh-7.5 cells and S29 cells, then detecting cPARP-positive cells in the S29 cell population. Co-culturing infected Huh-7.5 and S29 cells in a transwell plate was used to test the role of cell-to-cell contact in the induction of bystander apoptosis. Induction of pyroptosis was tested by measuring the LDH activity and by staining them with the caspase-1-specific FAM-YVAD-FMK-FLICA. The induction of pyroptosis was confirmed by testing the effect of inhibiting caspase-1 on DNA fragmentation. Bystander pyroptosis was tested by staining a co-culture of Huh-7.5 and S29 cells with FAM-YVAD-FMK-FLICA.

Result(s): Infection reduced the viability of Huh-7.5 cells and induced DNA fragmentation. HCV infection increased the number of cPARP-positive cells. Inhibiting caspase-3 resulted in a significant decrease in DNA fragmentation, indicating that HCV infection induces apoptosis. cPARP-positive cells were found in both Huh-7.5 and S29 cell populations demonstrating the induction of bystander apoptosis. We could not detect any increase in the number cPARP-positive S29 cells in a transwell co-culture, indicating that direct cell-to-cell interaction is required for the induction of bystander apoptosis. Virus infection increased the activity of LDH in the supernatant of infected cells. The number of active-caspase-1-positive cells increased significantly following infection. Inhibition of caspase-1 resulted in a significant reduction in the number of hypodiploid cells, confirming the induction of pyroptosis in the infected population. A significantly higher number of S29 cells stained positive for active-caspase-1 when co-cultured with infected Huh-7.5 cells, providing evidence for the induction of bystander pyroptosis.

Conclusion(s): HCV infection induces two forms of PCD: apoptosis and pyroptosis directly and indirectly (bystander). Bystander apoptosis was found to be contact dependent.

Poster Presentation: P.15

THE EFFECT OF HCV-ASSOCIATED APOLIPOPROTEINS ON VIRUS-NEUTRALISING ANTIBODIES

Lok Man John Law; Michael Logan; Darren Hockman; Amir Landi; Chao Chen; Janelle Johnson; Rineke Steenbergen; Michael Joyce; Lorne Tyrrell; Michael Houghton

Li Ka Shing Virology Institute, University of Alberta, Edmonton, AB

Background: While there is growing evidence that protection against chronic HCV infection depends in part on both the adaptive cellular and humoral immune responses, a possible role of viral-associated apolipoproteins in modulating the effect of neutralising antibodies warrants investigation.

Purpose: We show that the extent of antibody-mediated neutralisation of HCVcc grown in the presence of human serum, in which greater association of HCV with apolipoproteins occurs, is similar to that of HCVcc grown in the presence of FBS where less association of virus with apolipoproteins occurs.

Method: Human serum-derived HCVcc was fractionated by sucrose density gradient centrifugation into light and heavy fractions varying in the levels of associated apolipoproteins and were subjected to antibody-mediated neutralisation. Little effect on gross levels of virus neutralisation was observed although confirmatory experiments are in progress to determine the precise effects of antibody neutralisation on the viral specific infectivity index.

Result(s): Our data imply that while apolipoprotein masking of HCV could render antibody neutralisation more refractory, this does not appear to have a major modulatory effect using polyclonal antisera derived from immunisation with our recombinant gpE1/gpE2 vaccine candidate[1].

Conclusion(s): Based on chimpanzee protection data reported previously[1], we are preparing a vaccine based on a modified recombinant gpE1/gpE2 for clinical testing in the near future.

References:

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Poster Presentation: P.16

TARGETING THE ASSEMBLY OF ENVELOPED RNA VIRUS: A CRITICAL ROLE OF THE VERY LONG CHAIN FATTY ACID SYNTHESIS HSD17B12 ENZYME - AN HCV CORE INTERACTOR

Bassim M. Mohamed; Daniel Lamarre

UdeM CRCHUM, Montreal, QC

Background: Enveloped RNA virus Infection represents a major global health burden. In deciphering HCV mechanistic aspects of virus-host interactions, one could understand common strategy for assembly of other related viruses. We recently conducted an LC-MS/MS analysis to elucidate host protein interactors of HCV proteins (Germain et al, MCP 2014). The study revealed that HSD17B12 interacts with HCV capsid-forming core protein. HSD17B12 is an enzyme involved in very long chain fatty acid (VLFA) elongation that also interacts with other viral proteins.

Purpose: The current study aims at elucidating the functional role of HSD17B12 in the HCV life cycle.

Method: The knock down (KD) effect of HSD17B12 in human hepatoma Huh7.5 cells infected with the infectious HCVJ6/JFH1(2a) strain

Result(s): demonstrated a significant decrease in HCV core protein associated with 6-fold increase in intracellular HCV RNA. Concurrently, extracellular viral particle production was significantly decreased (>10-fold) in HSD17B12 KD cells. Upon immunofluorescence analysis, we showed that a reduction in lipid droplets used for HCV assembly, as well as a loss of integrity of the viral replication factories (membranous web) in HSD17B12 KD cells. Finally, we rescued core expression, HCV RNA intracellular levels and particles production by supplementation with oleic acids. The expression of a catalytically active HSD17B12 also restores HCV core expression in KD cells.

Conclusion(s): Together, these data suggest that HSD17B12 plays a critical role in transition from RNA replication to virus assembly and may be critically involved in other life cycles of enveloped RNA viruses that require *de novo* VLFA synthesis.

Poster Presentation: P.17

IMMUNE PHENOTYPE DURING DAA TREATMENT IN AN INCARCERATED POPULATION WITH HIGH RATES OF INJECTION DRUG USE

Sharon Oldford[1] Krista Arseneault[1] Lisa Barrett[1, 2]

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

Background: Immune mechanisms of achieving sustained virologic response among HCV infected subjects are unclear. Previous work has demonstrated immunologic augmentation with HCV direct acting antiviral (DAA) treatment but not specifically in a population of persons who inject drugs where immune function is known to be altered.

Purpose: Assess immune changes in an incarcerated population with a high incidence of injection drug use during interferon free anti-HCV DAA therapy.

Method: 8 HCV GT-1 subjects (7 with active injection drug use within 3 months, 1 with no injection drug use history) were treated with a triple DAA regimen 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, day 7, week 4, week 8 and end of treatment. Data comparing baseline and day 7 of treatment are described here.

Result(s): All patients had rapid decline of HCV viral load within 7 days of therapy, and all were undetectable at week 8. At baseline, $CD57^+$ and $PD\text{-}1^+$ T cells were more frequent in chronically HCV-infected individuals than uninfected individuals. CD57 levels decreased and CD28 levels increased on $CD8^+$ T cells, but did not return to those of the uninfected controls. B cell and NK cell exhaustion markers did not significantly change in 7 days. There were no significant differences in T, B, and NK cell phenotype between the persons who injected drugs and the 1 person who did not inject drugs.

Conclusion(s): Inhibition of HCV replication by a DAA regimen is rapidly associated with a less exhausted T cell immunophenotype in incarcerated injection drug users. Even in individuals with immune changes related to injection drug use, potent viral suppression rapidly alters T cell phenotype. These findings highlight the plasticity of immune phenotype and reversibility of immune exhaustion even in a population with lifestyle factors associated with altered immune function.

Poster Presentation: P.18

ELUCIDATION OF THE ROLE OF MIRNAS DIFFERENTIALLY EXPRESSED DURING INFECTION WITH HEPATITIS C VIRUS

Megan H. Powdrill; Ragunath Singaravelu; Curtis Quan; John P. Pezacki

University of Ottawa, Ottawa, ON

Background: Hepatitis C virus (HCV) infection-related morbidity and mortality is a major global health burden. MicroRNAs (miRNAs) have been shown to play an important role in HCV infection through modulation of host pathways essential for viral infection or through direct interactions with viral RNA.

The viral lifecycle of HCV relies heavily on lipid pathways for entry, replication and egress. Recently, our group has shown that 25-hydroxycholesterol, a sterol-lipid effector, exerts its antiviral effects in part though modulation of miRNAs involved in regulating lipid pathways.

Purpose: To better understand the role of miRNAs in the HCV lifecycle, we examined two miRNAs that we have found to be differentially expressed during infection with HCV.

Method: We utilized miRNA microarray analyses to identify miRNAs differentially expressed during treatment with 25-hydroxycholesterol and during infection with HCV. We then transfected cells expressing the HCV replicon with the identified miRNAs and performed gene profiling analysis.

Result(s): Transfection of synthetic mimics of differentially expressed miRNAs into Huh7.5 cells stably expressing a full length HCV replicon resulted in a 2-fold increase in HCV replication as measured by qPCR and an increase in HCV protein expression as determined by Western blot. Gene expression profiling analysis by microarray, following miRNA transfection of Huh7.5 cells expressing the HCV replicon, identified host pathways modulated by these miRNAs, individually.

Conclusion(s): Overall, these results further elucidate the role of miRNAs during viral infection and the immunometabolic response to infection in the liver.

Poster Presentation: P.19

INTERROGATING THE STRUCTURE OF DENGUE VIRUS (DENV) RNA USING LIVE CELL SHAPE ANALYSIS

Maaran M. Rajah; Selena M. Sagan

McGill University, Montreal, QC

Background: Dengue virus (DENV) is a positive sense RNA virus and relative of Hepatitis C virus that belongs to the flavivirus genus within the *Flaviviridae* family. The DENV genome is a dynamic structure that serves as a template for viral replication, translation, and packaging. In order to carry out all of its diverse functions, the viral RNA must unwind, elongate, and expose different regions of the genome to host and viral proteins. Traditional approaches to interrogating RNA structure have produced important information about the secondary structures in the DENV genome that are required for viral translation, genome circularization, and replication. However, no packaging signals have been identified for DENV and approximately 95% of the genome and the entire negative-strand replicative intermediate remain uncharacterized. It is also unclear how changes in the secondary structure and circularization of the viral RNA regulate the various stages of the life cycle, from the switch from translation to viral RNA replication and finally the assembly and packaging of viral particles. *We hypothesize that the DENV genomic RNA forms multiple dynamic structures that are critical to the viral life cycle.*

Purpose: The purpose of this project is to identify local and long-range RNA-RNA interactions by examining the structure of DENV genomic RNA in live cells and viral particles.

Method: We will perform **Selective 2' Hydroxyl Acylation analyzed by Primer Extension (SHAPE)** on DENV RNA in live cells using an *in vivo* SHAPE reagent. Flexible nucleotides are able to react with SHAPE reagents to form 2'-O-adducts that function as stops to reverse transcription initiated using end-labeled primers. The resulting lengths of the 5'-end labeled cDNA fragments can be visualized by gel electrophoresis and used to infer RNA structure.

Result(s): Previous results from our lab have shown that the live cell SHAPE reagent is able to modify RNA *in virio* for HCV and experiments are underway to demonstrate that the same is true for DENV. We have optimized SHAPE experiments in *live cells* using 5S ribosomal RNA and are currently working on optimizing oligos for the characterization of the DENV genomic RNA. In vivo click reactive SHAPE (icSHAPE) will be used to couple SHAPE to next generation sequencing.

Conclusion(s): We are working on creating SHAPE profiles for DENV RNA in *live cells*. We hope to identify RNA motifs that serve important functions in the viral life cycle and sites of interaction of viral and host proteins. We also hope to identify the elusive viral packaging signals. In future, we will expand our investigation to examine the differences in DENV RNA structures in human and mosquito cells.

Poster Presentation: P.20

HEPATITIS C VIRUS TRANSMISSION: CAN PATIENTS BE INFECTED THROUGH REUSE OF ANESTHETIC MEDICATION VIAL ACCESSED WITH CLEAN NEEDLES AND SYRINGES?

Nathan G. Taylor[1] Melanie Jaeger[2] Sophie Breton[2] Prameet Sheth[2] Rachel Phelan[2] Janet van Vlymen[2] Selena M. Sagan[1]

1. McGill University, Montreal, QC; 2. Queens University, Kingston, ON

Background: Despite modern guidelines to reduce nosocomial transmission of Hepatitis C in North America numerous cases continue to be reported. Patient-to-patient transfer is often attributed to the reuse of needles and syringes during anaesthetic procedures. Clinicians are educated to avoid contamination-prone practices and yet patients continue to be infected in the clinic. The common use of multi-dose medication vials provides an alternative possible route of contamination. Numerous medications are packaged in high volume vials providing multiple doses, over multiple patients.

Hepatitis C contamination on the lids of medication vials destined to be used for multiple patients could explain the aforementioned nosocomial phenomena. A clean needle could hypothetically puncture a contaminated vial lid and inoculate the medication with infectious virus, exponentially increasing the likelihood of patient-to-patient transfer. Multiple studies have demonstrated the viability of virus in common anaesthetics and further substantiate the hypothesis that infections may stem from reuse of such multi-dose medication vials.

Purpose: To investigate the plausibility that multi-dose medication vials serve as the origin of nosocomial transmission in modern clinics.

Method: We aim to interrogate the nature of vial contamination, the ability of virus to propagate in culture following inoculation into various commonly used anaesthetics, and the possible elimination of infectivity by decontaminating vial lids with common alcohol solutions preceding inoculation. As a proof of principle, we will dry 50 ul of high titre HCV cell culture supernatant on the rubber lids of sterile 5 ml medication vials containing cell culture media. A blunt fill needle will be used to puncture the lids of experimental and control vials at multiple time points and samples will be used to infect Huh-7.5 cells.

Cells will be passaged by trypsinization and supernatants will be taken every 3 days. Total RNA will be extracted from the cells and tested for viral RNA by qPCR. Supernatants will be subjected to focus forming unit (FFU) assay to assess infectivity.

Result(s): Preliminary data from proof of principle experiments will be presented.

Conclusion(s): To our knowledge this is the first time that vial contamination will be tested in the laboratory. Our results could influence the implementation of novel aseptic guidelines and serve as a proof-of-principle for other nosocomial transmissions.

Poster Presentation: P.21

DEFINING THE MOLECULAR MECHANISMS THAT CONTROL SELECTION OF DRUG RESISTANT HCV

Nicholas J. van Buuren[1] Christopher Richardson[2] Karla Kirkegaard[1]

1. Stanford University, Stanford, CA, USA; 2. Dalhousie University, Halifax, NS

Background: Emergence of drug resistant variants follows the basic evolutionary principles and requires two things: Diversity and Selection. We know that the low fidelity of the HCV polymerase contributes to a broadly diverse quasispecies composed of almost all possible single and double mutant variants. Our research aims to characterize viral selection and the molecular mechanisms that contribute to the emergence of drug resistance. Selection of drug resistant viruses is dependent on a variety of factors including the fitness of each variant, the frequency with which each variant arises, and, as we have shown, virus-virus interactions that occur within cells at the time new variants are "born".

Drug resistant viruses arise is in the same cell as their drug susceptible parents. It is at this time that drug resistant virus can be subject to dominant suppression by drug-bound viral proteins within the same cell.

Purpose: The Kirkegaard laboratory has established the "Dominant Drug Target" paradigm using poliovirus as a model and identified the poliovirus capsid as our first dominant drug target. My goal is to screen a variety of HCV encoded viral proteins and corresponding DAAs to determine which proteins constitute dominant drug targets.

Method: To mimic the situation in which a drug-resistant variant first arises, co-infection with wild-type and mutant viruses must be observed and quantified. To this end, we constructed a codon-altered JFH1 in which we introduced 247 non-coding mutations over a 918 nucleotide sequence located across NS2 and the N-terminus of NS3. This codon altered strain demonstrated wild-type growth kinetics in Huh7.5.1 cells. We then designed RNA *in situ* hybridization probes that differentiate between the codon-altered and wild-type JFH1 viruses to analyze growth of each strain independently and quantitatively using flow cytometry.

Result(s): Mutations conferring drug resistance to BILN-2061 (NS3), SR2486 (NS5A), and Daclatasvir (NS5A) have been cloned into the wild type JFH1 background. Huh7.5.1 cells have been co-infected with drug susceptible and drug resistant JFH1 strains in the absence and presence of drugs to quantify dominance relationships of these various strains of HCV. Our results indicate that the NS3/4A protease is a non-dominant drug target as we readily select drug resistant variants from our coinfected cells. This supports the observed low barrier to resistance of the protease inhibitors. However, our data suggest that NS5A is a dominant drug target. We observe repressed growth of NS5A variants in coinfected cells using our FlowRNA selection assay. Although the NS5A-targeting compounds are not labeled as having a "high-barrier" to resistance, clinical data suggest that they do have a higher barrier to resistance than NS3-targeting compounds.

Conclusion(s): Our data indicates that dominance could play a role in decreasing the selection of resistant variants while targeting NS5A. Ongoing experimentation is aimed to understand the molecular mechanisms that allow dominant suppression of drug resistant viruses during SR2486 treatment. We focus on NS5A:NS5A interactions between $Drug^S$ and $Drug^R$ variants, as well as electron microscopy analysis of membranous web structures when both $Drug^S$ and $Drug^R$ variants are co-expressed in cells.

Poster Presentation: P.22

THE EFFECT OF PTEN ON HCV INFECTION

Qi Wu; Qiang Liu

University of Saskatchewan, Saskatoon, SK

Background: Hepatitis C virus (HCV) infection causes serious global public health problems. There are more than 130 million chronic HCV patients worldwide. Hepatocellular carcinoma (HCC) is the most deadly clinical consequence of HCV infection. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) can suppress PI3K-AKT pathway, one of the most critical cancer-promoting pathways. PTEN is frequently mutated or deleted in tumors including HCC. However, the role of PTEN in HCV replication and pathogenesis is not well characterized. PTEN protein contains an N-terminal PIP2 (phosphatidylinositol-4,5-bisphosphate)-binding motif, a phosphatase domain, a C2 domain, a C-terminal tail containing two PEST (proline, glutamic acid, serine, threonine) sequences and a PDZ (PSD-95/DLG/ZO-1)-binding interaction motif at the end. Three naturally occurring mutations on the phosphatase domain disrupt PTEN's phosphatase activity: C124S mutation abrogates both lipid and protein phosphatase activity; G129E mutation abrogates lipid phosphatase only; and Y138L mutation abrogates protein phosphatase only.

Purpose: To determine the effect of PTEN on HCV infection and the underlying molecular mechanisms.

Method: We characterized HCV infection after PTEN overexpression or knocking down. We also determined whether PTEN interacts with HCV viral proteins as a mechanism for its effect on HCV infection.

Result(s): PTEN negatively regulated HCV viral entry by using HCV genotype 2a pseudo-particles. We also observed that PTEN Y138L (protein phosphatase deficient) but not C124S (lipid and protein phosphatase deficient) nor G129E (lipid phosphatase deficient) inhibited HCV viral entry. Knocking down PTEN significantly enhanced viral replication; consistently, PTEN overexpression significantly inhibited HCV replication and secretion. Interestingly, PTEN C124S and Y138L could no longer inhibit HCV replication and secretion. We also observed that neither knocking down nor overexpressing PTEN affected HCV RNA translation. In co-immunoprecipitation and pull-down assays, we showed that HCV core protein interacted with PTEN. HCV core aa. R50 was required for the interaction. PTEN could no longer inhibit HCV genomic replication carrying core R50A mutation.

Conclusion(s): PTEN regulates HCV viral entry, replication, and secretion, but not translation. The lipid phosphatase activity of PTEN is required for inhibiting HCV entry. The protein phosphatase activity of PTEN is required for inhibiting HCV replication and secretion. HCV core interacts with PTEN, which contributes to PTEN's effect on HCV replication. Our study may help justify further development of PTEN as a new drug target for HCV therapy.

Clinical Sciences

Poster Presentation: P.23

HCV RE-INFECTION IN HIGH-RISK PEOPLE WHO INJECT DRUGS

B Conway; S Vafadary; T Raycraft; F Zahedieh; S Sharma; S Hakobyan

Vancouver ID Research and Care Centre Society, Vancouver, BC

Background: People who inject drugs (PWID) constitute the majority of cases of HCV infection in Canada. Although a number of strategies have been developed to engage them in care, reluctance to implement them relates at least in part to concerns about re-infection following successful HCV treatment. We have examined this issue in a prospective longitudinal cohort to establish whether this concern is confirmed in clinical practice.

Method: Within a multidisciplinary program to engage and treat PWID, we have documented 45 cases of HCV therapy having resulted in a sustained virologic response (SVR) in which patients continued to engage in high-risk behaviour for HCV acquisition after SVR was achieved. These individuals have been followed prospectively to document recurrent viremia, with the performance of HCV RNA testing every 6 months, more frequently if elevated ALT or symptoms of acute hepatitis were noted. The endpoint of this analysis is a positive HCV RNA test following the clear establishment of an SVR.

Result(s): Among the 666 HCV positive patients, with a mean age of 52.8 years, there were 51 (7.6%) females. Of these patients, 86 (12.9%) were co-infected with HIV, 419 (62.9%) had genotype 1, and 616 (92.5%) were previously treatment naïve. In a mean of 5.95 person-years of follow-up/subject, 4 cases of re-infection were noted (1.49/100 person-years) with all being HIV co-infected patients and 3 being genotype 1. The only factor associated with an increased risk of HCV re-infection was use of stimulants.

Conclusion(s): In our cohort, PWID successfully treated for HCV infection experience re-infection at a lower rate than previously encountered in uninfected at-risk individuals, and this negative outcome is often associated with stimulant use. The risk of HCV re-infection in individuals receiving care in multidisciplinary programs such as ours has probably been overestimated.

Poster Presentation: P.24

THE COMMUNITY POP-UP CLINIC AS A TOOL OF ENGAGEMENT FOR VULNERABLE POPULATIONS WITH HCV AND HIV INFECTIONS

B Conway; S Vafadary; S Sharma; F Zahedieh; J Shravah; S Hakobyan

Vancouver ID Research and Care Centre Society, Vancouver, BC

Background: The Downtown East Side Vancouver (DTES) is known for a high prevalence of HCV and HIV infection. Despite available services, significant numbers of patients remain undiagnosed or unengaged in care. There is a need to develop innovative structures to address this issue and understand the level of knowledge about infection and the interest to seek care.

Purpose: There is a need to develop innovative structures to address this issue and understand the level of knowledge about infection and the interest to seek care.

Method: Participants were evaluated at community pop-up clinics (CPCs) held at DTES sites (including InSite, the only supervised injection facility in North America). HCV and HIV point-of-care testing was offered. Participants also completed targeted questionnaires to collect demographic information, knowledge about HCV infection, and desire to receive care. A $10 incentive was offered for participation.

Result(s): Since January 2014, 1,850 individuals (mean age 46.5, 82.0% male) were tested, with 631 (34.1%) infected with HCV including 57 (3.1%) co-infected with HIV. Of 840 PWID, 435 (51.8%) were infected with HCV, and 32 (1.7%) co-infected with HIV A total of 136 and 15 were not previously aware of being infected with HCV and HIV respectively. Participants identified HCV transmission as occurring through casual contact (14.1%), unprotected sex (36.9%), sharing needles (45.6%), sharing injection equipment (36.3%), or blood transfusion (42.2%). Only 37.1% were aware of curable treatment being available for HCV infection, and 53.7% would consider treatment for it where it was offered.

Conclusion(s): Despite the widespread availability of HIV and HCV services in DTES, our program identified 136 and 15 new cases of HCV and HIV infection and offered individuals the opportunity to engage in care. There is a significant gap in HCV transmission knowledge, but general willingness to receive care. Innovative low-threshold programs must be developed to engage those individuals in care.

Poster Presentation: P.26

INTRAHEPATIC IL-22 CORRELATES WITH ADVANCED LIVER FIBROSIS AND SENSITIZES HSCS TO TGF-B SIGNALING IN A P38-DEPENDENT MANNER

Thomas Fabre[1, 2, 4] Manuel Florés[1, 2, 4] Genevieve Soucy[1, 3, 4] Bernard Willems[1, 4] Jean-pierre Villeneuve[1, 4] Marc Bilodeau[1, 4] Naglaa H. Shoukry[1, 2, 4]

1. Centre de recherche du CHUM, Montréal, QC; 2. Département de micriobiologie, infectiologie et immunologie, Montréal, QC; 3. Département de biologie moléculaire et pathologie, Montréal, QC; 4. Faculté de médecine, Université de Montréal, Montréal, QC

Background: Activation of hepatic stellate cells (HSCs) is a key event in the initiation of hepatic liver fibrosis, characterized by enhanced extracellular matrix production and altered degradation. Both innate and adaptive immune cells modulate activation of HSCs. CD4 T cells subpopulations contribute either positively or negatively to this phenomenon. 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 have has pro-fibrogenic properties as it, IL-17A produced by these cells promotes activation of HSCs via direct and indirect mechanisms such as enhancing the response to the major fibrogenic cytokine TGF-β responses. Th17 cells also produce IL-22 an enigmatic cytokines with both pro- and anti-inflammatory properties and . IL-22 is a hepatoprotective properties cytokine that could limit progression of fibrosis by limiting the initial injury. On the other hand, IL-10 produced by regulatory T cells (Treg) control negatively modulates activation of HSCs via the secretion of IL-10. The immune signature associated tocontribution of the different CD4 T cell populations to progression of liver fibrosis progression in different liver pathologiesof different aetiologies is still unclear.

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

Method: We have characterized *ex vivo* intrahepatic the frequency of Th17 and Treg populations by flow cytometry and quantified using cytometry-based assay the cytokines production of intrahepaticand the cytokine profile of intrahepatic lymphocytes isolated from liver biopsies lymphocytes from patient (n=30) from patients with viral and non-viral hepatitis.

Result(s): We found observed increased Th17/Treg ratio in advanced fibrotic livers (F4, Metavir) as compared to moderate or non-fibrotic livers (F0-F2). Furthermore, We we observed a bias towards increased Th17/Th9 cytokine profile in fibrotic livers from the viral-hepatitis group, whereas in non-viral hepatitis the cytokine profile was Th17/Th2. Interestingly, in both groups of patient we observedexhibited a 5-fold increased of in IL-22 in fibrotic livers (P=0.0082). *In vitro* stimulation of primary human HSCs with IL-22 enhanced activation of HSCs *via* sensitization to the major pro-fibrotic cytokinesuboptimal doses of TGF-β. RNA-seq experiment analysis performed on primary human HSCs demonstrated activation of p38 in response to IL-22. *In vitro*, chemical inhibition of p38 suppressed the pro-fibrogenic properties of IL-22.

Conclusion(s): In conclusion, we demonstrated that Th17/Treg responses leading to progression of fibrosis are dependent of the pathologyour results suggest a dysregualteddysregulated 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 driver of fibrosis throughfactor in advanced liver fibrosis acting through sensitization of HSCs to TGF-β in a p38-dependent manner.

Poster Presentation: P.27

HCV TREATMENT OF HIV-HCV CO-INFECTED PWID AT A TERTIARY CLINIC

S Hakobyan; S Vafadary; S Sharma; T Raycraft; B Conway

Vancouver ID Research and Care Centre Society, Vancouver, BC

Background: There is an over-representation of people who inject drugs (PWID) among HIV-HCV co-infected adults. Recent data indicate that HCV treatment regimens are equally effective in the setting of HIV co-infection. However, within co-infected PWID populations, the feasibility (and success rates) of such therapy has not yet been clearly established outside of clinical trials. The aim of this analysis was to address this gap in knowledge.

Purpose: Our goal was to identify, recruit, and retain HCV-infected PWID in care. As such, we established a multi-disciplinary program targeted at maintaining a lasting relationship with such individuals. This program includes facilitated access to specialty medical care, access to support services, comprehensive management of social needs, and addiction treatment.

Method: We have conducted a retrospective analysis of all HIV co-infected patients treated for HCV infection at our centre. This analysis correlates the likelihood of achieving sustained virologic response (SVR) following HCV treatment with a range of baseline demographic and clinical variables, including housing and active drug use.

Result(s): Of 522 HIV-infected individuals regularly seen at our centre, 247 (47.3%) were co-infected with HCV. Among the latter, 167 (67.6%) were PWID and 77 (31.2%) have completed HCV treatment (72 interferon-based, 5 all-oral regimens), 46 (59.7%) of which had genotype 1 infection. The mean age of treated patients was 51, 70 (90.9%) were male, 24 (31.2%) were on opiate substitution, 73 (94.8%) were on HIV treatment (62/73 with full virologic suppression), 21 (27.3%) were homeless, and 33 (42.9%) attended weekly HCV support groups. The SVR rate was 46.8% (36/77), 3/5 (60%) on all-oral regimens, 21/46 (45.7%) with genotype 1 infection, and 3/3 (100%) for patients with genotype 1 on all-oral regimens. Success rates were higher in subjects on methadone at 16/24 (66.7%), and no lower in those who were homeless 11/21 (52.4%) or active PWID 26/54 (48.1%).

Conclusion(s): PWID with HIV co-infection can be successfully treated for HCV infection within multi-disciplinary programs such as ours. Such programs will serve as an important tool to address the HCV epidemics in vulnerable populations often considered as "core transmitters" of HCV and HIV infection, especially as highly effective all-oral regimens become the standard of care.

Poster Presentation: P.14

LIVER ENZYME NORMALIZE IN INTERFERON-FREE ORAL DAA RECIPIENTS AS AN ALTERNATIVE METHOD FOR MONITORING AND PREDICTING HCV TREATMENT SUCCESS

Sarwat T. Khan[1, 2] Daniel J. Corsi[2] Curtis L. Cooper[2]

1. Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, ON; 2. The Ottawa Hospital Research Institute, Ottawa, ON; 3. The Ottawa Hospital Viral Hepatitis Program, Ottawa, ON

Background: Historically, monitoring of HCV treatment response has been done by serial HCV RNA measurements. However, HCV RNA levels at treatment week 4 are not useful for predicting success on oral DAA therapies as almost all results are undetectable. HCV RNA testing is also expensive and not readily available in many developed and developing regions. Liver enzyme levels, which are elevated in chronic HCV and tend to normalize with therapy, may serve as an alternative (and less expensive) measure of monitoring response to treatment.

Purpose: n/a

Method: Ottawa Hospital Viral Hepatitis Clinic patients receiving interferon-free oral DAA treatments were assessed for liver enzymes and HCV RNA levels at baseline, week 4 and ≥12 weeks post treatment. Liver enzyme suppression cut points used for this analysis were ALT < 40U/L and AST < 30U/L.

Result(s): 81.2% (151/186) DAA treated patients had baseline ALT > 40U/L and 21.4% (38/178) had ALT above this cut-off by week 4. 81.1% (150/185) had AST above 30U/L at baseline and 33.3% (59/177) at week 4. SVR was achieved in 91.0% (101/111) overall, 94.1% (80/85) with week 4 ALT <40U/L and 97.5% (77/79) of patients with week 4 AST <30U/L. For patients who did not suppress ALT and AST by week 4, 79.3% (23/29) and 87.5% (21/24) went on to achieve SVR. At week 4, 68.2% (116/170) patients had cleared HCV RNA (BLLQ/TND), of which 95.6% (65/68) achieved SVR. Of 39 patients with any detectable HCV RNA at week 4, 87.2% (34/39) achieved SVR. Models using week 4 ALT suppression to predict SVR had a PPV of 94.1%, NPV of 12.5% and AUC (of ROC) of 0.58. Using AST suppression, a PPV of 97.5%, NPV of 20.7% and AUC of 0.76 was obtained. A similar model using HCV RNA levels at week 4, gave PPV of 95.6%, NPV of 12.8% and an AUC of 0.64. This suggests that week 4 liver enzyme levels have similar predictive power compared to week 4 HCV RNA levels in determining SVR.

Conclusion(s): This study indicates that enzyme levels provide a viable alternative to HCV RNA levels in predicting successful response to DAA therapy. Liver enzymes and viral kinetics have limited predictive value in determining treatment failure on oral DAA therapies. Multivariable models will be used to identify variables associated with SVR at baseline and week 4 for patients when data collection is completed.

Poster Presentation: P.29

POTENTIAL DEMAND FOR LIVER TRANSPLANTATION DUE TO BURDEN OF HEPATOCELLULAR CARCINOMA: CLINICAL PRACTICE AUDIT

James Kiberd[2] Geri Hirsch[1]

1. Nova Scotia Health/Dalhousie University, Halifax, NS; 2. Dalhousie University, Canada, NS

Background: Patients with cirrhosis regardless of etiology are at higher risk of developing hepatocellular carcinoma (HCC). These patients routinely receive surveillance abdominal ultrasound every 6-months. In Nova Scotia, the major underlying disease for HCC is alcohol-related cirrhosis (45%), cryptogenic cirrhosis (26%), or hepatitis C virus (HCV) (13%) – all of these conditions are still on the rise

Purpose: AIMS: The aim of this clinical practice audit was to describe cirrhotic patients who are undergoing HCC surveillance in the Chronic Liver Disease Clinic in Nova Scotia.

Method: Records were retrieved for patients seen between January 2007 and February 2014 with at least of 6-months follow-up. Patients with cirrhosis were identified by low platelet count (<150,000mm^3) and/or biopsy. Disease etiology, age, gender, and platelets were collected from the electronic practice management system. MELD score was calculated from creatinine, total bilirubin, and INR.

Result(s): 481 patients underwent surveillance at our center. Patients with prior HCC, cancer, or transplant recipients were excluded. The remaining 404 (84%) had four patients with missing laboratory values and were removed. 400 patients were included in this clinical practice audit. HCC was detected in 29 (7.25%) patients after a median follow-up of 5.8 years (IQR 3.4 to 7.2 years) with a rate of 1.4 cancers per 100 patient-years. Sixty-four percent were male with mean age 59.9 years (95%CI: 59.0,61.0). Disease etiologies were: HCV 219(55%), cryptogenic cirrhosis including fatty liver disease 80(20%), alcohol related cirrhosis 35(9%), primary biliary cholangitis 26(6%), autoimmune hepatitis 20(5%), hepatitis B 17(4.25%), and hemochromatosis 3(0.75%). Those who developed HCC were HCV 20 (69%), alcohol related cirrhosis 6(21%) and fatty liver disease 3(10%). Median MELD Score was 7 (IQR: 7 to 10). Only 16 (4%) patients had a calculated MELD score that was 15 or greater. Ascites was present in 18 (4.5%) of patients and 11 (3%) of patients had esophageal varices. No patients in this cohort were identified as having renal insufficiency.

Conclusion(s): Incidence of HCC was found to be 1.4% which is comparable to rates across Canada. Special attention to rising HCV infection rates and the large portion of patients with fatty liver disease in our province is needed to prevent rates of cirrhosis from increasing and planning future demands for liver transplantation.

Poster Presentation: P.30

ACCESS TO NEW HEPATITIS C THERAPY: DO THE SICKEST PATIENTS RECEIVE TREATMENT?

James Kiberd[2] Geri Hirsch[1]

1. Nova Scotia Health/Dalhousie University, Halifax, NS; 2. Dalhousie University, Halifax, NS

Background: BACKGROUND: Success rates of second generation Direct Acting Antiviral (DAA) therapy for Hepatitis C Virus (HCV) have climbed to 95% with very few adverse effects. The course of treatment has been halved with most achieving viral eradication in just 12 weeks. However, this new oral regimen is costly. In Nova Scotia, a 12-week regimen of oral therapy for HCV is covered under MSI only in the presence of borderline or severe fibrosis.

Purpose: AIMS: To determine if the patients who did not have third party coverage had worse liver disease compared to those who did have access through third party coverage. To determine the reasons that chronic HCV infected patients are not on new oral therapy in our center.

Method: METHODS: Retrospective chart review was performed on all patients who had documented HCV infection and had at least one-year follow-up from 01/04/2014-01/04/2015 in the Chronic Liver Disease Clinic. New treatment status, sex, age, platelets, liver biopsy, AST, ALT, INR, total bilirubin, and creatinine were recorded. MELD, FIB4, and APRI scores were calculated and used to assess liver disease severity. Reasons for not having access to new therapy were 'no third party coverage,' 'alcohol/opioid dependence,' 'considered palliative' or 'Other.'

Result(s): RESULTS: 454 patients were identified with chronic HCV infection. Fifty-one patients were removed because they did not have lab work or did not have coverage information resulting in 403 patients included in analysis. Sixty-two percent were male with a mean age of 55.8 years (95%CI: 54.8,56.8). Cirrhotic patients made up 42% (168) of the sample as defined by low platelet count and/or confirmatory biopsy. Thirty-seven percent (148) of patients received new therapy. Median MELD score was 6 (IQR: 6,8), median APRI was 0.75 (IQR: 0.38,1.62), and median FIB4 score was 2.06 (IQR: 1.26,4.28). Higher MELD score was predictive of new treatment (OR: 4.47, 95%CI: 2.02, 9.86). Both APRI and FIB4 scores were predictive of new treatment (p=0.01 and 0.01 respectively). Not having third party coverage was associated with lower MELD (p=0.01). APRI and FIB4 scores were not associated with coverage. Of the 244 patients who were not started on new oral therapy, 188 (77%) were due to lack of third party payer. Twelve patients (5%) were deemed to have ongoing substance abuse problems and were not considered for treatment. And 12 (5%) were considered palliative due to competing health problems.

Conclusion(s): CONCLUSIONS: In our clinic, patients who did not receive new second generation DAAs had comparable liver disease severity to those who did not receive drug. Despite this finding, patients who do have third party coverage had faster access to treatment as compassionate treatment was given to those only in the presence of severe liver disease.

Poster Presentation: P.31

ELABORATION OF A QUANTITATIVE ASSAY TO MEASURE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) SPECIFIC FOR HEPATITIS C VIRUS (HCV)

Kimberly Ann Milton McSween[1, 2] Doris Ransy[1] Rasika Kunden[4] Ariane Larouche[1, 2] Laurent Desrosiers[2] Armelle LeCampion[1, 2] Hugo Soudeyns[1, 2, 3]

1. Unité d'immunopathologie virale, Centre de recherche du CHU Sainte-Justine, Montréal, QC; 2. Department of Microbiology, Infectiology and Immunology, Université de Montréal, Montréal, QC; 3. Department of Pediatrics, Université de Montréal, Montréal, QC; 4. National Institute of Virology, Pune, MH, India

Background: More than 170 million people are infected with HCV. In developed countries, the major cause of infection in children is the mother to child transmission, which occurs in 10% of cases. For reasons that remain poorly understood, HCV viral load increases in the third trimester of gestation and decreases following delivery. This situation is often followed by exacerbation of hepatic pathology. Our hypothesis is that ADCC, an immunologic process in which antibodies direct effector cells towards target cells expressing a particular antigen, is implicated in the modulation of hepatitis C pathogenesis during pregnancy.

Purpose: We aim to characterize the variation of ADCC responses in pregnant women at different stages of pregnancy and after delivery.

Method: Serial serum samples that were collected from a group of pregnant women infected with HCV will be used in an assay that requires natural killer (NK) cell-resistant target cells (CEM.NKR) and effector cells collected from healthy donors. CEM.NKR cells will be modified to express E1 and E2 HCV glycoproteins on their external membrane surface. ADCC-caused mortality of CEM.NKR cells will be quantified by using a viability dye and flow cytometry.

Result(s): E1 and E2 were cloned downstream of the CMV promoter to generate lentiviral particles that were used to transduce CEM.NKR cells. Since the expression of E1/E2 was too low, the PGK promoter was used instead of the CMV promoter. Under these conditions, intracellular expression but not extracellular expression of E1/E2 was observed. We hypothesized that CD81, the primary receptor of HCV, which is expressed in CEM.NKR cells, could inhibit the migration of E1/E2 to the cell surface by interacting with these viral proteins in intracellular compartments. Our next approach, currently being optimized, will be to knockout CD81 expression using CRISPR-Cas9 technology.

Conclusion(s): This assay will help understand ADCC responses in pregnant women at different stages of pregnancy and after delivery and will provide insights into the pathogenesis of HCV infection in pregnant women. Results from this line of investigation could help improve the clinical care of pregnant women infected by HCV.

Poster Presentation: P.32

HCV PEER SUPPORTIVE CARE MODEL FOR SUCCESS

Daina M. Norndon

1. HIV Community Link, Calgary, AB; 2. University of Calgary, Calgary, AB; 3. Calgary Urban Projects Society, Calgary, AB

Background: C.U.P.S, Calgary Urban Projects Society, is a multi-disciplinary medical clinic that strives to provide the highest quality care to people living in poverty or otherwise marginalized. New direct-acting Antivirals are changing chronic Hepatitis C treatment for the better. Hepatitis C treatment has gone from 48 weeks duration to as a little as 8 weeks with 95% SVR. In coordination, CUPS and HIVCL offers the only Hepatitis C Support Group in Southern Alberta. We provide support in the form of education and peer support to people living with Hep C who are thinking of treatment, currently on treatment, have completed treatment, and those who are HCV + and not engaged with any treatment outcomes.

Purpose: This presentation will provide an overview of the new medication regimes and the impacts on our clients, clinic operations, and the overall health care system. In addtion it will highlight the 2 year journey of our peer supportive HCV treatment model combining psychosocial and medical care models with an emphasis on the positive effects such community alliances have on the overall support recieved in this sector. A call to action for similar programming development and community partnership will be encouraged.

Method: CUPS programs and mission statements align with the philosophies of harm reduction and primary health care by providing accessible non-judgemental care to address all the social determinants of health for our clients. The CUPS Hepatitis C team works closely with clients, their families and primary care providers to test, treat and monitor for HCV and associated liver disease. The development of the support group was realised in April of 2014 and has been growing in numbers ever since. Individuals who are

Result(s): Ongoing support session access for 16-20 participants, all at differeing stages of treatment or cured, focuses on the peer supportive wrap around care through bi-weekly programming offered by CUPS clinic and HIVCL supported psychosocial engagement. Topics around treatment, medications, nutrition, stigma, awarenss campaigns, interpersonal relationship development, peer support models of care, emotional regulation awareness and mental health education support.

Conclusion(s): Our goal is to promote the support group and encourage the development of similar programs in cities across the Country. By building community capacity we hope to reduce stigma associated with a Hep C diagnosis and increase awareness of current treatment realities. We would like to bring to light the opportunities for overall more positive health in our clients and those individuals affected by HCV by joining forces across sectors to create multidisciplinary support teams.

References:

http://cupscalgary.com/primary-care-clinic/

Poster Presentation: P.33

NK CELLS LACKING FCERIΓ ARE ASSOCIATED WITH REDUCED LIVER DAMAGE IN CHRONIC HCV

Jun S. Oh

University of Ottawa, Ottawa, ON

Background: A novel subset of human NK cells, which displays potent and broad anti-viral responsiveness in concert with virus-specific antibodies, was recently uncovered in CMV+ individuals. This subset was characterized by a deficiency in the expression of FcεRIγ adaptor protein (shortly g-NK) and the long-lasting memory-like NK cell phenotype, suggesting a role in chronic infections.

Purpose: This study investigates whether the novel g-NK cell subset is associated with the magnitude of liver disease during chronic HCV infection.

Method: Blood samples from healthy volunteers and chronically infected HCV+ individuals (i.e. > 6 months HCV RNA-positive) who were antiviral-naive were collected. A written informed consent was obtained from all participants, and the study was approved by The Ottawa Health Science Network Research Ethics Board.

Plasma samples were screened for CMV serological status using HCMV-specific ELISA kits. For the detection of CMV-specific T cell response, PBMCs were stimulated with HCMV-specific pp65 peptide pool.

Multicolor flow cytometry was performed to analyze NK cell subpopulations and phenotypes. To evaluate the Antibody-Dependent Cellular Cytotoxicity (ADCC) function, NK cells were stimulated with plate-bound anti-human CD16 antibody in the presence of Brefeldin A; and their IFN-γ production were analyzed via flow cytometry.

Fibrosis stages of the liver were determined by transient elastography and/or liver biopsy, and were grouped in accordance with the METAVIR stages (F0: no fibrosis, F1: minimal fibrosis, F2: spreading of fibrosis to other area of the liver including blood vessels, F3: spreading and presence of fibrosis network in the liver, F4: cirrhosis).

Result(s): Analysis of g-NK cell proportions and function in the PBMCs of healthy controls and chronic HCV subjects showed that chronic HCV subjects had slightly lower proportions of the g-NK cell subset having similarly enhanced ADCC responses compared to conventional NK cells. Notably, among CMV+ chronic HCV patients, lower levels of liver enzymes and fibrosis were found in those possessing g-NK cells. g-NK cells were predominant among the CD56neg NK cell population often found in chronic HCV patients, suggesting their involvement in immune response during HCV infection.

Conclusion(s): For the first time, our findings indicate that the presence of the g-NK cells in CMV+ individuals is associated with amelioration of liver disease in chronic HCV infection, suggesting the beneficial roles of g-NK cells during a chronic infection.

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Poster Presentation: P.34

SOCIOECONOMIC MARGINALIZATION IS ASSOCIATED WITH LOWER HEALTH UTILITIES (QUALITY OF LIFE) IN CHRONIC HEPATITIS C PATIENTS

Yasmin Saeed[1] Kate Mason[2] Suzanne Chung[3] Jason Altenberg[2] Jeff Powis[2] Julie Bruneau[4] Jordan Feld[5] Zeny Feng[6] Nicholas Mitsakakis[3] Valeria Rac[3] Karen Bremner[7] Murray Krahn[3] William Wong[3]

1. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON; 2. Toronto Community Hepatitis C Program (TCHCP), Toronto, ON; 3. Toronto Health Economics and Technology Assessment (THETA) Collaborative, University of Toronto, Toronto, ON; 4. Department of Family Medicine, Université de Montréal, Montréal, QC; 5. Toronto Centre for Liver Disease, University Health Network, Toronto, ON; 6. Department of Mathematics and Statistics, University of Guelph, Guelph, ON; 7. University Health Network, Toronto, ON

Background: Hepatitis C is reported to have the highest disease burden of any infectious disease in Ontario, and is the leading cause of liver transplants in Canada. With many promising but costly new treatments recently becoming available for chronic hepatitis C (CHC), it will be important to evaluate their cost-effectiveness to guide decision-making. A key component of these economic evaluations is health utility (quality of life) scores.

Thus far, economic evaluations of hepatitis C treatments have relied on utility data obtained from primarily middle-class patients in hospital settings. However, marginalized populations—including those who have difficulty accessing mainstream healthcare due to barriers such as past or current homelessness, low income, alcohol and/or drug use, and mental health issues—are disproportionately affected by hepatitis C. The omission of these populations is a major limitation of existing economic evaluations.

Purpose: To elicit health utilities from chronic hepatitis C patients participating in a community-based hepatitis C program who are experiencing significant social and economic marginalization.

Method: In this ongoing pilot study, we are measuring the health utilities of 100 CHC patients participating in the Toronto Community Hepatitis C Program (TCHCP) at community health centres in Toronto, Ontario. The TCHCP is a community-based interprofessional program designed to provide hepatitis C treatment, support, and education to marginalized individuals who have difficulty accessing mainstream healthcare due to socioeconomic barriers. This unique program allows us to access this otherwise hard-to-reach patient population.

Patients are being asked to complete the EQ-5D, HUI 2/3, VAS, and TTO utility instruments.

Result(s): Preliminary data have been collected from 75 patients to date. Most patients were male (65%) with an average age of 51. Patients primarily had Genotype 1 hepatitis C (68%) and METAVIR F0-F2 fibrosis (61%). Many patients also had a low level of education (67%), were unemployed (95%), had a history of substance dependence (89% IVDU, 63% alcohol), and/or had a history of mental illness (67%).

The mean (SD) utilities were: EQ-5D 0.692 (0.235); HUI2 0.696 (0.215); HUI3 0.510 (0.353); VAS 0.617 (0.191); and TTO 0.763 (0.324).

Multivariable regression showed that the variables with the greatest impact on utility ($p< 0.05$) were: liver cirrhosis, a history of mental illness, and low education. These factors were associated with lower utility scores.

Conclusion(s): Our preliminary results suggest that marginalized CHC patients have lower utilities (i.e. a lower quality of life) than previously reported in the literature for CHC. For example, a 2008 systematic review by McLernon et al. found mean utilities of: EQ-5D 0.747; HUI2 0.823; HUI3 0.741; VAS 0.674; and TTO 0.863 for patients with moderate CHC.

This disparity is likely due to the fact that patients from disadvantaged socioeconomic backgrounds were underrepresented in previous utility studies. This is a major limitation because CHC disproportionately affects marginalized individuals. Our findings will increase the accuracy of future economic evaluations of hepatitis C screening and treatment by providing utility data that is more reflective of the affected population.

Poster Presentation: P.35

STRATEGIES TO STRENGTHEN LINKAGE TO AND RETENTION IN HEPATITIS C CARE: GLOBAL HIV CLINICAL MENTORSHIP PROGRAMS

Denise Thomas

Canadian Association of Hepatology Nurses (CAHN), Vancouver, BC

Background: A local health care workforce with clinical expertise is essential for large scale up of hepatitis C care and treatment. Strategies to strengthen linkage to and retention in hepatitis C care could be adapted from other fields such as HIV. In 2005 when generic formulations of antiretroviral therapies (ART) were affordable the Government of Lesotho's Ministry of Health piloted an HIV Clinical Mentorship Program in collaboration with the Clinton HIV/AIDS Initiative (CHAI). Lessons learned from several SubSaharan African country program scale up could inform Canada's HCV approach to scale up and strengthening linkage to and retention in HCV care.

Purpose: A local health care workforce with clinical expertise is essential for large-scale Hepatitis C programs, yet is often absent in settings where Hepatitis C treatment is relatively new and human resources are scarce such as rural and remote Canadian communities.

Method: Sub Saharan African countries have strengthened its healthcare workforce through national clinical HIV mentoring programs. Clinical mentors provide coaching on topics such as disease staging, selection of ART regimens, patient monitoring, management of opportunistic infections, and organization of clinic flow. Mentoring reinforces didactic HIV training provided by the National health care providers working in rural and remote settings. Between 2005-2010 approximately 65 nurses and doctors were recruited and placed in Sub Saharan African countries as Clinical HIV Mentors with the Clinton HIV/AIDS Initiative in collaboration with national governments.

Result(s): Clinical mentoring accelerates ART scale-up. In one district hospital clinic in Lesotho, an average of 10.8 patients were enrolled each week during six (6) weeks of mentoring. This represents a three-fold increase over the average enrollment during the six (6) weeks immediately prior to mentoring (3.3 patients per week). Clinical mentoring is an effective method for rapidly developing HIV/AIDS expertise amongst professionals with limited training and experience. The effects are immediate and sustainable. The transition of externally sourced HIV clinicians to a local HIV clinical mentorship program requires five (5) years of clinical mentoring program experience two (2) additional years of program management support and monitoring and evaluation.

Conclusion(s): Clinical mentoring programs must be tailored to the specific needs of national ART programs. Given the scarcity of physicians in rural settings, nurses are the primary providers of healthcare, particularly at health centers. Lessons learned from rolling out ART at health centres to expand access at the community level, using a combination of didactic training and clinical mentoring could inform provinical HCV programming. Outcomes show that within 3 weeks, nurses in health centers with clinical mentoring can correctly initiate and monitor ART according to national guidelines. Strengthening linkage to and retention in HCV care may be achieved by adapating lessons learned from global HIV clinical mentorship programs.

Epidemiology and Public Health

Poster Presentation: P.36

EVALUATION OF TREATMENT OF HCV INFECTION IN PEOPLE WHO INJECT DRUGS

Arshia Alimohammadi; Shawn Sharma; Syune Hakobyan; Yu-Li Hsieh; Harout Tossonian; Alexanda King; Brian Conway

Vancouver Infectious Diseases Centre, Vancouver, BC

Background: Approximately 70% of HCV infected individuals in Canada are people who inject drugs (PWID). However, many healthcare providers require PWID to be drug-free for 6-12 months before commencing HCV treatment.

Purpose: The aim of this study was to illustrate that HCV treatment could be successful in PWID in the right circumstances, without requiring a mandated period of abstinence.

Method: A retrospective observational study was conducted in active PWID (currently injecting recreational drugs) receiving HCV therapy between 2011 and 2015 at a multi-disciplinary inner city clinic, favoring engagement and retention in care of the target population. Data regarding HCV treatment, HIV co-infection status, as well as demographic and social variables was collected. The primary endpoint was a sustained virologic response (SVR) with respect to HCV infection.

Result(s): We treated 40 eligible subjects (34 male) with a median age of 53 years, 24 (60%) genotype1a/b, 10 (25%) genotype 3, 33 (83%) previously treatment naïve, 11 (27.5%) co-infected with HIV. With respect to illicit drug use, there were 25 (63%) using heroin, 28 (70%) using cocaine, 9 (22.5%) using other stimulants and 23 (58%) on opiate substitution therapy. With respect to HCV therapy, 25 (63%) received IFN-based and 15 (37%) all-oral regimens. In total, 31 (78%) subjects achieved SVR, 17 (68%) and 14 (93%) on IFN-based and all-oral regimens ($p<0.05$ favoring all-oral regimens). Within the study population, 7 (64%) with HIV co-infection, 18 (75%) with genotype 1, 9 (90%) with genotype 3, 21 (84%) on heroin, 21 (75%) on cocaine and 7 (78%) using other stimulants achieved SVR. Three (8%) discontinued due to toxicity and 4 (10%) relapsed. Finally, with a mean of 560 days of follow-up, there were no cases of recurrent viremia.

Conclusion(s): Active PWID can be effectively treated for HCV infection with high SVR rates, especially with all-oral regimens. With structured post-treatment follow-up, rates of recurrent viremia can be minimized, enhancing the feasibility of programs to increase treatment uptake in high-risk populations of "core transmitters" of HCV infection.

Poster Presentation: P.37

ACCESS TO HCV ASSESSMENT AND TREATMENT AMONG ACUTELY HCV-INFECTED PEOPLE WHO INJECT DRUGS AND SUBSEQUENT INJECTION DRUG USE CHANGES: FINDINGS FROM THE IMPACT STUDY

Andreea A. Artenie[1, 2] Emmanuel Fortier[2, 3] Geng Zang[2] Didier Jutras-Aswad[2, 4] Marie-Eve Turcotte[2] Rachel Bouchard[2] Julie Bruneau[2, 3]

1. Department of Social and Preventive Medicine, School of Public Health, Université de Montréal, Montréal, QC; 2. Research Centre, Centre Hospitalier de l'Université de Montréal, Montréal, QC; 3. Department of Family and Emergency Medicine, Faculty of Medicine, Université de Montréal, Montréal, QC; 4. Department of Psychiatry, Faculty of Medicine, Université de Montréal, Montréal, QC

Background: Although there is some evidence to suggest that hepatitis C virus (HCV) treatment can lead to positive changes in injection drug use among people who inject drugs (PWID), to date, limited research has investigated this topic.

Purpose: The present study examined changes in injection drug use among recently HCV-infected PWID systematically referred for HCV clinical assessment and treatment and offered targeted health care services, over the course of one year.

Method: The study sample included PWID with documented HCV seroconversion recruited and followed-up semi-annually at least twice in IMPACT (2007- 2014), a longitudinal prospective study in Montréal. Participants with contra-indications to treatment due to severe physical or psychiatric co-morbidity were offered targeted health care services. Pegylated interferon-alpha (12–24weeks) was offered to all other participants who did not spontaneously resolve their infection. At each study visit, data were collected on socio-demographic factors and drug use patterns. Multivariable logistic regression analyses were used to assess changes in injection drug use at one-year follow-up.

Result(s): Of the 87 eligible participants (mean age: 35.6; 78.2% male), 21.8% received treatment [(RT), sustained virologic response: 84.2%], 25.3% spontaneously resolved their infection (SR), 14.9% had a contra-indication (CI) and 37.9% chose not to engage in HCV care (NT). In multivariate analyses adjusting for age, gender and injection drug use at baseline, the RT group was less likely to report injection drug use at follow-up compared to the NT group [Adjusted odds ratio (AOR): 0.18; 95% Confidence interval (CI): 0.04, 0.76)]. A lower likelihood of reporting injection drug use was also found in the SR group (AOR: 0.34; 95% CI: 0.08, 1.40) and the CI group (AOR: 0.24; 95% CI: 0.05, 1.22) relative to the NT group, though these associations were not statistically significant.

Conclusion(s): Our results indicate that PWID who received HCV treatment were less likely to report injection drug use at follow-up relative to those who opted not to engage in HCV care. These findings emphasize the importance of offering readily access to HCV assessment and treatment to HCV-infected PWID.

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Poster Presentation: P.38

WORKING OURSELVES OUT OF OUR JOBS - SAVING LIVES BY CREATING POLITICAL WILL AND CHANGE

Patricia Bacon

Action Hepatitis Canada, Whitehorse, YT

Background: In 2012 and again in 2014, Action Hepatitis Canada surveyed our federal, provincial and territorial governments on their response to issues relating to viral hepatitis in Canada.

Purpose: Surveys were conducted in order to develop a clear sense of the progress that our governments are making in addressing viral hepatitis in Canada. Data derived from survey responses help to establish an advocacy plan for Action Hepatitis Canada in the years to come.

Method: Repeated surveying of federal, provincial and territorial governments' progress on 6 areas identified by the World Health Organization and World Hepatitis Alliance as priorities in addressing viral hepatitis.

Result(s): The findings from our surveys reveal little action or progress by our governments in response to significant recent treatment and research advancements in the field.

Conclusion(s): This session will cover some of the reasons for this apparent apathy and inaction and will address approaches that advocates can take to drive political uptake and force appropriate public policy change.

Screening guidelines remain static despite knowledge of the lives that are lost everyday to a virus that could have been cured if diagnosed sooner. Provinces and territories have welcomed new treatments but, in most cases, have shied away from negotiating pricing that would ensure treatment access to all who would benefit.

Poster Presentation: P.39

DELAYED DIAGNOSIS AND POVERTY IMPEDE IMMIGRANTS FROM REALIZING OPTIMAL HEPATITIS C VIRUS INFECTION OUTCOMES

Curtis Cooper[1, 2, 3] Kednapa Thavorn[3] Daniel J. Corsi[3]

1. Associate Professor of Medicine, The Ottawa Hospital - Division of Infectious Diseases, Ottawa, ON; 2. Director - The Ottawa Hospital and Regional Hepatitis Program, Ottawa, ON; 3. Ottawa Hospital Research Institute, Ottawa, ON

Background: Hepatitis C (HCV)-infected immigrants from endemic regions contribute to the total prevalence in Canada and other developed nations. Little is known about engagement in care, access to service, and treatment outcomes in immigrants compared to Canadian-born patients living with HCV.

Purpose: n/a

Method: HCV patients were identified from a clinical database housed at The Ottawa Hospital Viral Hepatitis Clinic (2000-2013). Immigration history, country of origin, race, socioeconomic status, HCV work-up, treatment and outcome data was evaluated. A long-term immigrant was defined as residing in Canada for ≥ 15 years, the point at which risk factor profiles are thought to converge with native-born populations. HCV work-up, treatment and outcome were compared by immigration history (Chi square, Student's t test).

Result(s): 1872 HCV-infected patients were included, 1661 (88.7%) had data on immigration (22.5% of all patients) and length of time in Canada. A median 16 years (Quartiles: 5, 28) passed from immigration to referral. The mean age at the time of first HCV clinic evaluation was lower for Canadian-born referrals ($p<0.001$). Access to services and treatment as well were similar irrespective of immigrant status. HCV antiviral therapy sustained virological response outcomes where diminished in long-term immigrants. Poverty was a predictor of poor treatment outcome.

Conclusion(s): HCV screening and health care engagement at the time of immigration is recommended to optimize HCV care engagement and therapeutic outcomes.

Poster Presentation: P.40

DISTRIBUTION OF HEPATITIS C RISK FACTORS AND HCV TREATMENT OUTCOMES AMONG CENTRAL CANADIAN ABORIGINALS

Parmvir Parmar[1] Daniel J. Corsi[2] Curtis Cooper[3]

1. Faculty of Medicine, University of Ottawa, Ottawa, ON; 2. Ottawa Hospital Research Institute, Ottawa, ON; 3. Associate Professor of Medicine - Division of Infectious Diseases, The Ottawa Hospital, Ottawa, ON

Background: Aboriginal Canadians face higher levels of lifestyle risk factors for hepatitis C exposure including drug use and incarceration.

Purpose: We examined multiple risk factors clustering among Aboriginals.

Method: The Ottawa Hospital Viral Hepatitis Clinic Cohort (January 2000-August 2013) was evaluated. Demographic data, HCV infection risk factors, and HCV treatment outcomes were assessed. Markers of socioeconomic status were based on area-level indicators linked to postal code.

Result(s): 55 (2.8%) Aboriginal and 1923 (97.2%) non-Aboriginals were evaluated. Aboriginals were younger (45.6 vs. 49.6 years, p<0.01). The distribution of gender (63.6% vs. 68.3% male), HIV co-infection (9.1% vs. 8.1%), genotype 1 infection (68.5% vs. 65.4%), advanced fibrosis stage (29.2% vs. 28.0% F2+), and SVR rate (56.3% vs. 58.9%) was similar between Aboriginal and non-Aboriginals (*P*>0.10). Aboriginal status was associated with a higher number of HCV risk factors, (mean 4.2 risk factors vs 3.1, p<0.001) with an odds ratio of 2.5 (CI 1.4-4.4) for having at least 4 risk factors. This was not explained after adjustment for markers of socioeconomic status including income, social deprivation, and poor housing. Multivariable logistic regression suggested that SVR was unrelated to Aboriginal status (*P*=0.83). Aboriginal patients interrupted therapy more often due to lost-to-follow-up, lesser adherence and substance abuse (25.0% vs. 4.6%) and serious adverse events (25.0% vs. 21.3%), *P*<0.001).

Conclusion(s): Aboriginal Canadians have higher levels of HCV risk factors; even when adjusting for area-level socioeconomic status markers. Despite facing greater barriers to care, SVR rates were comparable with non-Aboriginals.

Poster Presentation: P.41

ADHERENCE TO RESPONSE-GUIDED PEG-INTERFERON AND RIBAVIRIN FOR PEOPLE WHO INJECT DRUGS WITH HCV GENOTYPE 2/3 INFECTION: THE ACTIVATE STUDY

Evan B. Cunningham[1] Behzad Hajarizadeh[1] Olav Dalgard[2] Brian Conway[3] Graham R. Foster[4] Philip Bruggmann[5] Markus Backmund[6] Tracy Swan[8] Janaki Amin[1] Pip Marks[1] Sophie Quiene[1] Martin Weltman[9] David Shaw[10] Adrian Dunlop[11] Margaret Hellard[12] Julie Bruneau[13] Stefan Bourgeois[14] Gregory Dore[1] Jason Grebely[1]

1. Kirby Institute, UNSW, Sydney, NSW, Australia; 2. Akershus University Hospital, Oslo, Norway; 3. Vancouver Infectious Diseases Center, Vancouver, BC; 4. The Liver Unit, Queen Marys University of London, London, United Kingdom; 5. Arud Centres for Addiction Medicine, Zurich, Switzerland; 6. Ludwig Maximilians-University Munich, Munich, Germany; 7. Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, Belgium; 8. Treatment Action Group, New York, NY, USA; 9. Nepean Hospital, Sydney, NSW, Australia; 10. Royal Adelaide Hospital, Adelaide, SA, Australia; 11. School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia; 12. Burnet Institute, Melbourne, VIC, Australia; 13. Universite de Montreal, Montreal, QC; 14. Stuivenberg ZNA, Antwerp, Belgium; 15. Division of Infectious Diseases, University Hospital and University of Bern, Bern, Switzerland

Background: Adherence to HCV therapy impacts SVR, but data is limited among people who inject drugs.

Purpose: This study assessed PEG-IFN adherence and associated factors.

Method: Participants with HCV G2/3 who had recently injected drugs (last 12 weeks) or receiving opioid substitution therapy were recruited (2012-14) and received directly observed PEG-IFN and self-administered RBV. Participants with an RVR received 12 weeks (shortened duration) and those without RVR received 24 weeks (standard duration) therapy. The primary endpoint was SVR12 and 80/80 PEG-IFN adherence.

Result(s): Overall, 93 initiated HCV treatment (mean age 42; 82% men; 87% G3; 55% injected drugs in the last month; 70% on OST at baseline). Sixty-five percent (n=60) received shortened treatment, while 29% (n=27) received standard treatment. Six participants discontinued prior to week 4. 80/80 PEG-IFN adherence was 81% (n=75), 6% missed ≥1 dose (on-treatment adherence >99%) and 27% (n=22) discontinued early [virological failure (n=1), lost to follow up/unwillingness (n=10) and side effects (n=11)]. Treatment completion was higher in those receiving 12 vs. 24 weeks of therapy (97% vs. 52%, *P*<0.01, Figure). Injecting drugs in the last month did not impact 80/80 adherence (81% vs. 80%, *P*=0.95). Treatment duration of 12 weeks (those with RVR) was the only factor associated with ≥80/80 adherence (vs. 24 weeks; AOR 40.6, 4.9-338.0). SVR was 63% (82% – 12 weeks; 37% – 24 weeks), and was associated with ≥80/80 adherence (79% vs. 0%,*P*<0.01).

Conclusion(s): High adherence to therapy was observed, irrespective of recent injecting drug use. Sub-optimal exposure was driven by early treatment discontinuation, not missed doses during therapy. Treatment completion and adherence were higher in people receiving 12 weeks of therapy compared to 24 weeks.

Poster Presentation: P.42

RESPONSIVE AND INTEGRATED PROGRAMMING APPROACHES FOR PRIORITY POPULATIONS IN HEPATITIS C

Melisa Dickie; Suzanne Fish; Timothy Rogers; Logan Broeckaert; Laurel Challacombe; Laurie Edmiston

CATIE: Canada's Source for HIV and hepatitis C information, Toronto, ON

Background: The changing landscape in hepatitis C has the potential to significantly transform and improve the national frontline response in prevention, testing, treatment and care for communities and individuals affected and at risk. Yet in order to achieve significant improvements, the health programs, organizations and structures must be able to properly reach, diagnose, treat, care and enable further prevention of hepatitis C in the populations most affected. Programs around the country are providing responsive hepatitis C services for priority populations across the continuum of care. In order to develop, replicate and scale up these effective programs, it is critical to identify the key factors of success at the programmatic, organizational, structural and systemic levels.

Purpose: CATIE hosted a *National Deliberative Dialogue on Responsive Integrated Approaches to Hepatitis C Programming and Services* to explore front-line hepatitis C continuum of care models (prevention, testing, treatment and support) for priority populations (Aboriginal peoples, people who inject drugs, immigrants and new comers and older adults) and to identify promising directions in hepatitis C programming, policy and knowledge exchange.

The deliberative dialogue had four primary objectives:

- inform priority directions for population-specific hepatitis C programming, services and policy that put service users at the centre of an integrated framework;
- provide guidance to new programs across Canada on hepatitis C continuum of care models for specific populations;
- facilitate multi-region, cross-sectorial collaboration, knowledge sharing and networking among hepatitis C programming leaders;
- inform a national strategic directions document.

Method: CATIE organized a national knowledge exchange meeting on February 11-12, 2015. Select individuals were invited to attend with the aim of ensuring regional diversity as well as representation from the broader sector. There were a total of 42 external participants, including eight Ontario representatives, four from Quebec, eight from British Columbia, six from the Prairies, five from the Atlantic Region, two from the Yukon/Territories, eight national representatives and one international speaker from the U.S. Recommended factors of success in hepatitis C programming were extrapolated from the presentations and discussions at the Deliberative Dialogue.

Result(s): Service providers and service users are responding to community needs by developing integrated hepatitis C models of care that also incorporate a range of broader support services all within specific cultural and community contexts. A total of 34 recommended factors of success were identified that foster integration and enable the development of responsive models of care which are accessible, relevant and effective at addressing hepatitis C. The recommended factors of success have been grouped into three levels – programmatic, organizational and structural/systemic.

Conclusion(s): In order to replicate, scale up and continue to improve the response to hepatitis C, the recommended factors identified at the Deliberative Dialogue may be critical to success.

Poster Presentation: P.43

ROOM FOR IMPROVEMENT: KNOWLEDGE EXCHANGE NEEDS OF PEOPLE LIVING WITH HCV

Ed Jackson[1] Laurel Challacombe[1] Melisa Dickie[2] Scott Anderson[1] Timothy Rogers[1] Laurie Edmiston[1]

1. CATIE: Canada's Source of HIV and hepatitis C information, Toronto, ON; 2. CATIE: Canada's Source for HIV and hepatitis C information, Toronto, ON

Background: Many people in Canada are affected by hepatitis C. An estimated 332,414 people in Canada were antibody positive for hepatitis C in 2011. An estimated 220,697 to 245,987 Canadians were chronically infected with hepatitis C in 2011.

Purpose: It is important to understand the information needs of people living with hepatitis C in order to support them to manage their health and to make informed decisions about treatment. In 2014-2015 CATIE undertook a national needs assessment of patients engaged in hepatitis C care. The needs assessment was designed to provide information on the priority knowledge needs of people living with hepatitis C and how these needs can be met.

Method: An online survey was developed and focus tested to assess the information needs of people engaged in hepatitis C care. Eight medical clinics serving people living with hepatitis located in British Columbia, Alberta, Saskatchewan, Manitoba and Ontario were engaged to recruit participants to complete the survey.

Result(s): In total, 326 people participated in the survey. Participant demographics included the following:

66% men

63% aged 46 and older

27% self-identified as Aboriginal

38% diagnosed within the past 10 years; 33% diagnosed 10-19 years ago; and 17% diagnosed 20 or more years ago

54% had some experience with treatment.

- Participants wanted to be involved in decision making about their care. Eighty-two percent were either very involved or somewhat involved in decision making around hepatitis C care. Forty-one percent wanted more involvement in making decisions about their care.
- Participants reported low levels of hepatitis C knowledge. Only 23% of participants reported knowing 'a lot' about hepatitis C generally and 20% reported knowing 'a lot' about hepatitis C treatment. Participants reported a large need for information; 85% reported needing at least 'a little' hepatitis C information.
- Participants ranked the importance of different topics. High priority/importance topics included: How hepatitis C affects the body; How to stay healthy; How to prevent transmitting hepatitis C to others.
- For hepatitis C treatment information, high priority/importance topics included: How to get ready to start treatment; How to deal with side effects; How to get and pay for treatment.
- Participants also ranked the importance of different formats for receiving information. Priority formats for receiving information were: Internet, brochures, and workshops.
- Participants primarily got their information from healthcare providers with ninety percent reporting doctors/nurses as the most common source of hepatitis C information. Substantially fewer reported using other sources of information.

Conclusion(s): There is a high level of need for information on hepatitis C generally and on hepatitis C treatment among people living with hepatitis C who are engaged in hepatitis C care. There are clear priorities on topic areas and on preferred formats for receiving information. These can be used to develop resources and tools that support people living with hepatitis C to manage their health and to make informed decisions about their treatment.

Poster Presentation: P.44

USING KNOWLEDGE EXCHANGE (KE) TO STRENGTHEN THE RESPONSE TO HEPATITIS C IN CANADA

Laurel Challacombe; Melisa Dickie; Suzanne Fish; Timothy Rogers; Laurie Edmiston

CATIE: Canada's Source for HIV and hepatitis C information, Toronto, ON

Background: Emerging research and innovative, integrated HCV programming approaches have the potential to significantly strengthen the hepatitis C response in Canada.

Purpose: CATIE champions and supports innovation and excellence in KE by collaborating with and building the capacity of front-line organizations to use knowledge effectively to respond to HIV and hepatitis C. CATIE uses a variety of KE activities to strengthen the frontline response which are tailored according to the target audience, the content of the knowledge and the purpose of the knowledge for the target audience. Many of these approaches have been evaluated and provide important information and insight regarding effective KE strategies.

Method: Various approaches to evaluation of KE activities included online surveys and in-person evaluation forms. Standard evaluation indictors were used to assess key KE outcomes, including relevance, usefulness, increased knowledge, and application of knowledge.

Result(s): The evaluation results of four different methods of KE were analyzed and compared. These methods were:

- deliberative dialogue on policy and programming implications for integrated hepatitis C programming approaches for priority populations;
- foundational trainings in hepatitis C core knowledge (hepatitis C blended learning model for front-line workers);
- a website providing comprehensive information on HIV and hepatitis C;
- learning institutes that support frontline workers to learn from research conferences and share findings with their communities.

The deliberative dialogue was relevant (100%); increased knowledge (97%); people can use/apply that knowledge (100%); increased capacity to respond to hepatitis C (100%). Participants also agreed that the deliberative dialogue was effective at providing guidance to programs across Canada on hepatitis C continuum of care models for specific populations (97%).

Hepatitis C blended learning curriculum was relevant (100%); useful for the work that front-line organizations do (100%); increased knowledge of hepatitis C (100%); and increased capacity to respond to hepatitis C within their community (100%).

The CATIE website was relevant (96%); increased knowledge (94%); people can use/apply that knowledge (96%); people were satisfied (94%); and found it useful for the work they do (95%).

Learning institutes were relevant (96%); increased knowledge (96%); people can use/apply that knowledge (96%); people were satisfied (100%); and found it useful for the work they do (100%).

Based on the participant/user evaluations, these methods of KE were relevant (96% to 100%) and useful (95% to 100%). They resulted in increased knowledge (94% to 100%) that was applied to the frontline response (96% to 100%). The evaluations also provided insight into the factors that contribute to successful KE.

Conclusion(s): CATIE has developed an extremely successful model for KE. Particular strengths of CATIE's model include: using multiple channels for KE, providing information on a broad range of topics for a diverse range of audiences, and translating treatment and prevention research into plain language. CATIE also ensures our KE methods are tailored to the audience, content and purpose for KE which strengthens the frontline response to hepatitis C in Canada.

Poster Presentation: P.45

ESTIMATION OF FIBROSIS PROGRESSION RATES FOR CHRONIC HEPATITIS C: A SYSTEMATIC REVIEW AND META-ANALYSIS UPDATE

Aysegul Erman[1, 2] Tawnya Hansen[3] Joanna M. Bielecki[2] Murray D. Krahn[2, 1, 4] Hla-Hla Thein[5]

1. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON; 2. Toronto Health Economics and Technology Assessment Collaborative (THETA), University of Toronto,, Toronto, ON; 3. Department of Medicine, University Health Network, University of Toronto, Toronto, ON; 4. Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON; 5. Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background: Chronic Hepatitis C viral infection (HCV) when left untreated is a leading cause of cirrhosis, liver failure, cancer and transplantation, making it a major medical and economic burden. Given the recent availability of highly effective but costly antivirals, 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 the most up-to-date stage-specific and stage-constant liver fibrosis progression rates (FPR) in individuals with chronic HCV infection though an updated systematic review and meta-analysis.

Method: Literature search was conducted using MEDLINE, EMBASE and PubMed databases covering a period of January 1990 to August 2014 and supplemented by reference and citation searches. In general, the review included published English and non-English peer-reviewed prognostic studies which examine liver fibrosis progression in HCV-infected individuals. Publication bias was assessed by Funnel plots and Egger's test for asymmetry. Stage-constant FPRs were estimated for each study via the indirect method using the fibrosis score distribution and the estimated duration of infection reported in each study. Stage-specific FPRs (F_{0-1}, F_{1-2} F_{2-3}, F_{3-4}) were estimated using the Markov Maximum Likelihood estimation (MMLE) method developed by Yi et al[1]. Random and fixed effects meta-analyses were used to obtain pooled stage constant and stage-specific FPR estimates.

Result(s): Overall, the updated systematic review included a total of 152 reports of HCV-infected individuals (n=53,982). The pooled stage-constant FPR estimates derived through the indirect method were 0.086 (95%CI, 0.085-0.086) and 0.102 (95%CI, 0.098-0.0106) METAVIR units per year for the fixed and random effects models respectively. The stage-specific FPRs based on the random effects model were F_{0-1}: 0.111 (95%CI, 0.101-0.122); F_{1-2}: 0.087 (95%CI, 0.078-0.096); F_{2-3}:0.121 (95%CI, 0.110-0.132); F_{3-4}: 0.115 (95%CI, 0.105-0.127).

Conclusion(s): The current study provides the most recent/updated estimates of both stage-constant and stage-specific liver disease progression rates associated with chronic HCV infections through an updated meta-analysis and systematic review. These results are consistent with the original study but suggest a slightly slower disease progression for stage-specific FPRs.

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Poster Presentation: P.46

THE EFFECT OF SHORT-TERM TRANSITIONS IN ROUTES OF DRUG ADMINISTRATION ON HIGH-RISK INJECTING BEHAVIOURS AMONG PEOPLE WHO INJECT DRUGS IN MONTRÉAL

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. Département de médecine familiale et de médecine d'urgence, Faculté de médecine, Université de Montréal, Montréal, QC; 2. Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, QC; 3. Département de médecine sociale et préventive, École de santé publique, Université de Montréal, Montréal, QC; 4. Département de psychiatrie, Faculté de médecine, Université de Montréal, Montréal, QC; 5. Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Longueuil, QC; 6. Institut national de santé publique, Montréal, QC; 7. Kirby Institute, UNSW Australia, Sydney, NSW, Australia

Background: The majority of new and existing cases of hepatitis C virus (HCV) infection in high- and middle-income countries occur among people who inject drugs (PWID). While drug dependence is considered a chronic condition [1], injecting drug use has shown to be a dynamic process, characterized by sequential transitions in routes of drug administration [2, 3]. However, little is known about the effect of short-term transitions, e.g. injection cessation and relapses, on high-risk injecting behaviours.

Purpose: The objective of this project is to assess the association between short-term transitions in routes of drug administration and high-risk injecting behaviours.

Method: 622 PWID recruited and followed-up in the HEPCO cohort study between 2011 and 2014 were included in this investigation. Participants were followed every 3 months. At each 3-monthly visit, participants completed an interviewer-administered questionnaire and were tested for HCV Ab/RNA. To assess short-term transitions in routes of drug administration, participants were asked if they injected within each of the last three months. Transition was defined as having switched from cessation to injection or vice versa at least once during the 3-month period. Outcomes of interest included sharing syringes and/or injection works the last 3 months. Univariate and multivariate generalized estimating equation (GEE) analyses for binary outcomes were used for analyses.

Result(s): The mean age of participants at baseline was 40 years, and 83% were male. The follow-up of 622 participants resulted in 3249 visits. No injection was reported in 727 visits (22%), at least one transition in 733 (23%) visits, and no transition in 1786 (55%) visits. Visits reporting no injection were excluded from further analyses. Sharing syringes was observed in 10% of the visits, sharing other injection works in 15% of the visits, and sharing injection material (syringes and/or injection works) in 18% of the visits. Univariate GEE analyses of the associations between short-term transitions and outcomes were as follows: sharing syringes, OR 0.67, 95%CI 0.47-0.94; sharing injection works other than syringes, OR 0.53, 95%CI 0.39-0.70; sharing injection material, OR 0.52, 95%CI 0.40-0.67. Multivariate analyses will be presented at the conference.

Conclusion(s): Negative associations between short-term transitions and all sharing outcomes were found in unadjusted analyses. Preliminary findings suggest that short-term transitions in routes of drug administration, even if consisting of short-duration episodes of injection cessation, could potentially contribute to the reduction of injecting-drug-related harm and transmission of blood-borne viruses. Further analyses, accounting for covariates and potential confounders, will be conducted to examine the potential impact of these findings on the development of targeted interventions.

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Poster Presentation: P.47

THE BC HEPATITIS TESTERS COHORT (BC-HTC): THE HEPATITIS C CASCADE OF CARE IN BRITISH COLUMBIA

Naveed Janjua[1, 2] Margot Kuo[1] Amanda Yu[1] Stanley Wong[1] Maria Alvarez[1] Mel Krajden[1, 2]

1. BC Centre for Disease Control, Vancouver, BC; 2. University of British Columbia, Vancouver, BC

Background: The BC Hepatitis Testers Cohort (BC-HTC) was established to characterize hepatitis C (HCV) disease burden, disparities in testing and care, healthcare utilization, treatment uptake and completion, treatment effectiveness and healthcare related costs in British Columbia. Monitoring HCV affected population across stages of a cascade of care provides a measure of population level program effectiveness and identifies service and access gaps.

Purpose: To present the population level cascade of care for HCV in British Columbia.

Method: The BC-HTC includes 1.5 million individuals tested for HCV and/or HIV or reported as a case of HCV, hepatitis B, HIV or active tuberculosis in BC from1990-2013 linked to their corresponding medical visits, hospitalizations, cancers, prescription drugs and mortality data. Results are presented on the HCV cascade of care as of 2012. We defined six HCV cascade of care stages: 1) Estimated population prevalence; 2) HCV diagnosed; 3) HCV RNA tested; 4) Genotyped; 5) Initiated antiviral treatment; and 6) achieved sustained viral response.

Result(s): We estimated 73,203 anti-HCV positive individuals in BC in 2012; 18,301 undiagnosed (25%); 54,902 (75%) diagnosed; 49,112 (67.1%) estimated viremic; 40,656 (55.5 %) had HCV RNA testing; 26,300 (35.9%) were genotyped; 8,532 (11.7%) had been dispensed antivirals and a SVR was achieved in 5,197 (7.1%).

Conclusion(s): Although there are gaps in RNA testing and genotyping after HCV diagnosis, the major gap in the cascade of care was low treatment initiation and, subsequently, a very small proportion achieved a SVR. Recently approved, direct acting antiviral drugs are expected to improve treatment uptake and SVR rates. The BC-HTC provides a unique capacity to identify gaps in HCV testing, care, treatment access, and outcomes at a population level. The BC-HTC analyses could inform future analysis and monitoring possibilities as part of the CanHepC Health Services and Data Core theme.

Poster Presentation: P.48

PREVALENCE OF BASELINE HCV NS5A RESISTANCE ASSOCIATED VARIANTS AMONGST HIV/HCV CO-INFECTED PATIENTS IN CANADA

Jeffrey B. Joy[1] Art F. Poon[1] Weiyan Dong[2] David A. Stephens[3] Anita Howe[2] Chanson J. Brumme[2] P. Richard Harrigan[1] Marina B. Klein[4]

1. BCCFE and UBC Department of Medicine, Vancouver, BC; 2. BC Centre for Excellence in HIV/AIDS, Vancouver, BC; 3. Department of Mathematics, McGill University, Montreal, QC; 4. McGill University Health Centre, Montreal, QC

Background: HCV genotype 1a infections harbouring resistance-associated variants (RAVs) in the NS5A gene can have reduced phenotypic susceptibility and virologic response to direct-acting antiviral (DAA) therapy. HIV/HCV co-infection accelerates HCV related liver disease. Co-infection rates vary greatly by risk categories with a disproportionate burden borne by people who inject drugs. The Canadian Co-infection Cohort follows 1,421 HIV/HCV co-infected patients from 18 centres across Canada. In this study we establish patterns of baseline NS5A inhibitor resistance in the cohort.

Purpose: n/a

Method: Baseline plasma samples were obtained from a selection (*n*=406) of treatment naïve and viremic patients. HCV RNA was extracted using a NucliSens easyMag and reverse-transcribed. Near full-length genome amplicons were generated using primers designed for all six HCV genotypes, sequenced on the Illumina MiSeq system, and processed with a custom pipeline. For each data set, regions of NS5A that failed to achieve a minimum of 100-fold coverage were censored from further analysis. Sequences were re-aligned using MAFFT v.7.54b[1] and visually inspected using AliView v.1.15[2] RAVs were defined as substitutions in the NS5A gene previously identified based on Lontok et al. 2015[3]. Resistance associated variants were deemed to be present when observed in >2% of sequences covering that site.

Result(s): Of 406 samples we obtained near full-length sequences of HCV for 333 patients and incomplete genomes for a further 24 patients (254 GT1a, 23 GT1b, 17 GT2, 50 GT3, 12 GT4, and 1 GT6). We were unable to obtain high quality sequence for the remaining 49 samples likely due to low viral load and/or poor sample quality. Samples failing sequencing generally had lower viral loads (<5 logs) than those successfully sequenced (>5 logs). Our sequence based genotype assignment often differed from clinically assigned genotypes (n=15) and that subtypes also often differed within genotypes (n=25). Sequence based methods were able to resolve HCV subtype in all cases where other methods failed to do so (n=77, 55 GT1a, 5 GT1b, 5 GT2, 7 GT3, 5 GT4). We recovered 344 NS5A sequences with >100 fold coverage (241 GT1a, 23 GT1b, 17 GT2, 52 GT3, 10 GT4, and 1 GT6). 32 infections (9.3%) were identified with baseline NS5a RAVs (GT1a: 1 M28V and Q30R, 8 M28V, 1 Q30R, 1 L31M, and 1 H58R; GT1b: 2 L31M; GT2a: 4 L28F and L31M; GT2q: 1 L28F and L31M; GT3a: 2 A30K; GT3l 1 A30K; GT4r: 2 L28M and L30R; GT4d: 3 L30R; GT4k: 1 L30R; GT4q: 2 L30R; GT4t: 1 L30R; GT4v: 1 L30R).

Conclusion(s): Our results show a substantial prevalence (9%) of NS5a RAVs in HIV/HCV co-infected patients. Non-sequence based clinical testing of HCV appears to incorrectly assign genotype or subtype in 11% of cases. A minority of individuals with HIV/HCV co-infection harbor NS5A RAVS, at least some of which could contribute to reduced clinical response.

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Poster Presentation: P.49

IS THE FACE OF HEPATITIS C CHANGING IN MONTREAL?

Nima Machouf; Chrissi Galanakis; Danièle Longpré; Sylvie Vézina; Marc Poliquin; Emmanuelle Huchet; Stephane Lavoie; Caroline Bedard; Benoit Trottier; Réjean Thomas

Clinique médicale l'Actuel, Montréal, QC

Background: HCV infected individuals have historically been injection drug users. However, the face of the epidemic appears to be changing. While HCV sexual transmission was long considered at low risk, this micro-phenomenon has been emerging in the last few years.

Purpose: The aim of this study is to assess the change in the epidemiological portrait of HCV in Montreal.

Method: All HCV infected patients attending Clinique médicale l'Actuel were assessed retrospectively. Information on risk factors and patient characteristics were collected from medical charts. Bivariate analyses were done by Chi2 and ANOVA.

Result(s): Clinique l'Actuel diagnoses an average of 50 new HCV cases each year representing a total of 1628 patients. Since 2007, there has been a steady decline in the overall incidence of HCV infections. The main risk factors for HCV transmission are injection drug use (IDU) (75%), sexual transmission (7%) and originating from an endemic region (4%). From 1990 to 2007, the distribution of risk factors was stable over time; however, as of 2007 there was a significant shift in the mode of transmission: sharp decrease in IDU related HCV infections paired with an increase in sexually transmitted HCV (s-HCV) with a peak in 2012 (30% of HCV infections) while IDU transmission also reached its lowest levels (44%). When comparing modes of transmission by sexual orientation, we noted a growing number of s-HCV in MSM patients. Among heterosexuals, the proportion of IDU infections has declined since 2007 (from 86% to 63%). However, this was not paralleled with a sharp increase in s-HCV; rather, s-HCV has increased slightly from 2007 (2% to 9%) while remaining relatively stable over time. Conversely, we observed opposing trends among the MSM patients at our clinic: from 2000 to 2007, both IDU and s-HCV were stable over time, while from 2007 onwards there was a large increase in s-HCV (30 to 74%). In MSM, 72% of HCV infection since 2007 were diagnosed in HIV co infected patients (vs. 57% before 2007; $p=0.047$). In heterosexual patients HIV co infection was less prevalent after 2007 (20% co-infection before 2007 vs. 8% after 2007; $p<0.001$). We suspect the increase in crystal meth use in Montreal as a possible contributing factor to this trend as its use has doubled since 2007 among our catchment population (9.8% in 2007 to 18.7% in 2014). The growing STD epidemic and decrease of protected sexual behaviour may be another as the number of HCV diagnosed with concomitant STDs (syphilis, HIV, gonorrhea, Chlamydia) has been on the rise since 2009 (16% to 71% in 2012, $p=0.02$). The only genotype that was differently distributed among pre 2007 and post 2007 HCV infection was genotype 2 (5% ≤2007 vs 12% >2007; $p=0.001$).

Conclusion(s): Current trend in epidemiology of HCV in Montreal include an apparent increase in sexual transmission, particularly in MSM population. Injection drug use no longer seems to be the prominent risk factor for HCV infection among Montreal MSM. Not all the sexually transmitted HCV occur in HIV co-infected patients. Future studies should examine factors associated to this emerging trend.

Poster Presentation: P.50

RESTRICTIONS FOR REIMBURSEMENT OF DIRECT-ACTING ANTIVIRAL TREATMENT FOR HEPATITIS C VIRUS INFECTION IN CANADA

Alison D. Marshall[1] Sahar Saeed[2] Lisa Barrett[3] Curtis L. Cooper[4] Carla Treloar[5] Julie Bruneau[6] Jordan J. Feld[7] Lesley Gallagher[8] Marina B. Klein[2] Mel Krajden[10] Lynn E. Taylor[9] Gregory J. Dore[1] Jason Grebely[1]

1. The Kirby Institute, UNSW Australia, Sydney, NSW, Australia; 2. Faculty of Medicine, McGill University, Montreal, QC; 3. Faculty of Medicine, Dalhousie University, Halifax, NS; 4. Department of Medicine, University of Ottawa, Ottawa, ON; 5. Centre for Social Research in Health, UNSW Australia, Sydney, NSW, Australia; 6. CRCHUM, Universite de Montreal, Montreal, QC; 7. University of Toronto, Toronto, ON; 8. Vancouver Coastal Health, Vancouver, BC; 9. Department of Medicine, Brown University, Providence, RI, USA; 10. BC Centre for Disease Control, Vancouver, BC

Background: Interferon-free, direct-acting antiviral (DAA) HCV regimens are highly effective, achieving sustained virologic response (SVR) above 90%. However, because the list price for these therapies is prohibitively high in Canada, universal drug coverage is a challenge.

Purpose: The aim of this study was to appraise reimbursement criteria for the following HCV DAA regimens in Canada: sofosbuvir, ledipasvir-sofosbuvir, simeprevir, and ombitasvir-paritaprevir-ritonavir plus dasabuvir.

Method: Reimbursement criteria for the four HCV DAA therapies were collected for ten provinces and three territories in Canada from April 22 to October 12, 2015. Data were extracted from health ministerial websites with a focus on: 1) minimum fibrosis stage required; 2) prescriber type restrictions; and 3) drug and alcohol use restrictions. Two investigators collected all data and then cross-checked responses.

Result(s): Depending on the HCV DAA therapy, 80-92% of provinces/territories limited access to persons with moderate fibrosis (≥F2 METAVIR or equivalent), and 25-55% of provinces/territories restricted prescriber type to specialists only. There were no drug and alcohol use restrictions. However, there were several inclusion/exclusion criteria that were left to the discretion of the physician (e.g. methadone or equivalent in prior 6 months).

Conclusion(s): This first review of HCV DAA funding eligibility criteria in Canada showed less reimbursement heterogeneity by jurisdiction compared to the United States. Nonetheless, substantial heterogeneity in provincial/territorial HCV reimbursement criteria exists, which could be minimised through the development and adoption of national management guidelines. Lastly, accessing criteria was challenging, supporting the need for greater transparency of information.

Poster Presentation: P.51

HCV CARE BY DESIGN: RAPID IMPLEMENTATION OF A COMPREHENSIVE HCV MODEL OF CARE THROUGH INNOVATIVE PARTNERING AND COLLABORATION

Robin Rankin[1] Jeremy Beck[2] Constance Hoare[1] Raj Khan[1] Daniel Smyth[1, 3] Gregory German[2] Lisa Barrett[1, 2]

1. Health PEI, Summerside, PE; 2. QEII hospital, Charlottetown, PE; 3. Horizon Health Authority, Moncton, NB

Background: In many provinces, HCV care is fragmented with little province-wide coordination, and limited real time evaluation. The result is delayed and inefficient care with frequent care gaps and service duplication. With the advent of curative but high cost HCV medications, it is critical to develop and implement a comprehensive HCV model of care with innovative cost containment solutions and improved access to patient care in a publicly funded system.

Purpose: Describe the successful implementation of a new model of care in HCV in a limited resource province.

Method: Between September 2014 and February 2015, care providers, government, industry, and HCV community groups partnered to review available data and design a province-wide HCV model of care in Prince Edward Island, Canada. A hybrid effectiveness-implementation type I mixed methods study design will be used to evaluate the treatment intervention, as well as program implementation.

Result(s): Based on literature review and needs assessment, the PEI HCV program was implemented in April 2015, and includes centralized referral and triage, HCV treatment specialists, public access to direct acting antiviral therapy, patient education and individualized follow-up with both public and industry-affiliated nursing and pharmacist support. The program assesses real-time evaluation of wait times, patient and provider satisfaction, subjective and objective medical outcomes, as well as cost tracking.

In the first 8 months of the program, new HCV referrals were dramatically increased. 150 HCV referrals were received from 24 providers (family doctors, nurse practitioners, internists, addictions services, other physicians) compared with only 5 in the same period last year. All of the previously identified HCV genotype 1 infections were assessed for treatment readiness (including transient elastography) and started on HCV treatment in a nurse-led, physician-oversight, pharmacist-supported provider paradigm. Before program implementation, there were only 2 on-treatment persons in the same time frame last year. Real time implementation data collection for patient outcomes, resource use and cost effectiveness is longitudinally assessed and will be analyzed at the one year mark.

Conclusion(s): In just 8 months, initial success of the provincial PEI HCV model supports this model for similar programs in publicly funded systems. This model also highlights the value of public and private partnerships to rapidly introduce highly effective programs for timely access to quality HCV care.

Poster Presentation: P.52

WHO'S GETTING DIRECT ACTING ANTIVIRALS IN A CANADIAN HIV/HEPATITIS C CO-INFECTED POPULATION?

Sahar Saeed; Erin Strumpf; Marina B. Klein; Canadian Co-Infection Cohort Study

McGill University, Montreal, QC

Background: In Canada approximately 14,000 people are co-infected with HIV and Hepatitis C (HCV). Co-infection accelerates progression to end-stage liver disease and is now, one of the leading causes of death in this population. To reduce the clinical and health system burdens of advanced liver disease, co-infected individuals need to be treated and cured of HCV. The new generation of Direct Antiviral Agents (DAAs) has been described as revolutionary. Higher efficacy and fewer side effects are hypothesized to increase treatment uptake dramatically. Historically in Canada, HCV treatment uptake among co-infected patients has been low, especially among people who inject drugs (PWID).

Purpose: Using data from the Canadian Co-Infection Cohort (CCC) Study, we investigated characteristics of participants who initiated second-generation DAA treatment until March 2015 (database closure).

Method: The CCC is a prospective longitudinal cohort of 1532 HIV/HCV co-infected individuals from 18 centers, representing ~23% the total co-infected population in Canada. Socio-demographic, clinical and behavioural information is collected via self-administered questionnaires/chart review bi-annually.

Result(s): Of the 1532 enrolled CCC participants, 749 had a positive HCV RNA and were actively participating in the cohort. Since the approval of simeprevir, sofosbuvir and ledipasvir by Health Canada, a total of 69 CCC participants initiated second generation DAAs, 44 (64%) through standard of care (SOC) and 25 (36%) of treatments were accessed through clinical trials. Sofosbuvir/ledipasvir was the most frequently used DAA combination accounting for 16 (36%) of treatments, followed by 10 (14%) sofosbuvir/ribavirin, 9 (13%) sofosbuvir/ribavirin/interferon (IFN), and 9 (13%) simeprevir/sofosbuvir. We compared CCC participants who initiated DAAs (n=44) to those who did not initiate DAAs (n=680). Fewer female CCC participants 16% compared to 30% initiated DAA therapy compared to those who did not. Similarly, fewer Aboriginals 5% vs 25%; active injection drug users; 5% vs 36% initiated DAAs. More CCC participants initiating DAAs were on combined antiretroviral therapy, 93% vs. 85% and had advance fibrosis (using an APRI score >1.5), 30% vs. 20% compared to those who did not initiate DAAs.

Conclusion(s): Health Canada approved simeprevir and sofosbuvir in late 2013, followed by ledipasvir in 2014, however provinces have been slow and restrictive at reimbursing DAA therapy. Populations under represented in the initial treatment wave were; women, Aboriginals and people who inject drugs. Steps should be taken to improve access to DAAs in these vulnerable populations.

Poster Presentation: P.53

CASE STUDY: CATIE'S HEPATITIS C ETHNOCULTURAL EDUCATION, OUTREACH, AND SOCIAL MARKETING PROGRAM

Hywel Tuscano; Fozia Tanveer; Logan Broeckaert; Mélisa Dickie

CATIE, Toronto, ON

Background: CATIE's Hepatitis C Ethnocultural Education, Outreach and Social Marketing Program is a hepatitis C awareness and educational outreach program for immigrants and newcomers in Ontario. The program works with four communities (Chinese, Pakistani, Punjabi and Filipino) and in four languages (Mandarin, Urdu, Punjabi and Tagalog).

This program was initiated as a four-year provincial pilot in 2010, funded by the AIDS and Hepatitis C Programs of the Ontario Ministry of Health and Long-term Care. It became an ongoing program with provincial funding in 2014. The Public Health Agency of Canada provides funding to print and distribute resources for use outside of Ontario.

The program addresses the hepatitis C health information needs of immigrants and newcomers. A case study has been developed to highlight the learnings of this project's first four years of work and frame the program models of community development and translation.

Purpose: In Canada, immigrants and newcomers are disproportionately affected by hepatitis C and hepatitis B. Immigrants and newcomers are estimated to represent 35 percent of all past or present hepatitis C infections in Canada.[1] The primary mode of transmission for this group is unsafe medical practices outside of Canada, including transfusions of contaminated blood and reuse of unsterilized medical or dental equipment. Hepatitis C is not routinely screened for during the immigration process, so many immigrants may not know they have the virus. The program was developed to address the unique health information needs of this population.

Method: In the program's first four years, CATIE developed and implemented a multi-level strategy including three major interconnected areas of work:

1. Education and outreach

2. Development and distribution of multilingual education resources

3. Media campaigns

The program takes a community development approach, which includes meaningful community involvement; engagement and partnerships with settlement, community and religious organizations; and a commitment to health equity.

Result(s): The program now has two effective models for **community development** and **translation** working with immigrant and newcomer communities. These models have produced ongoing meaningful partnerships, hepatitis C health information resources in 12 languages, an outreach and education program in four languages, and a social marketing campaign.

Evaluation and distribution metrics have also been collected for the last four years demonstrating effective engagement and reach in each of the communities.

Conclusion(s): The case study highlights many important lessons learned including:

Community ownership of the process helps create culturally appropriate and sensitive resources.

Working with faith-based groups and religious places helps the program reach out to the wider community.

Gender-segregated sessions can facilitate knowledge transfer especially among female participants.

There is no single way to understand stigma; it varies in different cultural contexts.

Meaningful partnership, community engagement and a strong interest in raising awareness of hepatitis C contribute to the program's success and improve its reach.

Targeted outreach and campaigns are important for newcomer and immigrant communities that don't receive a lot of health promotion and prevention messaging.

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Poster Presentation: P.54

COST-EFFECTIVENESS ANALYSIS OF DRUGS FOR CHRONIC HEPATITIS C INFECTION: RESULTS FROM CADTH THERAPEUTIC REVIEW

William W. L. Wong[1] Karen M. Lee[2] Sumeet Singh[2] Murray Krahn[1]

1. Toronto Health Economics and Technology Assessment (THETA) Collaborative, University of Toronto, Toronto, ON; 2. Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, ON

Background: Prior to 2011, pegylated interferon plus ribavirin (PR) was the standard therapy for chronic hepatitis C (CHC). Between 2014 and 2015, interferon-free direct-acting antiviral agents (DAAs) were approved. While these treatments appear to be more effective at achieving sustained virologic response in CHC patients, they are significantly more expensive than PR. Therefore decision makers require information on the comparative cost-effectiveness of DAAs and PR combination treatments for patients with CHC.

Purpose: The objective of this study is to evaluate the cost effectiveness of treatment regimens for CHC infection (genotypes 1 through 4) from the perspective of the public payer.

Method: A state-transition model was developed in the form of a cost-utility analysis. Regimens included in the analysis were approved in Canada, recommended by major guidelines, or considered to have a high likelihood of approval in Canada as of February 2015. The cohort under consideration had a mean age of 50 years; and defined by treatment status (naive versus experienced), and cirrhosis status (non-cirrhotic versus cirrhotic). Treatment effect estimates on SVR and relative risk of adverse events were obtained from a concurrent network meta-analysis. Other inputs for the economic model were derived from published sources and validated by clinical experts. Drug costs were obtained from the Canadian Provincial Formularies, or directly from manufacturers.

Result(s): For patients with genotype 1 CHC infection who are treatment-naive and non-cirrhotic, at a willingness to pay of $50,000 per quality-adjusted-life-year (QALY), paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks (PAR/RIT12 + OMB12 + DAS12) was likely to be the most cost-effective option compared with PR alone. For patients with genotype 1 CHC infection who are treatment-naive and cirrhotic, sofosbuvir + ledipasvir for 12 weeks (SOF12 + LDV12) was likely to be the most cost-effective option compared with PR alone. The analysis also suggests that for patients with genotype 1 CHC infection who are treatment-experienced and non-cirrhotic, PAR/RIT12 + OMB12 + DAS12 was likely to be the most cost-effective option compared with PR alone at a willingness to pay of $50,000 per QALY. For patients with genotype 1 CHC infection who are treatment-experienced and cirrhotic, response-guided therapy with simeprevir-PR was likely to be the most cost-effective option followed by sofosbuvir + ledipasvir + ribavirin for 12 weeks (SOF12 + LDV12 + RBV12) compared with PR alone. Analyses for genotype 2, genotype 3, and genotype 4 were also conducted.

Conclusion(s): For each genotype 1 population at least one of the interferon-free therapies appeared to be economically attractive compared with PR alone, at a willingness-to-pay of $50,000 per QALY. The drug that was the most cost-effective varied by population. For each genotype 2-4 treatment naive population, the interferon-free or the PR-based DAA therapies appeared not to be economically attractive compared with PR alone, at a willingness-to-pay of $50,000 per QALY. For each genotype 2-4 treatment-experienced population, there were interferon-free or the PR-based DAA therapies that appeared to be attractive at a willingness to pay of $50,000 per QALY when compared with no treatment.

Poster Presentation: P.56

HEPATITIS C VIRUS REGULATION BY MICRORNA-122 AND HOST PROTEIN FACTORS

Choudhary S Ahmed, Catherine L Jopling

Gene Regulation and RNA Biology group, School of Pharmacy, University of Nottingham, UK.

An estimated 2-3% of global population is living with Hepatitis C virus (HCV) infection and 60-90% of these infections become chronic, which ultimately leads to cirrhosis and liver cancer. While new antiviral therapies are emerging, a better understanding of how HCV interacts with host cells is important. HCV is a hepatotropic positive sense RNA virus. The HCV 5' untranslated region (UTR) contains two binding sites for a highly abundant liver-specific microRNA, miR-122. In contrast to the canonical function for microRNAs in binding to 3'UTR sites, leading to mRNA degradation and translational repression, HCV uses miR-122 as an essential positive regulator of viral replication. The mechanism of this regulation remains uncertain, with viral translation, RNA stability and replication all implicated in different studies.

We have investigated the mechanism of HCV regulation by miR-122 and the host protein factors. Eukaryotic initiation factor (eIF)4AII has been described as a binding partner of HCV RNA polymerase enzyme (NS5B) and is involved in miRNA regulation of translation at 3'UTR sites. We find that depletion of eIF4AII leads to a reduction in HCV RNA level in miR-122-mediated regulation of HCV translation, suggesting that these host factors cooperate to regulate HCV. By co-immunoprecipitation, we find that eIF4AII interacts with HCV RNA and miR-122 in a miR-122-dependent manner. Finally, we have investigated how miR-122 interacts with eIF4AII and regulates HCV RNA during the viral replication cycle.

Behavioural Sciences

Poster Presentation: P.01

THE TOLL-FREE TELEPHONE SURVEY METHOD TO FACILITATE SOCIO-BEHAVIOURAL RESEARCH WITH PEOPLE LIVING WITH HCV: LESSONS FROM HIV RESEARCH IN CANADA

Dan Allman

Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background: Given that Canada comprises more than 9,000,000 square kilometers and is home to over 35,000,000 individuals, researching populations in Canada equitably, efficiently and reliably can be challenging, particularly where covert, stigmatized or marginal behaviours or identities are concerned. The growth of the World Wide Web has brought developments in survey research technology, yet often these techniques face a variety of limitations in terms of cross-sectional survey science.

Purpose: The toll-free telephone survey method pre-dates web 2.0 survey techniques and in ways may appear antiquated in comparison. Despite some limitations, this paper argues toll-free telephone survey methods hold novel and promising application for socio-behavioural research with people in Canada, living with or at risk of becoming infected with Hepatitis C (HCV).

Method: Method: This paper presents a descriptive analysis of the benefits and challenges of implementing a toll-free telephone study to better understand the unique lives of people living with or at risk of becoming infected with HCV. This paper considers lessons learned from toll free telephone studies in the United Kingdom, New Zealand, Australia and Canada.

Result(s): Toll-free telephone studies are distinct from other kinds of telephone studies in that respondents initiate their own recruitment at little or no cost to themselves. First conducted in the UK by Weatherburn et al (1990) to study gay and bisexual men at risk of HIV infection, the toll free method was subsequently applied in Australia (Kippax and Crawford et al, 1992) New Zealand (Worth et al, 1995), and in Canada by Myers, Allman and Calzavara et al for the BISEX Survey (1996) and Male Call Canada (2012). For the BISEX Survey, 1,314 anonymous interviews of approximately 1 hour were conducted with eligible callers within the Province of Ontario. In it, interviewer-assisted surveys focussed on HIV knowledge, attitudes and behaviours (KAB) of men who self-identified sex with both men and women. For Male Call Canada, 1,235 interviews of approximately 1 hour were conducted nationally with eligible callers. The study sought gay, bisexual and other MSM participants, collecting KAB information related to HIV, hepatitis viruses and STIs. Calls were received from all provinces and territories, and from over 50% of the Nation's Forward Sorting Areas (FSAs). For both these Canadian studies, in-house resource databases were developed to assist interviewers to provide respondents with referrals to health and social care services, if requested.

Conclusion(s): The toll-free telephone survey method facilitates accessible and efficient survey research, particularly where populations may be marginal and stigmatized and where behaviours may be illicit and covert. Unlike venue-based studies, cross-sectional toll-free telephone studies allow great geographical reach. Toll-free studies may prove more costly than web-based surveys, but the results are more replicable and reliable. The experience of HIV research in Canada would suggest the method can provide better understandings of those living with or at risk of becoming infected with HCV. The method can deliver on multiple aims by gathering self-reported KAB data while providing education, referral and social support to participants who self-recruit.

Poster Presentation: P.02

ILLICIT DRUG USE, HCV, & SOCIAL EXCLUSION: A CRITICAL ANALYSIS OF THE HARM REDUCTION PARADIGM IN CANADA

Rusty Souleymanov; Dan Allman

University of Toronto, Toronto, ON

Background: The hepatitis C virus (HCV) associated with illicit drug use remains a significant health and social care consequence. Research has begun to question: a) whether current harm reduction practices are sufficient to address the ongoing HCV epidemic among people who use illicit drugs, in particular, those who use injection drugs; and, b) whether health and social care workers are truly prepared to address the ongoing epidemic of HCV, including the impact of increasing diagnoses on services in Canada, and other Western nations.

Purpose: In this presentation, we outline the epidemiological context of HCV relative to an epistemological analysis of the development of harm reduction efforts in Canada.

Method: Applying a critical interpretation of policy and practice we: a) present an analysis of the developments surrounding harm reduction policies and practices in Canada; and b) articulate connections between elements of the harm reduction paradigm, and the marginalization of people who use illicit drugs.

Result(s): We find that multiple historical junctures (social movements, institutional interests, legislation, community practices, and stigma), rather than a single cause of social exclusion engender the processes of marginalization of people who use illicit drugs in Canada. While rhetoric on harm reduction is widespread, a bias towards abstinence and a failure to account for pleasure as a meaningful component of illicit drug use are evident within this discourse.

Conclusion(s): Researchers, policy-makers and practitioners are encouraged to consider the utility of a critical stance when reflecting on the elements of a harm reduction approach. This will renew attention on the structural context and pragmatics of drug use and its intersection with blood-borne infections, like HCV. Based on our review of the literature, this presentation provides: a) recommendations for researchers and practitioners interested in the intersection of drug use, HCV prevention and harm reduction fields; b) a platform for discussion for health care professionals and policy makers interested in the expansion of training and services, and a rise in awareness of the issues pertaining to drug use and its proximity to HCV.

Participants list – Liste des participants

First Name	Last Name	Email Address	* Institution
Christopher	Ablenas	christopher.ablenas@mail.mcgill.ca	McGill University
Choudhary	Ahmed	ahmedshoaib77@yahoo.co.uk	University of Nottingham
Faria	Ahmed	fahme097@uottawa.ca	Ottawa Hospital Research Institute
Arshia	Alimohammadi	aarshia@alumni.ubc.ca	Vancouver Infectious Diseases Centre
Cheryl	Allen	callencowan@yahoo.ca	Coverdale clinic
Dan	Allman	dan.allman@utoronto.ca	Dalla Lana School of Public Health, University of Toronto
Yalena	Amador-Canizares	yalena.ac@usask.ca	University of Saskatchewan
Scott	Anderson	jvanveen@catie.ca	CATIE
Aslam	Anis	aslam.anis@ubc.ca	Centre for Health Evaluation and Outcome Sciences
Andreea Adelina	Artenie	adelina.artenie@gmail.com	Université de Montréal
Patricia	Bacon	pbacon@actionhep.ca	Action Hepatitis Canada
Michael	Bailey	jvanveen@catie.ca	CATIE
Kotsoros	Barbara	barbara.kotsoros.chum@ssss.gouv.qc.ca	CHUM, hôpital St-Luc
Lisa	Barrett	lisa.barrett@nshealth.ca	Nova Scotia Health Authority
Shelley	Beckstead	shelleyb@streethealth.kchc.ca	Street Health Centre
Nathalie	Bédard	nathalie.bedard.chum@ssss.gouv.qc.ca	CRCHUM
Helene	Belanger	helene.belanger@gov.yk.ca	YCDC
Ed	Bennet	jvanveen@catie.ca	Canadian Aboriginal Aids Network
Annie	Bernier	annie.bernier@mail.mcgill.ca	McGill University
Glenn	Betteridge	glenn@ctac.ca	Canadian Treatment Action Council
Frank	Bialystok	franklinb@sympatico.ca	University of Toronto
Marc	Bilodeau	marc.bilodeau@umontreal.ca	CHUM
MaryFrances	Bjorgum	mfrances@telus.net	alberta health services
Jennifer	Block	jennifer.block@viha.ca	Island Health
Maude	Boisvert	maude.boisvert@gmail.com	CR-CHUM
Chris	Boodram	christopher.boodram@phac-aspc.gc.ca	Public Health Agency of Canada
Julie	Bouchard	coordoproximite@cactusmontreal.org	CACTUS Montréal
Michel	Boudreau	mboudreau@wechc.org	WECHC
Patricia	Boyd	pboyd@lakeridgehealth.on.ca	Positive Care Clinic
Suzanne	Brissette	suzanne.brissette@umontreal.ca	CHUM
Julie	Bruneau	julie.bruneau@umontreal.ca	Université de Montréal
Chantal	Burelle	chantal.burelle@mcgill.ca	McGrill
Angelina	Butt	jvanveen@catie.ca	AIDS Committee of Newfoundland and Labrador
Christian	Caldji	christian.caldji@bms.com	BMS
Marc-Andre	Caron	marc-andre.caron@merck.com	Merck

Jasmin	Chahal	jasmin.chahal@mail.mcgill.ca	McGill University
Morgan	Chalifoux	mchalifoux@boylestreet.org	streetworks
Norma	Choucha	Ncrtp.hepc@gmail.com	CRCHUM
Karen	Chow	karen.chow2@gilead.com	Gilead Sciences Canada, Inc.
Sarah	Cloutier	jvanveen@catie.ca	Blood Ties Four Directions
Che	Colpitts	colpitts@unistra.fr	Inserm U1110,University of Strasbourg
Maureen	Colpitts	mcolpitts@elevatenwo.org	Elevate NWO
Brian	Conway	brian.conway@vidc.ca	Vancouver Infectious Diseases Centre
Adam	Cook	jvanveen@catie.ca	Canadian Treatment Action Council
Curtis	Cooper	ccooper@toh.on.ca	The Ottawa Hospital
Patrick	Coté	Patrick.Cote.4@umontreal.ca	Centre de recherche du CHUM (CRCHUM)
Pierre	Coté	dufresne.cote@sympatico.ca	Clinique du Quartier Latin
Sophie	Cousineau	sophie.cousineau@mail.mcgill.ca	McGill University
Andrea L.	Cox	acox@jhmi.edu	Johns Hopkins University
Joseph	Cox	joseph.cox@mcgill.ca	McGill University Health Centre
Shelley	Crawford	scrawford@paphr.sk.ca	Prince Albert Positive Care Program
Angela	Crawley	acrawley@ohri.ca	Ottawa Hospital Research Institute
Michelle	Crosby	michelle.crosby@viha.ca	Island Health
Pam	Crotty	pcrotty@ucalgary.ca	University of Calgary
Evan	Cunningham	ecunningham@kirby.unsw.edu.au	Kirby Institute
Ecaterina	Damian	edamian@csih.org	CSIH
Felicia	Deonarine	fdeon092@uottawa.ca	Ottawa Hospital Research Institute
Melisa	Dickie	mdickie@catie.ca	CATIE
Zoe	Dodds	jvanveen@catie.ca	South Riverdale Community Health Centre
Brett	Dow	jvanveen@catie.ca	First Nations and Inuit Health Branch
Martine	Drolet	martine.drolet@merck.com	Merck
Carol	Dupasquier	dupasquier@shaw.ca	Mount Carmel Community Hepatology Clinic
Meriem	EL BAKALI	Mery_b85@hotmail.fr	Hôpital maisonneuve rosemont
Manal H.	El-Sayed	manalhelsayed@yahoo.co.uk	Ain Shams University
Aysegul	Erman	aysegul.erman@mail.utoronto.ca	University of Toronto
Patrick	Ethier	Patrick.ethier@abbvie.com	Abbvie
Thomas	Fabre	thomas-fabre@live.fr	CRCHUM
Gary	Fagan	gfagan@liver.ca	Canadian Liver Foundation
Jordan	Feld	jordan.feld@uhn.ca	University Health Network
Sophia	Ferchiou	sophia3059@hotmail.com	Université de Montréal
Benedikt	Fischer	benedikt.fischer@utoronto.ca	University of Toronto
Suzanne	Fish	sfish@catie.ca	CATIE
Jennifer	Flemming	flemmij@hdh.kari.net	Queen's University

Manuel	Flores Molina	manuel_floresm@yahoo.ca	CRCHUM Université de Montréal
Emmanuel	Fortier	emmanuel.fortier@umontreal.ca	Université de Montréal
Lorraine	Fradette	lorrainefradette@gmail.com	CRCHUM
Mary	Freidin	Mfreidin@coverdaleclinic.ca	Coverdale Hepatology Clinic
Renee	Gagnon	renee.gagnon@csc-scc.gc.ca	Correctional Service Canada
Margaret	Gale-Rowe	margaret.galerowe@phac-aspc.gc.ca	PHAC
Lesley	Gallagher	lesley.gallagher@vch.ca	Saskatchewan Infectious Disease Care Network
Lindsay	Gibbons	lindsayjgibbons@hotmail.com	None
judith	goplen	jglivergirl@gmail.com	cobblestone clinic
Matthias	Götte	gotte@ualberta.ca	University of Alberta
Amélie	Goyette	ameliegoyette@cactusmontreal.org	CACTUS Montréal
Jason	Grebely	Jgrebely@kirby.unsw.edu.au	University of New South Wales
Chris	Greenaway	ca.greenaway@mcgill.ca	Jewish General Hospital
Karin	Hagen	karin.hagen@merck.com	Merck
Jodi	Halsey-Brandt	jodi.halsey-brandt@merck.com	Merck
Richard	Harrigan	prharrigan@cfenet.ubc.ca	BC Centre for Excellence in HIV
Sonja	Hartz	sonja.hartz@viha.ca	Vancouver Island Health Authority
Janet	Hatcher Roberts	janetroberts@ca.inter.net	Canadian Society for International Health
sandra	hawker	sandrahawker9@gmail.com	South Health Campus
Kanna	Hayashi	khayashi@cfenet.ubc.ca	BC Centre for Excellence in HIV/AIDS
Lisa	Heslip	lisa.heslip@ahs.ca	Boyle McCauley Health Centre
Matthew	Hickman	Matthew.Hickman@bristol.ac.uk	University of Bristol
Lindsay	Hillbom	lhillbom@gmail.com	Queen Elizabeth II Hospital
Geralynn (Geri)	Hirsch	geri.hirsch@nshealth.ca	NS Health
Julia	Holliday-Scott	julia.hollidayscott@hotmail.com	AIDS Saskatoon
Michael	Houghton	mhoughton@ualberta.ca	University of Alberta
Pierre	Hould	jvanveen@catie.ca	Ontario Aboriginal HIV/AIDS Strategy
Steeve	Houle	steeve.houle@gilead.com	Gilead Sciences Canada Inc.
Anastasia	Hyrina	ahyrina@mail.ubc.ca	University of British Columbia
Moheshwarnath	Issur	moheshwarnath.issur@mail.mcgill.ca	McGill University
Naveed	Janjua	naveed.janjua@bccdc.ca	BC Centre for Disease Control
Jeffrey	Joy	jjoy@cfenet.ubc.ca	University of British Columbia
Louis-Christophe	Juteau	louis-christophe.juteau@umontreal.ca	CHUM
Didier	Jutras-Aswad	didier.jutras-aswad@umontreal.ca	CRCHUM
Sarwat Tahsin	Khan	skhan177@uottawa.ca	University of Ottawa/ Ottawa Hospital Research Institute
Alexandra	King	alexandra.king@ubc.ca	Simon Fraser University
Malcolm	King	malcolm_king@sfu.ca	Simon Fraser University
Carolyn	Klassen	carolyngklassen@gmail.com	Abbvie Canada

Marina	Klein	marina.klein@mcgill.ca	McGill University Health Centre
Tina	Knorr	tinak@streethealth.kchc.ca	Street Health Centre
Jennifer	Kocilowicz	Jennifer.Kocilowicz@muhc.mcgill.ca	McGill
Hassan	Kofahi	hassanmk@mun.ca	Memorial University
Mel	Krajden	Mel.Krajden@bccdc.ca	BC Centre for Disease Control
Jeff	Kwong	jeff.kwong@utoronto.ca	Institute for Clinical Evaluative Sciences
Douglas	Laird	bioxyzen@yahoo.ca	HepC BC
Alain	Lamarre	alain.lamarre@iaf.inrs.ca	INRS-Institut Armand-Frappier
Daniel	Lamarre	Daniel.lamarre@umontreal.ca	CRCHUM / Université de Montréal
Regan	Lavoie	reganl@kchc.ca	Street Health Centre
John	Law	llaw@ualberta.ca	University of Alberta
Lynda	Lennox	lynda.lennox@mail.mcgill.ca	McGill
Isabelle	Létourneau	isabelle.letourneau@crchudequebec.ulaval.ca	CIHR - Institute of Infection and Immunity
Simon	Ling	simon.ling@sickkids.ca	The Hospital for Sick Children
Qiang	Liu	qiang.liu@usask.ca	University of Saskatchewan
Michel	Long	mlong@hemophilia.ca	Société canadienne de l'hémophilie
Danièle	Longpré	longpredaniele@gmail.com	Clinique médicale l'Actuel
Daryl	Luster	dluster@telus.net	PHCN/AHC
Nima	Machouf	nima.machouf@lactuel.ca	Clinique médicale l'Actuel
Chris	Macklin	cmacklin@sfu.ca	Simon Fraser University
Sonya	MacParland	sonyamacparland@gmail.com	University of Toronto
Gisela	Macphail	gisela.macphail@shaw.ca	CUPS
Alison	Marshall	amarshall@kirby.unsw.edu.au	The Kirby Institute, UNSW Australia
Valérie	Martel-Laferrière	vmlaferriere@gmail.com	CHUM
Renee	Masching	reneem@caan.ca	Canadian Aboriginal AIDS Network
Stephanie	Massey	jvanveen@catie.ca	Public Health PEI
Sabrina	Mazouz	mazouz.sabrina@gmail.com	Université de Montréal
Vera	McArthur	vmcarthur@elevatenwo.org	Elevate NWO
Mark	McGovern	mark_mcgovern@merck.com	Merck
Liza	McGuinness	liza.mcguinness@bccdc.ca	BC Centre for Disease Control
David	McLay	jvanveen@catie.ca	CATIE
Hayley	McPhail	hayley@percuro.ca	PerCuro Clinical Research Ltd.
Jeanne	Menge	jmenge@laircentre.com	LAIR Centre
Tarik	Messaoud	tarik.messaoud@merck.com	Merck
Thomas	Michalak	timich@mun.ca	Memorial University
Liam	Michaud	jvanveen@catie.ca	CATIE
M-J	Milloy	mjmilloy@cfenet.ubc.ca	BC Centre for Excellence in HIV/AIDS
Roz	Milne	rmilne@coolaid.org	Cool Aid Community Health Centre
Kimberly Ann	Milton McSween	kimberlyannmm@gmail.com	CHU Sainte-Justine

Bassim	Mohamed	bassim.mohamed@umontreal.ca	CRCHUM-UdeM
Laurence	Montréal	direction@capahc.com	CAPAHC
Marie-Eve	Morin	marieeve.morin@cliniquecameleon.com	Clinique Caméléon
Dylana	Mumm	dylana.mumm@gilead.com	Gilead Sciences Canada
Yanie	Nam	yanie.nam@gmail.com	Research
David R.	Nelson	nelsodr@ufl.edu	University of Florida
Hugh	Ngo	hugh.ngo@gilead.com	Gilead Sciences Canada
Howard	Njoo	Howard.Njoo@phac-aspc.gc.ca	PHAC
Daina	Norndon	dnorndon@gmail.com	University of Calgary
Arlene	Nugent	Arlene.nugent@abbvie.com	Abbvie
Cindy	Ocampo	cindyo@streethealth.kchc.ca	Street health Centre
Jun	Oh	joh011@uottawa.ca	University of Ottawa
Kelly	O'neill	Koneill@ochc.ca	Oshawa community health centre
Amy	Palumbo	Amy.Palumbo@viha.ca	Island Health
Barb	Panter	jvanveen@catie.ca	CATIE
Michelle	Peel	Michelle.Peel@cihr-irsc.gc.ca	Canadian Institutes of Health Research
Diane	Perreault	diane.perreault@gmail.com	Coverdale Clinic
Laila	Peterson	laila@percuro.ca	PerCuro Clinical Research Ltd.
John	Pezacki	John.Pezacki@nrc-cnrc.gc.ca	University of Ottawa
Rhyan	Pineada	rpineda.cvis@gmail.com	McGill
Crystal	Poley	cpoley@laircentre.com	LAIR Centre
Emery	Potter	epotter@sherbourne.on.ca	Sherbourne Health Centre
Megan	Powdrill	mpowdril@uottawa.ca	University of Ottawa
Marie	Prévost	marie.prevost@abbvie.com	AbbVie
Leona	Quewezance	jvanveen@catie.ca	CATIE
Maaran	Rajah	maaran.rajah@mail.mcgill.ca	McGill University
Colleen	Regehr	colleen_gerard@yahoo.com	Interior Health
Christopher	Richardson	chris.richardson@dal.ca	Dalhousie University
Gavin	Risi	grisi@nkshealth.ca	NKS Health
Eve	Roberts	eve.roberts@dal.ca	University of Toronto
Jenny	Robichaud	jenny.robichaud@csc-scc.gc.ca	Correctional Service Canada
Carmine	Rossi	carmine.rossi@mail.mcgill.ca	McGill University
Rod	Russell	rodney.russell@med.mun.ca	Memorial University
Atul	Sabharwal	sabharwal_atul@live.ca	NSHA
Sahar	Saeed	zssaeed@gmail.com	McGill
Yasmin	Saeed	yasmin.saeed@mail.utoronto.ca	University of Toronto
Selena	Sagan	selena.sagan@mcgill.ca	McGill University
Golasa	Samadi Kochaksaraei	golasa63@gmail.com	University of Calgary
Beate	Sander	beate.sander@oahpp.ca	Public Health Ontario
Mohammed	Sarhan	msarhan@ualberta.ca	University of Alberta
Luis	Schang	luis.schang@ualberta.ca	University of Alberta
Dena	Schanzer	dena.schanzer@phac-aspc.gc.ca	Public Health Agency of Canada

Wendy	Schaufert	schau4t@gmail.com	South Health Campus
Deb	Schmitz	deb@pacifichepc.org	Pacific Hepatitis C Network
Nazia	Selzner	nazia.selzner@uhn.ca	University of Toronto
Karen	Seto	kseto@liver.ca	Canadian Liver Foundation
Thomas	Shaw-Stiffel	tshawstiffel@toh.on.ca	University of Ottawa - The Ottawa Hospital
Morris	Sherman	morris.sherman@uhn.on.ca	University of Toronto
Naglaa	Shoukry	naglaa.shoukry@umontreal.ca	CRCHUM
Asiyah	Siddique	asiyah.siddique@mail.mcgill.ca	CRCHUM
nancy	simonot	nsimonot@nkshealth.ca	NKS Health
Lucy	Smith	lucy.smith@mun.ca	Memorial University of Newfoundland
Maria Eugenia	Socias	esocias@cfenet.ubc.ca	BC Centre for Excellence in HIV/AIDS
Hugo	Soudeyns	hugo.soudeyns@recherche-ste-justine.qc.ca	Centre de recherche du CHU Sainte-Justine
Rusty	Souleymanov	rusty.souleymanov@mail.utoronto.ca	University of Toronto
Liz	Stirling	liz.stirling@cihr-irsc.gc.ca	CIHR
Suzanne	Sumner	suzanne.sumner@ahs.ca	Hepatitis Support Program, UAH
Melodie	Talbot	jvanveen@catie.ca	L'Association Québécoise pour la promotion de la santé des personnes utilisatrices de drogues
Nathan	Taylor	nathan.taylor2@mcgill.ca	McGill
Shannon	Taylor	radioshan@gmail.com	Toronto Community Hep C Program
Rosie	Thein	rosie.thein@utoronto.ca	University of Toronto
Denise	Thomas	denise.thomas@fnha.ca	First Nations Health Authority
Lianping	Ti	mintti@cfenet.ubc.ca	BC Centre for Excellence in HIV/AIDS
Natasha	Touesnard	jvanveen@catie.ca	CATIE
Sarah	Tran	sarah.tran.chum@ssss.gouv.qc.ca	CRCHUM
Janie	Trepanier	janie.trepanier@merck.com	Merck
Irina	Tsarevsky	irina.tsarevsky@msss.gouv.qc.ca	MSSS gouvernement du Québec
Marie-eve	Turcotte	marie-eve.turcotte.chum@ssss.gouv.qc.ca	CRCHUM Cohorte St-Luc
Karen	Turner	jvanveen@catie.ca	Streetworks
Hywel	Tuscano	jvanveen@catie.ca	CATIE
Mark	Tyndall	mark.tyndall@bccdc.ca	BC Centre for Disease Control
D Lorne	Tyrrell	lorne.tyrrell@ualberta.ca	Li Ka Shing Institute of Virology - University of Alberta
Marla	Ullman	marlaullman@hotmail.com	Coverdale Infusion Clinics
Chris	Usaty	chris.usaty@abbvie.com	AbbVie
Marie-Louise	Vachon	marie-louise.vachon@mail.chuq.qc.ca	CHU de Québec
Chantal	Vaillancourt	chantal@percuro.ca	PerCuro Clinical Research Ltd.
Jackie	Valois	jvanveen@catie.ca	Prince Albert Correctional Centre
Nicholas	van Buuren	njv@stanford.edu	Stanford University

Vanessa	Van Deventer	Venessa.VanDeventer@bms.com	BMS
Diane	Veilleux	diane.veilleux@merck.com	Merck
Lori Lee	Walston	lwalston@laircentre.com	LAIR Centre
Bessie	Wang	bessie.wang@gilead.com	Gilead
Claire	Wartelle-Bladou	clairewartelle@gmail.com	Hôpital St-Luc CHUM
Ted	Watson	ted.watson@merck.com	Merck
Lynda	Watson Waddington	lyndaw@cupscalgary.com	CUPS
Daniel	Werb	dwerb@ucsd.edu	University of California San Diego / St. Michael's Hospital, Toronto
Andrea	Westbrook	awestbrook@sherbourne.on.ca	Sherbourne Health Centre
Joyce	Wilson	joyce.wilson@usask.ca	University of Saskatchewan
Jung	Wo Jao	jvanveen@catie.ca	CATIE
Wendy	Wobeser	wlw@queensu.ca	Queen's University
David	Wong	Dave.Wong@uhn.ca	University Health Network
Jason	Wong	jasonale@ualberta.ca	Li Ka Shing Institute of Virology, Dept of MMI, University of Alberta
Nicholas	Wong	nicholas.wong@Gilead.com	Gilead
William W. L.	Wong	william.wong@theta.utoronto.ca	Toronto Health Economics and Technology Assessment (THETA) Collaborative, University of Toronto
Amanda	Wood	amanda.wood@csc-scc.gc.ca	Correctional Service Canada
Qi	Wu	qiw186@mail.usask.ca	University of Saskatchewan

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