National CIHR Research Training Program in Hepatitis C
Subvention nationale de formation des IRSC sur l'hépatite C

3rd Canadian Symposium on Hepatitis C Virus

3ème Symposium canadien sur le virus de l'hépatite C

February 7, 2014 – 7 février 2014

Metro Toronto Convention Centre, Toronto, ON

Program and Abstracts
Programme et résumés

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Welcome Message

Dear colleagues,

We would like to welcome you to the 3rd Canadian Symposium on Hepatitis C Virus (HCV). Over the past 10 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.

Despite this internationally recognized success, it is evident that interactions between Canadian scientists, clinicians and the affected community need to be strengthened in order to effectively respond to current and future challenges in the management of the disease. We believe that the Canadian HCV conference 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 third annual symposium will build on the success of the first 2 meetings and continue to foster knowledge translation for researchers, healthcare practitioners and community-based groups working in the field of HCV. With the recently approved new antiviral drugs, it is indeed an exciting moment for anyone doing research, treating individuals and also for many who remain infected. Let us share our enthusiasm with all of you!

The National Canadian Research Training Program in Hepatitis C (NCRTP-HepC) 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 this meeting and to the beautiful city of Toronto. 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.

The organizing committee

Message d'accueil

Chers collègues,

Nous vous souhaitons la bienvenue au 3ème Symposium canadien sur l'hépatite C. Au cours des 10 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 d'un modèle de souris humanisée de l'infection par le VHC, l'identification de nouveaux biomarqueurs de la progression de la maladie et les déterminants de l'accès au traitement antiviral chez les populations marginalisées, notamment les individus infectés par le VIH, les utilisateurs de drogues illicites (UDI) et les citoyens faisant partie des Premières nations. Malgré ces succès reconnus internationalement, il est apparu évident que les interactions entre les scientifiques et les cliniciens canadiens avaient besoin d'être renforcées afin de répondre efficacement aux défis présents et futurs que soulèvent l'infection par le VHC. Lorsque nous avons mis sur pied la première conférence canadienne sur le VHC, nous étions convaincus qu'un tel forum était devenu nécessaire de façon à disséminer les résultats de la recherche, promouvoir les collaborations, offrir un forum d'échange et créer une synergie entre les chercheurs canadiens de tous les horizons. Devant le succès remporté par nos 2 premiers symposiums, et à la l'aube de l'arrivée sur le marché de nouvelles molécules antivirales qui ont toutes les chances de révolutionner le traitement et le pronostic de cette infection, la troisième édition de ce symposium s'annonce des plus excitante. Nous espérons que vous partagerez notre enthousiasme en ce sens.

Le Programme de subvention nationale de formation des Instituts de recherche en santé du Canada sur l'hépatite C (NCRTP-HepC) a contribué de façon significative à la formation de nouveaux étudiants et à la diffusion des connaissances dans le domaine de l'hépatite C. En particulier, ce programme a permis d'augmenter le nombre d'étudiants et 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. Il était donc de mise que le NCRTP-Hep C prenne l'initiative de l'organisation de cette conférence.

Nous tenons à vous souhaiter la bienvenue à Toronto. 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.

Le comité organisateur

Program – Programme

07h00 - 08h00 Registration, Breakfast, Exhibition and Poster Area Opens

08h00 - 08h15 Welcome and Introductions
Dr. Marc Bilodeau, Université de Montréal, Montréal, Canada

08:15 - 08h45 Opening Keynote: Access to Care for HCV Infected Individuals
O Canada - How do you C Hepatitis?
Dr. Lorne Tyrrell, University of Alberta, Edmonton, Canada

Clinical Sciences
Chairs: Dr. Eve Roberts and Dr. Curtis Cooper

08h45 - 09h15 Project ECHO: A Model to Improve Care in Canada
Dr. Sanjeev Arora, University of New Mexico, New Mexico, USA

09h15 - 09h30 The Canadian Co-infection Cohort Study: Building the Case for Increased Access to HCV Therapy for HIV-HCV Co-Infected Persons
Dr. Marina Klein, McGill University, Montréal, Canada

Oral Presentations

09h30 - 09h45 IL-17A Enhances Liver Fibrosis through Upregulation of the TGF-β Receptor on Hepatic Stellate Cells in a JNK Dependent Manner
Thomas Fabre, Centre de Recherche du CHUM (CRCHUM), Montréal, Canada

09h45 - 10h00 Molecular Phylogenetics of Hepatitis C Virus (HCV) as a Tool to Understand the HCV Epidemic in British Columbia
Dr. Andrea D. Olmstead, BCCDC, Vancouver, Canada

10h00 - 10h15 Coffee Break

Biomedical Sciences
Chairs: Dr. Michael Houghton and Dr. Chris Richardson

10h15 - 10h45 The Role of the Innate Immune Response in HCV in the Era of Interferon-Free Therapy
Dr. Markus Heim, Hospital Basel, Basel, Switzerland

10h45 - 11h00 Immune Signatures During Acute HCV
Dr. Naglaa Shoukry, Université de Montréal, Montréal, Canada

Oral Presentations

11h00 - 11h15 Investigating the Role of PCBP2 in the HCV Life Cycle
Dr. Selena Sagan, McGill University, Montréal, Canada

11h15 - 11h30 Use of Codon-Altered JFH1 to Quantify HCV Co-Infections
Dr. Nicholas van Buuren, Stanford University, CA, USA

Behavioural Sciences
Chairs: Dr. Jason Grebely and Dr. Julie Bruneau

11h30 - 12h00 Social Issues in HCV
Prof. Carla Treloar, University of New South Wales, Sydney, Australia

12h00 - 12h15 Bio-Psycho-Social Framework for HCV Treatment Care: Psychology in the Middle
Dr. Louise Balfour, University of Ottawa, Ottawa, Canada

Oral Presentations

12h15 - 12h30 Continued Low Uptake of Treatment for Hepatitis C Virus Infection in a Large Community-Based Cohort of Inner City Residents
Dr. Jason Grebely, The Kirby Institute, University of New South Wales, Sydney, Australia

12h30 - 12h45 Treating the "Difficult to Treat": A Prospective Study of a Community-Based, Collaborative Care, Group Support Model of HCV Treatment
Dr. Jeff Powis, Toronto East General Hospital; Toronto Community Hep C Program, Toronto, Canada

12h45 - 14h00 Lunch

14h00 - 14h15 Developing Estimates of the Prevalent and Undiagnosed HCV Infections in Canada in 2011
Dr. Maxim Trubnikov, PHAC, Ottawa, Canada

14h15 - 14h30 The Public Health Agency of Canada Actions in Hepatitis C Prevention and Control
Dr. Margaret Gale-Rowe, PHAC, Ottawa, Canada

Epidemiology and Public Health
Chairs: Dr. Mel Krajden and Dr. Marina Klein

14h30 - 15h00 Delivering Care to PWID & Those with Substance/Mental Health Issues
Dr. Kim Page, UCSF, San Francisco, USA

15h00 - 15h15 Barriers to Care in the Canadian Aboriginal Population
Dr. Kathy Pouteau, Sioux Lookout, Canada

Oral Presentations

15h15 - 15h30 Phylogenetic Clustering of Hepatitis C Virus Among People Who Inject Drugs in Vancouver, Canada
Brandan Jacka, The Kirby Institute, University of New South Wales, Sydney, Australia

15h30 - 15h45 Association Between HCV RNA Status and All-Cause Mortality in a Cohort of HCV-HIV Co-Infected Canadians
Carmine Rossi, McGill University, Montréal, Canada

15h45 - 16h00 Coffee Break

Debate: Be it resolved that…Treatment should be strictly delivered by specialists rather than by primary care practitioners in the community

16h00 - 16h15 Pro: **Dr. Curtis Cooper,** Clinician Investigator, Ottawa, Canada

16h15 - 16h30 Con: **Dr. Julie Bruneau**, Primary Care Physician, Montreal, Canada

16h30 - 17h00 Panel discussion moderated by Dr. Jordan Feld: **Dr. Sanjeev Arora, Dr. Julie Bruneau, Dr. Markus Heim, Dr. Curtis Cooper and Community Representatives.**

17h00 - 17h15 Closing Remarks
Dr. Jordan Feld, University Health Network, Toronto, Canada

17h15 - 18h30 Cocktail and Poster Session

Committees – Comités

Organizing Committee - Comité organisateur

Louise Balfour, University of Ottawa
Frank Bialystok, University of Toronto
Marc Bilodeau, Université de Montréal
Julie Bruneau, Université de Montréal
Jordan Feld, University Health Network (Chair)
Jason Grebely, University of New South Wales
Michael Houghton, University of Alberta
Mel Krajden, University of British Columbia
Sonya MacParland, University of Toronto (Co-Chair)
Jennifer Raven, CIHR
Eve Roberts, University of Toronto
Rodney Russell, Memorial University
Selena M. Sagan, McGill University
Patricia Thibault, University of Saskatchewan
Lorne Tyrrell, University of Alberta
Tom Wong, PHAC

Abstract Reviewers - Réviseurs des résumés

Louise Balfour, University of Ottawa
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Marion Depla, Université de Montréal
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Sonya MacParland, University of Toronto
Andrea Olmstead, University of British Columbia
Rodney Russell, Memorial University
Selena Sagan, McGill University
Luis M. Schang, University of Alberta
Mark Tyndall, University of Ottawa
Nicholas van Buuren, Stanford University
Joyce Wilson, University of Saskatchewan

Session Chairs - Modérateurs de sessions

Clinical Sciences: Eve Roberts, University of Toronto and Curtis Cooper, University of Ottawa
Biomedical Sciences: Michael Houghton, University of Alberta and Chris Richardson, Dalhousie University
Behavioral Sciences: Jason Grebely, University of New South Wales and Julie Bruneau, Université de Montréal
Epidemiology & Public Health: Mel Krajden, University of British Columbia and Marina Klein, McGill University

Speakers Biographies and Abstracts – Biographies des conférenciers et résumés

Clinical Sciences

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

Biography

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

Dr. Tyrrell was the Dean of the Faculty of Medicine and Dentistry from 1994-2004. Since leaving the Deanship in 2004, Dr. Tyrrell has taken on a number of important board positions in healthcare in Alberta and Canada. These include the Chair of the Board of the Institute of Health Economics and the Chair of the Board of the Health Quality Council of Alberta (2003-2012). He is the Chair of the Gairdner Foundation Board and serves on the Research Advisory Council for the Canadian Institute for Advanced Research and was recently appointed to the Science Advisory Board to Health Canada.

For his studies on viral hepatitis, Dr. Tyrrell has received numerous prestigious awards including the Gold Medal of the Canadian Liver Foundation (2000), the Alberta Order of Excellence (2000), Officer of the Order of Canada (2002), Fellow of the Royal Society (2004), FNG Starr Award of the Canadian Medical Association (2004), and the Principal Award of the Manning Foundation (2005). He was awarded the University Distinguished Professorship at the University of Alberta and was inducted into the Canadian Medical Hall of Fame in April 2011.

Abstract

O Canada - How do you C hepatitis?

There are few diseases in medicine that have undergone the rapid transitions in diagnosis and treatment than hepatitis C. Hepatitis C has an extremely important place in Canada's medical history – from the Krever Inquiry of the "tainted blood" issue in the late 1980s, to the discovery of the virus in 1989 which led to rapidly improved diagnostics, and now the reality of having the ability to "cure" chronic HCV carriers with highly effective direct acting antiviral agents. This is the first persistent viral infection that can be cured, but the cost of therapy is high. Government will feel the pressure of patient advocates, companies will be implored to lower drug prices, and provincial and federal governments will need to implement policies as therapies will be simplified and safe, and will cure HCV patients with relatively short treatment courses. The ability to control or eliminate HCV in Canada will require co-operation between governments, healthcare providers, patients, and industry. Are we, as a collective, willing to work together to meet this challenge?

Dr. Sanjeev Arora, University of New Mexico, New Mexico, USA

Biography

Sanjeev Arora, MD, FACP, FACG, is the Director of Project ECHO® (Extension for Community Healthcare Outcomes). He is a Distinguished Professor of Medicine, and has been involved in management of viral hepatitis for over 15 years, and developed and implemented the Hepatitis C Disease Management Program at UNMHSC.

Dr. Arora developed the Project ECHO® model as a platform for service delivery, education and evaluation. Using video-conferencing technology and case-based learning, primary care clinicians from rural and underserved areas and prisons are trained and mentored by ECHO's medical specialists to deliver best-practice management of complex health conditions in their communities or correctional institutions. A key component of the ECHO® model is an innovation known as Knowledge Networks, in which the expertise of a single specialist is shared with numerous primary clinicians through teleECHO clinics, thereby increasing access to care in rural areas without having to recruit, retain and fund additional clinicians.

Abstract

Project ECHO: A Model to improve Care in Canada

Project ECHO is a disruptive innovation that dramatically improves both capacity and access to specialty care for rural and underserved populations. This low-cost, high-impact intervention is accomplished by linking expert inter-disciplinary specialist teams with primary care clinicians through teleECHO™ clinics, in which the experts co-manage patient cases and share their expertise via mentoring, guidance, feedback and didactic education. This enables primary care clinicians to develop the skills and knowledge to treat patients with common, complex diseases in their own communities which reduces travel costs, wait times, and avoidable complications. Technology is used to leverage scare healthcare resources, and the specialists at Academic Medical Centers (AMCs) are better able to attend the most complex, high-risk patients. The ECHO model™ is not "telemedicine" where the specialist assumes the care of the patient, but instead a guided practice model where the primary care clinician retains responsibility for managing the patient, operating with increasing independence as their skills and self-efficacy grow.

The mission of Project ECHO is to develop the capacity to safely and effectively treat chronic, common, and complex diseases in rural and underserved areas, and to monitor outcomes of this treatment.

Dr. Marina Klein, McGill University, Montréal, Canada

Biography

Dr. Marina Klein is an Associate Professor of Medicine, McGill University, Montreal, Canada in the Division of Infectious Diseases/Chronic Viral Illnesses. She graduated from McGill Medical School (1991) and received her training in Internal Medicine at the Royal Victoria Hospital in Montreal. She completed a research fellowship in Infectious Diseases at the University of Minnesota in 1998 and then returned to McGill University where she received a Master's degree in Epidemiology and Biostatistics (2003). Her clinical interests focus on treatment of patients with HIV and chronic viral hepatitis. She is a prominent researcher in clinical and epidemiologic aspects of HIV and Hepatitis C co-infection and leads a Canadian Institutes of Health Research funded prospective cohort study of over 1200 HIV-HCV co-infected patients to study the interaction of these chronic viral infections. She has also been a principal investigator in several clinical trials of HIV-HCV co-infection. She is also involved in a number of observational epidemiologic research collaborations (e.g. NA-ACCORD and CANOC) focused on understanding long term clinical and treatment outcomes in HIV and in HIV-HCV co-infection where she has assumed a leadership role in scientific steering committees. She was elected to the IAS Governing Council in 2012 representing the North American Region.

Abstract

The Canadian Co-infection Cohort Study: Building the Case for Increased Access to HCV Therapy for HIV-HCV Co-Infected Persons

Over 20% of HIV-infected Canadians are also infected with HCV. Patients co-infected with HIV and HCV experience accelerated to progression to end stage liver disease, although the minority has been treated for HCV thus far. The Canadian Co-infection Cohort (www.cocstudy.ca) is a prospective multi-centre cohort study that has recruited co-infected patients from existing HIV clinic populations at 18 centres across six Canadian provinces over the last 10 years. With now over 1200 patients followed we have built a translational research program that has investigated the interactions of these two viral infections and the documented the impact of co-infection on health outcomes in this population. This presentation will document how co-infection impairs HIV associated immune reconstitution and increases this risk for fibrosis, cirrhosis and death from end stage liver disease. The presentation will focus on identifying modifiable risk factors and interventions that could improve health outcomes in this population. In particular, enhancing access to and the potential benefits of HCV therapy for HIV-HCV co-infected patients will be discussed.

Biomedical Sciences

Dr. Markus Heim, Hospital Basel, Basel, Switzerland

Biography

Markus H. Heim, M.D., Professor of Medicine, Chief, Division of Gastroenterology and Hepatology, University Hospital Basel and Group Leader of the Hepatology Laboratory at the Department of Biomedicine of the University Basel, Switzerland

Heim earned his medical degree at the University of Basel, Switzerland. He then trained for 3 years in basic biomedical science at the Biozentrum in Basel with U.A.Meyer investigating genetic polymorphisms of drug metabolism. Following two years in Internal Medicine at Basel University Hospital, Heim joined the laboratory of James E. Darnell at Rockefeller University, New York, as a postdoctoral fellow, where he worked on basic aspects of Jak-STAT signal transduction. He then completed his internal medicine training and obtained a full training in gastroenterology and hepatology at the University Hospitals in Freiburg, Germany, and Basel, Switzerland. Since 1999 he is Group Leader of the Hepatology Laboratory. He was appointed head of the Hepatology service at the Basel University Hospital in 2003, and chief of the division of Gastroenterology and Hepatology in 2012. In 2011, Heim spent a sabbatical in Frank Chisari's Lab at the Scripps Research Institute in La Jolla, CA. In 2012, Heim was awarded the Otto-Naegeli Prize.

His research focuses on signal transduction in liver disease. He is specifically interested in the role of interferons in acute and chronic viral hepatitis.

Abstract

The role of the Innate Immune Response in HCV in the Era of Interferon-Free Therapy

Chronic hepatitis C (CHC) is a leading cause of liver disease worldwide. For the last 25 years, recombinant interferon-α (IFNα) has been the main component of treatments against hepatitis C virus (HCV). Treatment efficacy improved stepwise following pegylation of IFNα and its combined use with ribavirin and more recently with HCV protease inhibitors. Non-response to pegIFNα/ribavirin therapies is strongly linked to allelic variants of the IFNλ3/4 gene locus. CHC patients carrying one ore two minor alleles are significantly more likely to have an induction of hundreds of IFN stimulated genes (ISGs) in the liver already before treatment. The activation of the endogenous IFN system is not only ineffective in clearing the infection, but also prevents response to IFNα based treatments. This state of IFNα non-response seems to depend directly on ongoing viral replication in the liver. Studies with anti-miR122 oligos in HCV infected chimpanzees found a rapid decline of ISG expression following inhibition of viral replication. The new generation of potent direct acting antivirals might exert part of their activity by restoring responsiveness to endogenous IFNs that are produced by infected hepatocytes or by immune cells

Dr. Naglaa Shoukry, Université de Montréal, Montréal, Canada

Biography

Dr. Naglaa H. Shoukry obtained her Pharmacy degree from Cairo University (1991) and her Ph.D. in Immunology from McGill University (2000) under the supervision of Dr. Rafick P. Sekaly. This was followed by postdoctoral training in the laboratory of Dr. Christopher M. Walker at Children's Research Institute, Ohio State University (1999-2004). Her postdoctoral research has established the essential and complementary roles of CD8+ and CD4+ T cells in resolution and protection from hepatitis C virus (HCV) infection in the chimpanzee model. She joined the University of Montreal Hospital Research Center (CRCHUM) in January 2005 where she has established a translational research program focused on studying immunity to HCV and mechanisms underlying failure of the immune response during acute HCV infection. More recently, her work has focused on understanding protective immunity during multiple episodes of HCV infection and immunological mechanisms of liver disease progression. Her research was/is funded by CIHR, FRQS, the Dana Foundation, CANFAR and the Canadian Liver Foundation (CLF). Dr. Shoukry is the recipient of numerous awards from the American Liver Foundation, CIHR and FRQS. She is an Academic Editor for PLoS One and a mentor in the National Canadian Research Training Program on Hepatitis C (NCRTP-HepC).

Abstract

Immune Signatures during Acute HCV

Despite the recent development of highly effective direct acting antivirals against hepatitis C virus (HCV), there is no vaccine to prevent viral transmission and incidence of new infections. The problem is more apparent in vulnerable populations who have limited access to treatment like injection drug users (IDUs), men who have sex with men and aboriginal populations. Hence, the urgent need for an effective prophylactic vaccine to limit HCV transmission and new infections. Vaccine development is hampered by our limited understanding of protective immunity against HCV.

To understand correlated of protective immunity, we have built a cohort of IDUs at high risk of HCV infection in Montreal where we were able to document and follow many cases of acute HCV and through multiple infections. In this presentation, I will present a short summary of our findings about the phenotypic, functional and genomic characterization of HCV-specific immunity during acute resolving primary HCV infection, establishment of T cell memory and recall responses upon re-exposure to the virus in this high risk population. I will also draw parallels of our human studies with our earlier work in the chimpanzee model and the relevance to vaccine development for HCV and other viruses.

Behavioural Sciences

Prof. Carla Treloar, University of New South Wales, Sydney, Australia

Biography

Professor Carla Treloar is Deputy Director of the Centre for Social Research in Health at The University of New South Wales, Australia. Carla is a member of numerous advisory committees for government, health agencies and non-government organisations. She is a board member of the *International Journal of Drug Policy* and an associate editor for *Addiction*. She has published over 110 peer reviewed articles and been awarded over $13 million in research funding. She has a background in multidisciplinary research across social and health psychology, and public health. Her work covers risk and prevention, chronic illness and treatment and the use of mixed and innovative methods. In particular, her research encompasses the social aspects of drug use in relation to prevention of drug-related harms (particularly hepatitis C), engagement of people who use drugs in health and other services, and critical analysis of the structure and operation of services for people who use drugs. Carla is committed to the effective translation of research into policy and practice and to ethical and respectful conduct of research in close collaboration with affected communities.

Abstract

Social Issues in HCV

There has been concerted effort for over a decade to engage more people who inject drugs in hepatitis C care. Alongside these efforts has been a steady research pipeline examining barriers to such engagement at patient, provider and systems levels. The number and extent of barriers identified is overwhelming and there is little guidance on the optimal ways to redress these barriers. Developing HCV care models that respond to this myriad of inter-related factors is indeed a challenge. However, a number of innovative ways to engage and retain PWID in HCV care have been implemented and evaluated.

This presentation will draw on a number of models of HCV care and treatment using concepts and evidence from social science research. The experiences of stigma, social exclusion, structural violence and symbolic violence are all important in shaping the trust a person with HCV may have in a clinical service and its workers, and their decision whether to engage with the service. Rather than serving as further barriers to clinicians, these concepts can provide a new lens with which to view their service and assist in generating approaches that aim to promote trust in the service among people with HCV and people who inject drugs. While there can be no absolute answers in this complex field, insights from social research can be used as tools by clinicians to shape their approach to care with the aim of building positive, enabling relationships between patient, health worker and health setting.

Dr. Louise Balfour, University of Ottawa, Ottawa, Canada

Biography

Dr. Louise Balfour is currently an Associate Professor with the Division of Infectious Diseases in the Faculty of Medicine at The University of Ottawa. She has also worked as a Clinical Health Psychologist in the HIV clinic at The Ottawa Hospital since 1996.

Dr. Balfour obtained her Bachelor degree in Montreal at McGill University and her Masters and Ph.D. in Clinical Psychology at Concordia University.

Dr. Balfour currently holds several CIHR research grants and she has an active Psychological Behavioral Medicine Research Lab at The Ottawa Hospital.

Dr. Balfour's program of clinical research aims to improve the lives of people living with HIV/HCV co-infection and focuses on: Increasing patients' psychological readiness for starting medications and improving their medication adherence; helping patients cope with symptoms of depression and reducing HIV/HCV related stigma.

Dr Balfour is also currently conducting a novel CIHR and CTN funded multi-site RCT clinical trial to help HIV patients quit smoking cigarettes.

Dr Balfour has also worked on several international HIV collaborations with the goal of improving HIV treatment knowledge and adherence in Guyana, Colombia, and South Africa.

Abstract

Bio-Psycho-Social Framework for HCV Treatment Care: Psychology in the Middle

Research has demonstrated that the rate of Hepatitis C Treatment initiation and success is increased in the presence of a multidisciplinary approach. HCV treatment guidelines highlight the importance of using a Bio-psycho-social framework in which Hepatitis C treatment care is provided by a comprehensive multi-disciplinary team. The Ontario Ministry of Health and Long-term Care has developed detailed Hepatitis C Team Program Guidelines which describe the important roles and contributions of diverse team members including the roles of *physicians, Hepatitis C Treatment Nurses, Social Workers, Clinical Psychologists , Community Coordinators, and Outreach Workers/ peer involvement.*

A Hepatitis C Clinical Psychologist can provide detailed psychological assessments, interventions, and treatment recommendations for Hepatitis C patients and work as integral member of the Hepatitis C multidisciplinary team. The importance of assessing mental health co-morbidities and providing timely and effective mental health interventions during Hepatitis C treatments is critical to Hepatitis C treatment success. Psychologists also provide expertise in facilitating patients' treatment readiness, adherence, and success. Psychologists draw from evidenced based clinical research work, such as using Motivational Interviewing techniques, that can facilitate patients' readiness for starting treatment, enhances patients' skills in achieving optimal treatment adherence, and increase rates of successful viral clearance. The challenges associated with Hepatitis C treatments, the costs of non-adherence, and strategies to facilitate optimal treatment uptake, adherence, and successful treatment outcomes will be reviewed.

Dr. Maxim Trubnikov, PHAC, Ottawa, Canada

Biography

Max is an epidemiologist with the Surveillance and Epidemiology Division of the Centre for Communicable Diseases and Infection Control of the Public Health Agency of Canada. In this capacity, Max leads the data analysis and knowledge products development in the field of surveillance and epidemiology of viral hepatitis in Canada. He has 10+ year experience in the disease surveillance, epidemiological research, policy analysis and project management, largely in the field of sexually-transmitted and blood borne pathogens both in Canada and internationally. Max holds an MD (1999), PhD in Social Medicine (2005) and MSc in Epidemiology (2011).

Abstract

Developing estimates of the prevalent and undiagnosed HCV infections in Canada in 2011

In Canada, information about the prevalence of HCV infection is generally limited to laboratory and national routine and enhanced surveillance data, findings of regional, and population-specific studies, and modeled estimates. These data sources have limitations, including uncertainty, under-reporting and restricted generalizability.

In November 2013, Rotermann and colleagues reported measures of HCV prevalence and infectious status awareness from the Canadian Health Measures Survey (CHMS). As CHMS did not study a number of populations presumably highly affected by HCV, its estimates likely have underestimated the true HCV seroprevalence in Canada.

Prevalent and potentially undiagnosed HCV infections in Canada were estimated through a combination of methods, including back-calculation and the workbook method. Their own limitations notwithstanding, the new estimates will help to better target strategies for identifying persons unaware of their HCV infection status and shape public health activities to address the needs of populations affected by HCV in Canada.

Dr. Margaret, Gale-Rowe, PHAC, Ottawa, Canada

Biography

Dr. Gale-Rowe received her Bachelor of Science degree in Microbiology from the University of Guelph, and her Doctor of Medicine degree from the University of Ottawa. Following her medical training, she practiced as a general practitioner, before completing her Masters of Public Health in Disease Control, at the University of Texas-Houston. She did a residency in Preventive Medicine and Public Health and is ABMS Certified in Preventive Medicine. Dr. Gale-Rowe worked as a Communicable Disease physician (STI) for the Houston Department of Health and Human Services before joining the Public Health Agency of Canada as a Medical Advisor in 2008. She is a Manager in the Centre for Communicable Diseases and Infection Control.

Abstract

The Public Health Agency of Canada actions in Hepatitis C Prevention and Control

The Public Health Agency of Canada contributes to the prevention of disease and the promotion of health. The Agency's Centre for Communicable Diseases and Infection Control collaborates with other Federal departments to address challenges to the prevention and management of the hepatitis C virus (HCV) in Canada, as well as internationally.

The Hepatitis C Prevention, Support and Research Program was introduced in 1999 in response to the report of the Krever Commission. In 2009, national consultations identified key areas for Federal action, summarised in the *Renewed Public Health Response to Address Hepatitis C*, which has served as the basis for the current Agency response.

This presentation will review the Federal role as well as the current Agency response to Hepatitis C, and will provide an outline of how the Agency is moving forward to address HCV within an integrated approach to STBBIs.

Epidemiology and Public Health

Dr. Kim Page, UCSF, San Francisco, USA

Biography

Dr. Kimberly Page is a Professor in Residence in the Department of Epidemiology and Biostatistics at the University of California San Francisco. She holds joint appointments in Global Health Sciences, the Department of Medicine, and in the School of Dentistry at UCSF, as well as the San Francisco Veteran's Administration Medical Center Department of Medicine. Dr. Page is an infectious disease epidemiologist; she conducts epidemiological and clinical on studies aimed at preventing HIV and hepatitis C virus (HCV) infections in vulnerable populations including injecting drug users and female sex workers. In San Francisco, she leads a large observational cohort study, the UFO Study, one of the longest running studies of incident HCV in the U.S. The UFO Study has contributed to further knowledge of outcomes of acute HCV infection including factors associated with clearance, and reinfection, and of gender differences in risk and infection outcomes. She is the PI of a several other large NIH funded grants, including a large international collaboration merging data from other large observational cohorts of HIV and HCV in injecting drug users in Australia, Canada and Netherlands. She is involved in HCV vaccine research and is currently co-leading a Phase II trial studying a prophylactic HCV vaccine in the U.S.. In Cambodia she is leading a large trial in high risk female entertainment workers aimed at reducing drug use and HIV risk. Her work overseas, including South America and South East Asia extends into training, where she is committed to capacity building in epidemiology and clinical research.

Abstract

Delivering care to PWID and those with Substance/Mental Health Issues.

Kimberly Page, Ph.D., MPH; Professor of Epidemiology & Biostatistics, School of Medicine; Global Health Sciences, University of California San Francisco

Significant challenges exist in delivering care to PWID; a significant proportion have multiple clinical, psychological, and social problems. In the context of hepatitis C virus (HCV) infection, PWID are the population most significantly impacted. They are at the core of the HCV epidemic with highest incidence and prevalence of infection globally. Up to 80% of all new infection are in PWID and over half of all existing infections are estimated to be in current or former PWID. HCV treatment uptake is low overall, and especially among current PWID due to multiple patient, provider and structural barriers. Active drug use and mental health problems are often key factors affecting HCV treatment decision by both patients and providers. Some of these barriers are associated with clinical side-effects, factors that affect therapy adherence, and concerns regarding reinfection. This presentation will review the HCV "treatment cascade" in PWID, how drug use and mental health issues may impact care delivery, and review strategies that may impact successful delivery of care in this population.

Dr. Kathy Pouteau, Sioux Lookout, Canada

Biography

Kathy Pouteau is a Family Physician working in Sioux Lookout and Kasabonika Lake First Nation. She is the Chair of the regional STBBI Working Group, and Practice Coordinator for a group of physicians providing care to remote First Nations' communities in northwestern Ontario.

Abstract

Barriers to Care in the Canadian Aboriginal Population

Chiefs of the Nishnawbe Aski Nation declared a state of emergency around prescription drug abuse in their communities in 2009, and First Nations in northwestern Ontario are now experiencing increased rates of hepatitis C. Dr. Pouteau will describe the challenges, opportunities, and collaborative response of health service providers and First Nations in the prevention and management of hepatitis C in rural and remote communities in the Sioux Lookout area.

Debate

Dr. Julie Bruneau, Université de Montréal, Montréal, Canada

Biography

Dr Julie Bruneau is a clinical researcher and Professor in the Department of Family Medicine at the University of Montreal. As a clinician, she is recognized as a leader in the development of addiction medicine in Canada. She was one of the founding member of the Canadian Society of Addiction Medicine, and implemented the largest University-based Addiction Medicine Facility in Quebec. For the past twenty years, she has conducted epidemiological research among active injecting drug users (IDU), and published her work in high-impact journals. Her research accomplishments have significantly contributed to a better understanding of the dynamics of HIV and HCV transmission among IDUs. Her work on the relation between syringe access and HIV transmission, albeit controversial at times, directly influenced changes in prevention strategies to better address injector needs nationally and around the world. Recently, she has expanded her research program to examine the impact of various approaches including treatment and motivational interviewing, on the behaviors and quality of life of active injection drug users (IDU). She is also a member of the research team on the development of a vaccine against HCV, led by Drs Tyrrell and Houghton.

Dr. Curtis Cooper, Clinician Investigator, Ottawa, Canada

Biography

Dr. Curtis Cooper trained at the University of Saskatchewan (MD 1994). He received certification in Internal Medicine in 1997 and in Infectious Diseases in 1999 while at the University of Manitoba. He completed an HIV Research Fellowship and Masters of Epidemiology in 2002 at the University of Ottawa. He is currently an Associate Professor with the University of Ottawa, Scientist with the Ottawa Hospital Research Institute, Infectious Diseases Consultant with the Ottawa Hospital Division of Infectious Diseases, Director of The Ottawa Hospital Viral Hepatitis Program and holds an Applied HIV research Chair with the Ontario HIV Treatment Network. As a clinical researcher, his research activities encompass viral hepatitis, HIV, and vaccine development. His work is focused on the development of new therapeutic agents and the delivery of treatment that maximizes safety, adherence and safety. Is an active researcher with several cohort studies (CANOC, OHTN Cohort Study). He is co-chair of the CIHR Canadian HIV Trials Network Co-Infection Core research group and a member of the Canadian Association of HIV Researchers executive.

Dr. Jordan Feld, University Health Network, Toronto, Canada

Biography

After completing clinical training in Internal Medicine and Gastroenterology, Dr. Feld spent 4 years doing clinical and laboratory research in the Liver Diseases Branch of the National Institutes of Health. He received a Masters of Public Health from Johns Hopkins University and has worked extensively abroad, maintaining a strong interest in International Health.

Dr. Feld returned to Toronto to join the faculty of the University of Toronto as an Assistant Professor of Medicine and clinician-scientist based at the Toronto Western Hospital Liver Center and the Sandra Rotman Centre for Global Health. His laboratory focuses on understanding treatment non-response in hepatitis C infection and more broadly on understanding the antiviral immune response with the goal of developing new strategies for the treatment of viral hepatitis.

Oral Abstracts – résumés oraux

Clinical Sciences

Oral presentation at 09h30

IL-17A ENHANCES LIVER FIBROSIS THROUGH UPREGULATION OF THE TGF-B RECEPTOR ON HEPATIC STELLATE CELLS IN A JNK DEPENDENT MANNER

Thomas Fabre (1), Hassen Kared (1), Scott L. Friedman (2), Naglaa Shoukry (3)
(1) Centre de Recherche du CHUM (CRCHUM), Montréal, QC, Canada (Montreal, Canada); (2) Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA (New york, United States); (3) Département de médecine, Université de Montréal, Montréal, QC, Canada (Montreal, Canada)

Background: Activation of hepatic stellate cells (HSCs) is a key event in the initiation of hepatic fibrosis, characterized by enhanced extracellular matrix (ECM) production and altered degradation. Activation of HSCs can be modulated by cytokines produced by immune cells. Recent reports have implicated the pro-inflammatory cytokine IL-17A, in liver fibrosis progression.

Purpose: We hypothesized that IL-17A may enhance activation of HSC and induction of the fibrogenic signals in these cells.

Method: The human HSC line LX2 and primary human HSCs were stimulated with increasing doses of IL-17A and compared to TGF-β and PBS-treated cells as positive and negative controls, respectively.

Result(s): IL-17A alone did not induce activation of HSC. However, IL-17A sensitized HSCs to the action of suboptimal doses of TGF-β as confirmed by strong induction of alpha-smooth muscle actin (α-SMA), collagen type I (COL1A1) and tissue inhibitor of matrix metalloproteinase I (TIMP-I) gene expression and protein production.IL-17A specifically upregulated the cell surface expression of TGF-β-RII following stimulation. Pretreatment of HSCs with IL-17A enhanced signaling through the TGF-β-RII as observed by increased phosphorylation of SMAD2/3 in response to stimulation with suboptimal doses of TGF-β. This enhanced TGF-β response of HSCs induced by IL-17A was JNK-dependent.

Conclusion(s): Our results suggest a novel pro-fibrotic function for IL-17A through sensitization of HSCs to the action of TGF-β through activation of the JNK pathway. IL-17A acts through up-regulation and stabilization of the TGF-β-RII leading to increased SMAD2/3 signaling. These findings represent a novel example of cooperative signaling between an immune cytokine and a fibrogenic receptor.

Funding source(f): Canadian Institutes for Health Research

Oral presentation at 09h45

MOLECULAR PHYLOGENETICS OF HEPATITIS C VIRUS (HCV) AS A TOOL TO UNDERSTAND THE HCV EPIDEMIC IN BRITISH COLUMBIA

Andrea D. Olmstead (1), Vincent Montoya (2), Jeffrey B. Joy (3), Art F.Y. Poon (3), Jason Grebely (4), P. Richard Harrigan (3), Mel Krajden (2)

(1) BCCDC (Vancouver, Canada); (2) BC Centre for Disease Control and University of British Columbia (Vancouver, Canada); (3) BC Centre for Excellence in HIV/AIDS (Vancouver, Canada); (4) Viral Hepatitis Clinical Research Program, Kirby Institute, UNSW (Sydney NSW, Australia)

Background: Sequence-based molecular phylogenetics of Hepatitis C virus (HCV) has become an important epidemiological tool used to provide evidence of person-to-person transmission events, estimate transmission dates and model HCV spread within and between populations.

Purpose: To assess the utility of sequence-based molecular epidemiology for characterizing the HCV epidemic in British Columbia, identify HCV transmission clusters, and to predict incident versus prevalent infections.

Method: A total of 1,540 HCV seropositive samples from the BC Centre for Disease Control underwent PCR based detection followed by Sanger sequencing of a 587 bp NS5b region. A maximum likelihood phylogeny was used to summarize the relationship between all sequences. Pairwise genetic distances between sequences were calculated and used for cluster analysis.

Result(s): Sequences from 594 samples from 569 individuals were generated. Based on patristic distance cutoffs of 0.03, 0.02, 0.01 we identified 15, 18 and 4 sequence clusters linking different individuals. An additional, 20 sequence pairs with 99% or greater homology were also identified. The 99% similarity pairs and clusters are consistent with recent, closely linked transmission events, whereas the larger more distant transmission clusters likely represent networks of transmission that occurred more remotely. Integration of risk factor, demographic and temporal data as well as next generation sequencing data will be used to further characterize these transmission networks.

Conclusion(s): Systematic, molecular epidemiological analysis of HCV RNA reactive samples provides a tool to differentiate core transmission nodes from individuals who are remotely infected. This information when combined with traditional epidemiological surveillance data can help guide the development and evaluation of targeted prevention, care and treatment programs aimed at HCV eradication.

Funding source(f): National CIHR Research Training Program in Hepatitis C

Biomedical Sciences

Oral presentation at 11h00

INVESTIGATING THE ROLE OF PCBP2 IN THE HCV LIFE CYCLE

Lance Martin (1), Selena Sagan (2), Ryan Flynn (1), Robert Spitale (1), Steve Quake (1), Peter Sarnow (1), Howard Chang (1)
(1) Stanford University (Stanford, United States); (2) McGill University (Montreal, Canada)

Background: Hepatitis C virus (HCV) infection is a rapidly increasing global health problem with over 170 million people infected worldwide. Our previous work suggested a new model for miR-122: HCV RNA interactions at the 5' terminus of the HCV genome in which the site 1-bound miR-122 molecule binds to the HCV genome across stem-loop 1 (SLI, nts 5-20) (Machlin, Sarnow and Sagan, PNAS 2011). This interaction is predicted to stabilize SLI. Since SLI is required for viral RNA replication, we were curious whether stabilization of SLI by miR-122 provided a platform for recruitment of host or viral proteins required for viral replication. A literature search revealed that the poly-rC binding protein 2 (PCBP2) binds to SLI of the HCV genome.

PCBPs are nucleic acid binding proteins with preference for C-rich motifs. PCBPs 1/2 have roles in RNA processing, translational control and mRNA stabilization. Interestingly, PCBP2 gene expression is induced by type I IFN or virus infection, and it has been implicated in the life cycles of diverse RNA viruses, including HCV. PCBPs bind to SLI and the HCV IRES, as well as an undefined region in the 3' UTR. Depletion of PCBP2 results in a loss in viral RNA and in vitro studies suggest that PCBP2 can circularize dsRNAs flanked by the HCV 5' and 3' UTRs. We also found that PCBPs immunoprecipitate miR-122 in Huh-7 cells. These results led us to hypothesize that PCBPs bind to the HCV genome and miR-122 and that these interactions facilitate RNA replication by circularizing the HCV genome.

Purpose: The purpose of this research is to identify and characterize PCBP binding sites on the HCV genome and elucidate whether PCBPs and miR-122 form a functional complex at the 5' terminus of the genome that facilitates genome circularization and/or the switch from active translation to viral RNA replication.

Method: To identify PCBP binding sites in the HCV genome, we performed individual nucleotide-resolution crosslinking immunoprecipitation (iCLIP) analysis of PCBPs in JFH-1 (2a)-infected, H77 (1a)-HCV RNA harboring, and uninfected Huh-7 cells.

Result(s): Preliminary mapping of reads to the HCV genome revealed high confidence binding sites by comparing iCLIP reads from genotypes 1a and 2a. Conserved PCBP binding sites mapped to six distinct regions across the HCV genome including the poly-U/UC region. Remarkably, while two PCBP binding sites map to the ORF, four of the PCBP binding sites mapped to structural motifs in the viral genome with annotated roles in the HCV life cycle. To investigate the roles of PCBPs in the HCV life cycle, we will combine mutagenesis studies with assays for viral translation, replication, genome circularization, and particle production.

Conclusion(s): We find that PCBPs interact with six conserved binding sites in the HCV genome as well as with miR-122. We anticipate that our mutational analyses will reveal the role of PCBPs in the HCV life cycle. Given that miR-122 immunoprecipitates with PCBPs in HCV-infected cells, it is likely that PCBPs and miR-122 coordinate to regulate HCV RNA accumulation.

Oral presentation at 11h15

USE OF CODON-ALTERED JFH1 TO QUANTIFY HCV CO-INFECTIONS

Nicholas van Buuren (1), Karla Kirkegaard (1)
(1) Stanford University (Palo Alto, United States)

Background: This is a very exciting time in HCV research as several exciting new treatment regimens are currently or soon to be on the market for treatment of HCV. However, even though many of these treatments potently inhibit HCV replication in patients, many still suffer from complications due to drug resistance. We have high hopes for what we term "Trans-Dominant Inhibition" as a mechanism to suppress the outgrowth of drug resistant variants.

Not all direct acting antivirals lead to the outgrowth of drug resistant variants. All mutant viruses arise from mixed infected cells; it is at that time that drug-resistant variants are vulnerable to inhibition by drug-bound viral proteins made by parental viruses. We are interested in identifying targets for antivirals that, because their targets are oligomeric, will suppress the outgrowth of drug-resistant variants. These studies offer a new paradigm for the targeting of anti-viral compounds.

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 in the C-terminus of NS3. This codon altered strain showed 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 confocal microscopy and flow cytometry. We have co-infected Huh7.5.1 cells with the codon-altered/drug-sensitive JFH1 along with drug-resistant strains of JFH1 in the presence of direct acting antivirals to test dominance relationships in these co-infected cells.

To obtain drug-resistant variants that can arise during low-MOI infections, we passaged the JFH1 strain of HCV in the presence of direct-acting antivirals that include a protease inhibitor, BILN-2061, polymerase inhibitors MK0608 and R1479 and a NS5A inhibitor SR2486. Several point mutations, some previously reported from replicon selections and some novel, have been identified through sequencing of passaged virus. These mutations have been cloned back into JFH1 constructs and their drug-resistance profiles tested.

Result(s): Two sets of mutations that confer resistance to BILN-2061 have been cloned that demonstrate strong resistance profiles. We expect, from the monomeric nature of NS3/4A protease that little dominance of the drug-susceptible virus will be observed using BILN-2061. Preliminary results support this hypothesis. Compounds targeting the highly oligomeric NS5B, NS5A and core proteins are more likely to demonstrate trans-dominance. We have co-transfected Huh7.5.1 cells with the codon-altered/drug-sensitive JFH1 along with drug-resistant strains of JFH1 in the presence of direct acting antivirals to test dominance relationships in these co-infected cells.

Conclusion(s): The identification of dominant drug targets in HCV has the potential to drastically alter future HCV combination therapies leading to decreased risk for the development of drug resistance.

Funding source(f):NCRTP-HepC

Behavioral Sciences

Oral presentation at 12h15

CONTINUED LOW UPTAKE OF TREATMENT FOR HEPATITIS C VIRUS INFECTION IN A LARGE COMMUNITY-BASED COHORT OF INNER CITY RESIDENTS

Maryam Alavi (1), Grebely Jason (1), Jesse Raffa (2), Gregory Deans (3), Calvin Lai (4), Mel Krajden (5), Gregory Dore (1), Mark Tyndall (6), Jason Grebely (1)

(1) The Kirby Institute, University of New South Wales (Sydney, Australia); (2) Department of Statistics, University of Washington (Seattle , United States); (3) Division of Infectious Diseases, Department of Medicine, University of British Columbia (Vancouver, Canada); (4) British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital (Vancouver, Canada); (5) British Columbia Centre for Disease Control (Vancouver, Canada); (6) Division of Infectious Diseases, Department of Medicine, University of Ottawa (Ottawa, Canada)

Background: Despite advances in HCV treatment, recent data on treatment uptake is sparse, particularly among people who inject drugs.

Purpose: HCV treatment uptake and associated factors were evaluated in a community-based cohort in Vancouver, Canada.

Method: The CHASE study is a cohort of inner city residents recruited from January 2003-June 2004. HCV status and treatment were retrospectively and prospectively determined through data linkages with provincial virology and pharmacy databases. Logistic regression analyses were used to identify factors associated with HCV treatment uptake.

Result(s): Among 2,913, HCV antibody testing was performed in 2,405, 64% were HCV antibody-positive (n=1,533). Individuals with spontaneous clearance (18%, n=276) were excluded. Among the remaining 1,257 HCV antibody-positive participants (mean age 42, 71% male), 29% were Aboriginal. At enrolment, the majority reported recent injecting (60%) and non-injecting drug use (87%). Between January 1998 and March 2010, 6% (77 of 1,257) initiated HCV treatment. In adjusted analyses, Aboriginal ethnicity [adjusted odds ratio (AOR) 0.23; 95% CI 0.10, 0.51] and crack cocaine use (AOR 0.61; 95% CI 0.37, 0.99) were associated with a decreased odds of receiving HCV treatment, while methamphetamine injecting (AOR 0.16; 95% CI 0.02, 1.18) trended towards a lower odds of receiving treatment. HCV treatment uptake ranged from 0.2 (95% CI 0.0, 0.7) per 100 person-years (PYs) in 2003 to 1.6 (95% CI 0.9, 2.6) per 100 PYs in 2009.

Conclusion(s): HCV treatment uptake remains low in this large community-based cohort of inner city residents with a high HCV prevalence and access to universal healthcare. Strategies are needed to enhance assessment and uptake of HCV treatment in this population to prevent future HCV-related morbidity and mortality.

Oral presentation at 12h30

TREATING THE "DIFFICULT TO TREAT": A PROSPECTIVE STUDY OF A COMMUNITY-BASED, COLLABORATIVE CARE, GROUP SUPPORT MODEL OF HCV TREATMENT

Jeff Powis (1), Jason Altenberg (2), Zoe Dodd (2), Dr. Sanjeev Sockalingam (3), Christopher Meaney (4), Kate Mason (5)
(1) Toronto East General Hospital; Toronto Community Hep C Program (Toronto, Canada); (2) South Riverdale Community Health Centre, Toronto Community Hep C Program (Toronto, Canada); (3) University Health Network, University of Toronto; Toronto Community Hep C Program (Toronto, Canada); (4) Dept of Family & Community Medicine, University of Toronto (Toronto, Canada); (5) Toronto Community Hep C Program (Toronto, Canada)

Background: The Toronto Community Hepatitis C Program (TCHCP) is a community-based model of HCV treatment offering weekly group support and access to HCV treatment for people who are active substance users and/or have serious mental health issues. A previous retrospective study of the TCHCP model has demonstrated treatment initiation and success rates which are comparable to those in traditional health care settings (Charlebois et al. 2012).

Purpose: This is a preliminary analysis of a larger prospective study. The purpose of this analysis was to provide a detailed description of the social demographics, substance use patterns, social marginalization and mental health comorbidities of clients involved in the program.

Method: Questionnaires were administered to all new program clients who attended at least one group session beginnning in January 2011. The comprehensive survey tool included questions concerning income, housing, food security, access to health care, criminal justice system involvement, quality of life and well-being. Levels of depression and anxiety were measured by the PHQ 9 and GAD-7. Problematic substance use was measured using the Addiction Severity Index self-reported number of problem days in the past month. Social support was mesured using the Medical Outcomes Study – Social Support Survey (MOS SSS). REB approval for this study was obtained through the University of Toronto.

Result(s): Data was available for 81 clients. Most were male (75.3%) with an average age of 48 years. The vast majority (88.9%) reported very low income (< $2,000/mos) and 45.7% had unstable housing at program enrolment. Rates of self-reported drug use were high with 52% reporting crack cocaine use and 19% IVDU within the past 6 months. The average number of problematic days due to drug use in the past month was 5.37 (SD=9.53) and for alcohol was 2.9 (SD=7.9). Mental health comorbidities were common, with 40% reporting a history of at least one psychiatric hospitalization and 49.3% currently receiving disability income for mental health reasons. Clients reported moderate levels of depression and mild anxiety at baseline. Levels of social support were also low (mean score = 58.68; SD=26.53), especially when compared with other chronic disease patients (Sockalingam et al. 2011).

Conclusion(s): The population served by the TCHCP is highly marginalized with high rates of unemployment, substance use, mental health comorbidities and poverty. A community based, collaborative care model of HCV care is a promising model for delivery of HCV antiviral therapy with potential benefits beyond SVR.

Funding source(f): Funded by Toronto Community Hep C Program.

References:

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Epidemiology and Public Health

Oral presentation at 15h15

PHYLOGENETIC CLUSTERING OF HEPATITIS C VIRUS AMONG PEOPLE WHO INJECT DRUGS IN VANCOUVER, CANADA

Brendan Jacka (1), Mel Krajden (2), Tanya Applegate (3), Andrea Olmstead (2), Richard Harrigan (4), Kora DeBeck (5), M-J Milloy (6), Francois Lamoury (3), Conan Woods (4), Zabrina Brumme (7), Sabina Dobrer (4)
(1) Viral Hepatitis Clinical Research Program, The Kirby Institute (Sydney, Australia); (2) British Columbia Centre for Disease Control, Vancouver BC (Vancouver, Canada); (3) Viral Hepatitis Clinical Research Program, The Kirby Institute, University of New South Wales, Sydney NSW (Sydney, Australia); (4) British Columbia Centre for Excellence in HIV/AIDS, St Paul's Hospital, Vancouver BC (Vancouver, Canada); (5) British Columbia Centre for Excellence in HIV/AIDS, St Paul's Hospital, Vancouver BC, and School of Public Policy, Simon Fraser University, Vancouver, BC, Canada (Vancouver, Canada); (6) British Columbia Centre for Excellence in HIV/AIDS, St Paul's Hospital, Vancouver BC, and Department of Family Practice, Faculty of Medicine, University of British Columbia, Vancouver, BC (Vancouver, Canada); (7) British Columbia Centre for Excellence in HIV/AIDS, St Paul's Hospital, Vancouver BC, and Faculty of Health Sciences, Simon Fraser University, Vancouver BC (Vancouver, Canada)

Background: Factors associated with an increased risk of hepatitis C virus (HCV) acquisition among people who inject drugs (PWID) have been described, but little is known about factors associated with HCV transmission. We characterized phylogenetic clustering of HCV genotype 1a and 3a infection and associated factors among PWID recruited between 1996 and 2012 in Vancouver, Canada.

Method: Data were derived from two ongoing prospective cohorts of PWID in Vancouver (VIDUS and ARYS). Participants that were HCV antibody positive at baseline, or had HCV antibody seroconversion during follow-up were tested for HCV RNA. HCV RNA positive samples were sequenced using the Core-HVR1. Phylogenetic trees were inferred using maximum likelihood analysis and clusters were identified using PhyloPart (90% bootstrap threshold and a 2.5% distance distribution threshold). Factors associated with clustering were assessed using logistic regression.

Result(s): Among 1,107 HCV RNA positive participants, 629 (57%) had available Core-HVR1 sequences. The HCV genotype prevalence was: G1a: 47% (n=296), G1b: 7% (n=42), G2a: 3% (n=17), G2b: 7% (n=46), G3a: 34% (n=216), G4a: <1% (n=4), G6a: 1% (n=7) and G6e <1% (n=1). Overall, the mean age was 35.6 years (SD, 8), 27% were female and 24% were HIV positive. Among participants with HCV G1a, 32% (93 of 296) were in a pair or cluster, with a mean patristic distance of 0.076. Among participants with HCV G3a, 28% (60 of 216) were in a pair or cluster, with a mean patristic distance of 0.017. Among participants infected with HCV G1a, phylogenetic clustering was more common among those with HIV infection (40% vs. 29%, P=0.058) and those with HCV seroconversion during follow-up (50% vs. 30%, P=0.045). Among participants infected with G3a, compared to those infected prior to 1980 (15%), those infected in 1980-1989 (28%, P=0.058) and those infected in 1990-1999 (45%, P¬<0.001) were more likely to be in a pair or cluster, whereas those infected in 2000-2009 (17%, P= 0.887) were not. Factors independently associated with phylogenetic clustering in participants with G1a included HIV infection [adjusted odds ratio (AOR) 1.93; 95%CI 1.12, 3.36], and HCV seroconversion (AOR 3.14, 95%CI 1.30, 7.57). Year of infection was the only factor significantly associated with phylogenetic clustering in participants with G3a.

Conclusion(s): In this population of people who inject drugs in Vancouver, one-third of individuals demonstrated phylogenetic clustering. Factors associated with HCV transmission included HIV infection, HCV seroconversion and year of infection, with differences in clustering observed between HCV genotypes. Strategies to enhance the identification and delivery of prevention and/or treatment strategies to those with HIV infection and PWID with newly acquired HCV infection should be explored, given an increased likelihood of HCV transmission by these groups.

Funding source(f):Funding for this study was provided by the National Institutes of Health (NIH) (VIDUS-R01DA011591; R03DA033851-01) and the Canadian Institutes of Health (CIHR) (HHP-67262, MOP-125948).

Oral presentation at 15h30

ASSOCIATION BETWEEN HCV RNA STATUS AND ALL-CAUSE MORTALITY IN A COHORT OF HCV-HIV CO-INFECTED CANADIANS

Carmine Rossi (1), Kathleen Rollet (2), Laurence Brunet (1), Marina Klein (2)
(1) Department of Epidemiology, Biostatistics and Occupational Health, McGill University (Montreal, Canada);
(2) Chronic Viral Illness Service, McGill University Health Centre (Montreal, Canada)

Background: Results from studies that have examined HCV prognostic markers and mortality have been conflicting. One study from Denmark, which reported high mortality in HCV-HIV co-infected subjects, found no association between viral replication and all-cause mortality, while other European studies have reported a strong association between HCV RNA status and liver disease mortality.

Purpose: We examined the association between the presence of replicating HCV RNA and all-cause mortality and liver disease-related mortality in HCV-HIV co-infected patients, taking into account that patients may change HCV RNA status during follow-up through treatment, spontaneous clearance, or reinfection.

Method: We utilized data from the Canadian Co-Infection Cohort, which has recruited 1,209 HCV-HIV co-infected patients as of July 2013. Demographic, behavioral, and clinical information was obtained at cohort entry and during subsequent study visits, which were scheduled every six months. Viral replication was measured through qualitative HCV RNA serum analysis (Roche AMPLICOR HCV Test). Mortality was ascertained from clinical reports and linked to vital statistics and was classified independently by two principal investigators following the Coding of Death in HIV (CoDe) system. Patients were excluded if they had only a baseline visit (n=129) or did not have any HCV RNA tests (n=52). When HCV RNA was missing during follow-up, we carried forward the last available result. Time-dependent Cox Proportional Hazards models were used to model the association between HCV RNA status and all-cause mortality, with adjustment for sex, HCV genotype and time-updated age, CD4+ cell count, intravenous injection drug use, liver fibrosis (APRI ≥1.5), and HCV treatment use. A secondary analysis considered the association between HCV RNA and liver disease-related mortality, with adjustment for the same covariates.

Result(s): We included 1,028 co-infected patients in our analysis. There were 135 deaths (13%) during 3,767 person-years of follow-up, yielding a mortality rate of 358 per 10,000 person-years. The most frequent causes of death were end-stage liver disease (n=26, 19%), overdose (n=23, 17%) and cancer (n=13, 10%). At baseline, 822 patients (80%) were HCV RNA positive, 132 (13%) were HCV RNA negative, and 74 (7%) had unknown HCV RNA status. Compared to those who were HCV RNA negative at baseline, patients who were HCV RNA positive were more likely to be injection drug users (37% vs. 28%), be HCV treatment naïve (87% vs. 70%), and have liver fibrosis (23% vs. 2%). After adjustment, being HCV RNA positive was independently associated with a 1.71 times greater risk of all-cause mortality (95% CI: 1.02 – 2.88), compared to those who were HCV RNA negative when death occurred (Table). For liver disease-related deaths, being HCV RNA positive was associated with a 1.75 times greater risk of mortality (95% CI: 0.38 – 8.10), after adjustment for confounders, although the number of events was small.

Conclusion(s): HCV RNA positive co-infected patients had a greater risk of death overall than those who experienced a sustained virologic response or cleared the infection. This suggests that HCV eradication from HCV antiviral therapy may provide benefits to more than just liver disease-related mortality.

Funding source(f): CIHR doctoral award in HIV/AIDS research.

Posters - Affiches

Clinical Sciences

Poster number: 100

ROMIPLOSTIM'S EFFECT TO OPTIMIZE SVR WITH TELAPREVIR, RIBAVIRIN, AND PEG INTERFERON-ALFA 2A IN THROMBOCYTOPENIC CIRRHOTICS WITH CHC. RESTRAINT-C TRIAL

P Patrick Basu (1), Niraj James Shah (2), Mark Aloysius (3), Ravi Siriki (3), Md Rahaman (3)

(1) Columbia University College of Physicians and Surgeons, NY, NSLIJHS/ Hofstra North Shore LIJ School of Medicine, NY (Pelham Manor, United States); (2) James J. Peters VA Medical Center, Mount Sinai School of Medicine, NY (New York, United States); (3) NSLIJHS/ Hofstra North Shore LIJ School of Medicine, NY (New York, United States)

Background: Treating CHC (Chronic hepatitis C) cirrhotic patients with thrombocytopenia is often challenging; requiring dose reduction or even discontinuation of treatment to avoid complications. Significant dose reduction affects the response guided therapy (RGT); adversely affecting outcomes. Thrombopoietin (TPO) agonists are used to avoid disruption or therapeutic failure to optimize SVR (Sustained Virological response).

Purpose: This study evaluated the use of TPO agonist in thrombocytopenia in cirrhotics with treatment experienced CHC-GT1 (CHC-Genotype 1) on treatment with Telaprevir, Ribavirin (RBV) and Peg Interferon-alfa 2a (p-IFNα-2a).

Method: Total of Forty five (n=45) cirrhotic treatment experienced CHC-GT1 patients with a mean MELD of 16 and mean platelet count 95 thousand were recruited and subdivided into three groups. Group A- (n=15) Received placebo plus reduced dose of p-IFNα-2a with RBV and Telaprevir. Group B (n=15) Received Romiplostim 500 mcg lead in 1 month prior to initiation of therapy and SOC with Telaprevir. Group C (n=15) Received Elthrombopag 50mg orally daily lead in prior 15 days and SOC with Telaprevir for 12 weeks. RGT was analyzed with serial platelet counts, hemoglobin/hematocrit, absolute neutrophils count and platelet antibodies. HCV RNA quantitative count was measured at 1ST, 2ND, 4TH, 12TH 24TH, 36TH and 60th weeks for SVR

Result(s): See table. (VRVR- Very Rapid Virological Response, ETVR- End to treatment Virological Response, R- Relapser, PR- Partial Responder, BT- Break through)

Conclusion(s): This study demonstrates the efficacy of Romiplostim in thrombocytopenic cirrhotics with treatment experienced CHC-GT1 in optimizing SVR (Group A- 53%, Group B- 67% and Group C- 60%). A larger trial is needed to validate.

Poster number: 101

TELAPREVIR WITH ADJUSTED DOSE OF RIBAVIRIN IN NAIVE CHC-G1: EFFICACY AND TREATMENT IN CHC IN HEMODIALYSIS POPULATION. TARGET-C TRIAL

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Background: The prevalence of Chronic hepatitis C (CHC) in Hemodialysis population is 3%. Standard of care (SOC) offers reduced dose of Peg IFN Alfa (p-IFNα) and reduced Ribavirin (RBV) doses eliciting sub optimal SVR of 27%. Morbidity and mortality of CHC has impact on liver kidney transplant and graft failure. Triple therapy is SOC in CHC patients. Telaprevir is not cleared renally and hence is safe in the hemo-dialysis population

Purpose: This study evaluated the efficacy of triple therapy with Telaprevir, adjusted dose of RBV and p-IFNα in naïve CHC-G1(CHC Genotype 1) individuals on hemodialysis as a Respond Guided Therapy (RGT)

Method: Total of thirty five (n=36) na ve CHC-G1 were recruited and subdivided into three sub-groups.
Group A - (n=12): p-IFN 135mcg weekly for 24 weeks, Telaprevir 750mg two tablets – TID for four days and three tablets BID post dialysis for three days for first 12 weeks. RBV 400mg daily for 24 weeks.
Group B - (n=12): p-IFN 135mcg weekly for 36 weeks, Telaprevir 750mg two tablets – TID for four days and three tablets BID post dialysis for three days for first 12 weeks. RBV 400mg daily for 36 weeks.
Group C - (n=12): p-IFN 135mcg weekly for 48 weeks, No Telaprevir. RBV 400mg daily for 48 weeks.

The IL28B was evaluated for all individuals. Hematological, Liver and renal parameters were followed regularly during the trial. Viral load was followed to evaluate for response guided therapy (RGT) in all individuals.

Result(s): See table (VRVR- Very Rapid Virological Response, ETVR- End to treatment Virological Response)

Conclusion(s): This study demonstrates higher SVR comparing traditional SOC on hemodialysis CHC-G1 patients. The extended 48 weeks of therapy showed no added benefits. Multi-center trials to follow.

Poster number: 102

SUBCLINICAL CIRRHOSIS: AN EMERGING CLINICAL ENTITY IN CHRONIC HEPATITIS C

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Background: Chronic hepatitis C virus (CHC) is a major cause of hepatocellular carcinoma (HCC) and a leading indication for liver transplantation in Canada. Identifying affected individuals with advanced fibrosis is crucial for prognosis and treatment decisions. However, in 20% of cases cirrhosis is diagnosed only after end-stage complications arise, mainly due to the lack of clinical signs at the subclinical stage of the disease.

Purpose: Transient elastography (Fibroscan) proved to be highly accurate for the non-invasive diagnosis of cirrhosis, but its value for the diagnosis of subclinical cirrhosis is unknown.

Method: Between November 2009 and April 2013, a valid Fibroscan was obtained in 406 consecutive patients with either HCV mono-infection or HIV/HCV co-infection in our centre. Unreliable Fibroscan (failure, IQR>30%, <10 valid measures, risk of false positivity) were excluded. Patients were divided into three groups: subclinical cirrhosis (Fibroscan>13kPa and absence of thrombocytopenia, ultrasonographic signs of advanced liver disease/splenomegaly, esophageal varices, ascites); clinically overt (CO) cirrhosis (Fibroscan>13kPa with any of the above mentioned signs); and non-cirrhotic CHC (Fibroscan<13kPa).

Result(s): During a mean follow-up of 13 months (range 6-36, 49% of patients had >12 months), we evaluated longitudinally the clinical outcome of subclinical cirrhosis as compared to CO cirrhosis and non-cirrhotic CHC groups. The outcomes were determined by cumulative incidence of complications related to cirrhosis during the follow-up period. Overall, the distribution of the study groups was as follows: 63 patients (15.5%) had subclinical cirrhosis, 99 (24.4%) had CO cirrhosis, 244 (60.1%) had non-cirrhotic CHC. Of the total 162 cases with Fibroscan>13kPa indicating cirrhosis, subclinical cirrhosis represented 38.9%. As compared to non-cirrhotic CHC, subclinical cirrhosis patients were older (53 vs 49 yrs, p=0.008), had higher BMI (28 vs 25, p<0.001) and higher values of fibrosis biomarkers, including APRI (1.1 vs 0.7, p<0.05) and Fib-4 (1.9 vs 1.6, p<0.05). Importantly, during the longitudinal follow-up, the subclinical cirrhosis group had a higher incidence of cirrhosis-related events as compared to non-cirrhotic CHC group, including HCC (Table).

Conclusion(s): Subclinical cirrhosis diagnosed by Fibroscan represents 38.9% of the HCV patients with cirrhosis and 15.5% of all CHC patients seen in a liver unit. Serious complications, including HCC, may develop in this patient population. Early identification of subclinical cirrhosis, by incorporating Fibroscan into the initial assessment, can help facilitate risk stratification of these HCV patients and to establish a surveillance program for HCC and varices.

Funding source(f): Internal funding

Poster number: 103

SIMEPREVIR (TMC435) PLUS PEGINTERFERON/RIBAVIRIN IN PATIENTS CO-INFECTED WITH HCV GENOTYPE-1 AND HIV-1: PRIMARY ANALYSIS OF THE C212 STUDY

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Background: HIV co-infection accelerates progression of HCV-associated liver disease. Simeprevir is a potent, oral, HCV NS3/4A protease inhibitor in late-stage development for the treatment of chronic HCV infection. Given once-daily (QD) as a single pill, simeprevir is active against HCV genotypes 1, 2, 4, 5 and 6, with a favourable safety profile.

Purpose: This Phase III, open-label trial evaluated the safety and efficacy of simeprevir (versus historic controls) in patients co-infected with HCV genotype-1 and HIV-1

Method: Patients received simeprevir (150 mg QD) with peginterferon and ribavirin (PR) for 12 weeks. Treatment-naïve patients and prior relapsers (without cirrhosis) received response-guided therapy (RGT) with PR up to 24 or 48 weeks. All other patients (prior null responders, -partial responders and all patients with cirrhosis) received PR up to 48 weeks. The primary endpoint was the sustained virologic response (SVR) rate 12 weeks after end of treatment (EOT).

Result(s): 106 patients were enrolled and treated, 93 were receiving HAART. SVR12 rates were 79.2% in HCV treatment-naive patients, 57.1% in prior null responders (both $p<0.001$ versus historic controls; ITT), 86.7% in -relapsers and 70.0% in -partial responders (Table 1). Most eligible patients (88.5%; 54/61) met RGT criteria, 87% (47/54) of whom achieved SVR12. SVR12 rates were high irrespective of baseline Metavir fibrosis score: 80.0% and 63.6% overall for patients with of F0–F2 and F3–F4 respectively although sub-groups were small (Table 1). Up to Week 12, the most common adverse events (AEs) were consistent with peginterferon-based therapy (fatigue, headache, nausea, neutropenia). Most AEs were grade 1 or 2. Serious AEs occurred in 5.7% of patients, none were fatal.

Conclusion(s): Simeprevir was generally well tolerated with safety similar to studies in patients without HIV and high SVR12 rates in HCV treatment-naïve patients, prior null-responders, -partial responders and -relapsers co-infected with HIV-1.

Funding source(f): Please note that the entire abstract is attached to the submission and should be considered as is. I am submitting on behalf of Dre Marina Klein. Thank you. Elyse

Poster number: 104

RIBAVIRIN MONOTHERAPY CONTROLS HEPATITIS FLARES IN HCV INFECTED PATIENTS UNDERGOING CHEMOTHERAPY FOR HEMATOLOGICAL MALIGNANCIES

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Background: HCV-related hepatitis flares during cancer chemotherapy are associated with progressive liver disease and increased malignancy relapse rates. Immunesuppresssion and blood cytopenias caused by cancer chemotherapy, however, prompt for an alternative therapy than interferon to control hepatitis flares.

Purpose: This study evaluates the role of ribavirin monotherapy in normalizing transaminases in HCV-infected patients with hematological malignancies undergoing long-term chemotherapy.

Method: This study included 65 (M: F 38: 27) children and adolescents with hematologic malignancies on chemotherapy; 23 HCV-RNA+ patients on ribavirin monotherapy (15 mg/kgbw/d; indicated for ALT flares>5X UNL) (group I), 19 HCV-RNA+ patients receiving no antiviral therapy (group II) and 23 HCV-RNA negative patients on chemotherapy (group III). ALT levels were recorded every 3 months for an average of 2 years following HCV diagnosis and at every phase of chemotherapy. The number of hepatitis flares, hemoglobin level, total bilirubin level, and HCV viral load were compared pre- and during ribavirin therapy and between the three groups.

Result(s): The mean duration of ribavirin monotherapy in group I was 17 months (±9.2 SD; range 6-36 months). Comparing the 3 groups, ALT level was higher in group I in the first 6 months following HCV diagnosis, and then declined to be comparable with group II, yet both groups had higher levels than controls especially during the intensification and continuation phases of chemotherapy. Group III had lower number of hepatitis flares than groups I and II (P<0.0001) with a shorter duration than group I (P=0.002). A significant decline in ALT level (median: 116 IU/L; interquartile range (IQR) 92-201) (P<0.0001) and number of hepatitis flares (median: 1; IQR: 0-2) (P=0.02) were recorded during ribavirin therapy compared to before therapy (median: 612 IU/L IQR: 426-904; median: 2, IQR: 1-3 respectively). Accordingly no further modification of chemotherapy doses was noted. Although HCV viral load decreased after ribavirin therapy, the difference was not statistically significant. No significant decline in hemoglobin level post ribavirin therapy was recorded yet the total bilirubin levels significantly increased after therapy.

Conclusion(s): Ribavirin monotherapy, administered concurrently with chemotherapy, is effective in controlling hepatitis flares in HCV-infected cancer patients, yet its effect on the HCV viral load is not satisfactory. Access to newer therapies for treatment of children and adolescents during chemotherapy is crucial to prevent relentless progression of liver disease.

Funding source(f): Ain Shams University

Poster number: 105

ASSESSMENT AND TREATMENT FOR HCV INFECTION AMONG PEOPLE WHO INJECT DRUGS IN THE OPIOID SUBSTITUTION SETTING: THE ETHOS STUDY

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Background: Access to hepatitis C virus (HCV) treatment remains extremely limited among people who inject drugs (PWID). It is important to evaluate strategies to enhance HCV assessment and treatment among this group, given that they are the core of the HCV epidemic among many high-income and middle-income countries.

Purpose: HCV assessment and treatment was evaluated through an innovative model for the provision of HCV care among PWID with chronic HCV infection.

Method: The Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) study is a prospective observational cohort, evaluating an innovative model for the provision of HCV assessment and treatment among people with a history of injecting drug use and chronic HCV. Recruitment occurred between 2007 and 2012 through five opioid substitution therapy (OST) clinics, two community health centres and one Aboriginal community controlled health organization in New South Wales, Australia. Follow-up is ongoing; however, a preliminary treatment analysis was undertaken. Participants initiating pegylated interferon/ribavirin (PEG-IFN/RBV) treatment between February 2009 and December 2011 (genotype 1, G1) or June 2012 (genotypes 2/3, G2/3) were included to allow adequate follow-up. Statistical analyses were performed using Chi-squared or Fisher's exact tests, as appropriate.

Result(s): Among 387 enrolled participants, mean age was 41 years, 71% were male, and 15% were of Aboriginal ethnicity. Specialist assessment was undertaken in 191 (49%) participants, and 84 (22%) commenced interferon-based treatment. In adjusted analysis, HCV treatment was associated with non-Aboriginal ethnicity (AOR, 4.59; 95% CI, 1.49-14.12), living with the support of family and/or friends (AOR, 2.15; 95% CI, 1.25-3.71), never receiving OST (AOR, 4.40; 95% CI, 2.27-8.54), no recent methamphetamine use (AOR, 2.26; 95% CI, 1.12-4.57), and non-1 HCV genotype (AOR, 3.07; 95% CI, 1.67-5.64). Among those treated between 2009 and 2012 (n=73, mean age 43 years, 77% male), 30% (n=22) had injected drugs in the past six months and 56% (n=41) were currently receiving either methadone or buprenorphine. In an intent-to-treat analysis, the sustained virological response (SVR) was 68% overall (50 of 73), 81% in G1 (17 of 21) and 63% in G2/3 (33 of 52). There was no difference in SVR between those never receiving OST (70%, 19 of 27) and those currently receiving OST (71%, 29 of 41, 0.99). SVR was lower in those with no injecting drug use in the past six months (30 of 50, 60%) compared to those with injecting drug use in the past six months (20 of 23, 87% P=0.027).

Conclusion(s): HCV treatment uptake and response to PEG-IFN/RBV treatment was relatively high among this highly marginalized population of PWID. Potentially modifiable factors associated with treatment uptake include drug use and social support. These data suggest that programs to enhance HCV treatment in OST or community health clinics can be successful. The expansion of HCV assessment and treatment services to clinics already offering drug and alcohol care is a feasible strategy to improve treatment access among PWID.

Funding source(f): National Health and Medical Research Council and New South Wales Health.

Poster number: 106

FALDAPREVIR PLUS PEGYLATED INTERFERON/RIBAVIRIN FOR 12 WEEKS IS AS EFFECTIVE AS 24 WEEKS TREATMENT IN PATIENTS WITH HCV GENOTYPE-1 INFECTION

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Background: Faldaprevir is a potent NS3/4A protease inhibitor that, when used in combination with pegylated interferon α-2a and ribavirin (PR), has demonstrated high SVR rates in Phase III trials of patients with HCV genotype-1 infection. The majority of patients achieved early treatment success (ETS, defined as HCV RNA <25 IU/mL at Week 4 and HCV RNA undetectable at Week 8) and we sought to compare virologic outcomes with 12 versus 24 weeks of faldaprevir 120 mg treatment (plus PR) in patients enrolled in the Phase III STARTVerso1 and 2 trials.

Method: In STARTVerso1 and 2, treatment-naïve patients infected with HCV genotype-1 were randomized 1: 2: 2 to receive 48 weeks of PR plus: placebo for 24 weeks; faldaprevir 120 mg QD for 12 weeks (STARTVerso1, if ETS achieved) or 24 weeks; or faldaprevir 240 mg QD for 12 weeks. Patients receiving faldaprevir stopped all treatment at Week 24 after achieving ETS. The current analysis addresses only patients receiving faldaprevir 120 mg QD.

Result(s): Virologic outcomes are summarized in the table. The majority of patients (84%) achieved ETS and were eligible for shortened treatment duration (24 weeks). Overall, 73% of patients randomized to faldaprevir 120 mg QD achieved SVR12; of these patients, 95% previously achieved ETS. SVR12, virologic breakthrough and relapse rates were similar in all patients who achieved ETS regardless of faldaprevir treatment duration.

Conclusion(s): In treatment-naïve patients with HCV genotype-1 infection who achieved ETS on faldaprevir 120 mg 12 or 24 weeks (plus PR), the shorter course of faldaprevir did not seem to adversely affect virologic outcome.

Funding source(f): Boehringer Ingelheim Pharmaceuticals

Poster number: 107

ENTENTE (ENGAGE-TEST-ENGAGE-TREAT-ENGAGE): A MODEL OF CARE DESIGNED FOR HCV-INFECTED SUBSTANCE USERS

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Background: Unique models of care need to be developed to engage and treat inner city substance users with high HCV prevalence rates (>70%). Traditional models of health care delivery have not been effective, leading to treatment of 5% or less of the target population. We have developed and begun to evaluate a unique multidisciplinary program to address this issue.

Method: Through a community-academic partnership, we have designed the EnTEnTE program. Initial engagement occurs at one of four fixed sites frequented by inner city substance users to obtain meals and/or services. We engage up to 30 individuals/event, offering point-of-care testing for HCV antibodies using the OraSure technology. Alternatively, if an individual's HCV status is known, we offer on-the-spot consultation to review and interpret prior test results. Same week tertiary care appointments are offered for follow-up. These are held in conjunction with peer-support groups at which food is served and multi-disciplinary care is offered to address urgent health and social needs. Patients are offered HCV treatment as medically indicated. If treatment proceeds, weekly interferon injections are administered in the clinic, along with weekly dispensing of other medications, comprehensive medical support of side effects and any other required clinical or social interventions.

Result(s): The addition of the point-of-care testing and immediate specialist consultation service to our previous model has increased uptake significantly and allows new engagement of a median of 8 individuals/event (regularly attending clinic in the next 2 months). Over the past 6 months, there have been 33 treatment starts. Key baseline characteristics include: 25 male, 5 HIV co-infected, 22 genotype 1, 25 previously treatment naïve. Through week 12 of treatment, 91% patients remain engaged in care. Additional results of virologic efficacy will be presented.

Conclusion(s): The addition of point-of-care testing and immediate specialist consultation has enhanced community-based efforts to recruit and engage HCV-infected substance users who do not traditionally seek medical care, often despite prior knowledge of their HCV infection status. This will be an important tool in our strategy to address the HCV epidemic in our inner city.

Poster number: 108

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

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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 partly relates to concerns about re-infection following successful 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 70 cases of HCV therapy having resulted in a sustained virologic response (SVR) in which patients continued to engage in significant 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 (i.e. other than undetectable) following the clear establishment that an SVR had occurred.

Result(s): Among the 70 eligible patients, there were 67 males, mean age of 53 years. Disease characteristics included: 13 HIV co-infected, 51 genotype 1, 56 previously treatment naïve. In a mean of 1.98 person-years of follow-up/subject, 4 cases of re-infection were noted (2.89/100 person-years) with 3 of the re-infections being noted in co-infected patients and 3 being genotype 1. The only factor associated with an increased risk of re-infection was frequent use of stimulants. If our overall study population is considered (138 successful courses of HCV therapy in PWID), the effective rate of re-infection is 1.47/100 person-years.

Conclusion(s): PWID successfully treated for HCV infection experience re-infection at a much lower rate than previously encountered in uninfected at-risk individuals, and this negative outcome is most often associated with stimulant use. As more HCV-infected PWID are treated, strategies are needed to deal with ongoing high-risk addiction behaviors to maximize the benefits of the intervention and further reduce the rate of re-infection.

Poster number: 109

HCV TREATMENT OUTCOMES IN INNER CITY HIV/HCV CO-INFECTED INDIVIDUALS

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Background: To determine HCV treatment outcomes and predictors of sustained virologic response (SVR) in HIV/HCV co-infected individuals from an inner city population in a "real-world" clinical setting.

Method: A retrospective observational study was conducted in HIV/HCV co-infected individuals seen at an inner city clinic in Vancouver between January 2002 and June 2013. Data with respect to HCV diagnosis and treatment including baseline characteristics, HIV co-infection status, and lifestyle-related co-morbid conditions were collected through chart review, with patient informed consent. Both treatment naïve and treatment experienced individuals were included. Those who were still on treatment and those whose treatment information was unavailable were excluded from this analysis. HCV treatment responses were evaluated, and multivariable logistic regression was performed to identify the predictors of sustained virologic response (SVR).

Result(s): Data were available for a total of 38 treatment courses in 33 patients (31 male), median age 50 years, 90% genotype 1, 16% compensated cirrhotic, and 90% on antiretroviral therapy. The median baseline CD4 cell count was 490/mm3 and HIV virologic suppression was observed in 27 (71%) cases. Other co-morbid conditions included: past (87%) or current (34%) illicit drug use, past (55%) or current (24%) ethanol abuse, and past (46%) or current (36%) methadone maintenance therapy. Treatment outcomes included: premature discontinuation due to toxicity (8%), null/partial response (33%), relapse (11%), SVR (50%). At the end of HCV treatment, the median CD4 cell count decreased to 290/mm3 while HIV virologic suppression was achieved/maintained in 29 (85%) cases. In multivariable analysis, no clinical or behavioral predictors of SVR were identified.

Conclusion(s): HCV infection can be treated successfully in inner city HIV/HCV co-infected individuals with response rates approaching those seen in other populations, despite the prevalence of identified co-morbidities thought to affect such response rates, especially in this vulnerable population.

Biomedical Sciences

Poster number: 200

DYNAMICS OF THE VIRUS-SPECIFIC CD8 T-CELL REPERTOIRE DURING HCV REINFECTION

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Background: We have previously demonstrated that protection against chronic HCV upon reinfection correlates with expansion of virus-specific effector memory T cells and higher polyfunctional potential. In addition, we observed increased breadth and shifting epitope dominance suggesting generation of de novo T cell responses. In contrast, viral persistence was associated with limited expansion of virus-specific T cells and infection with variant viral strains. In this follow-up study, we examined the dynamics of the T cell receptor (TCR) repertoire relative to changes in the sequences of infecting HCV variants.

Purpose: Our objectives were: 1) to distinguish the role of pre-existing memory versus de novo T cell responses in protection; and 2) to determine the importance of flexibility in the T-cell repertoire in controlling infection with variant viruses.

We hypothesize that CD8 T cell clonotypes bearing specific TCRs will provide superior control of infection due to having higher functional avidity and flexibility that will enable efficient recognition of different viral variants.

Method: Longitudinal analysis of the HCV-specific T cell repertoire during HCV reinfection was performed in two groups of patients who spontaneously resolved two successive HCV infections (SR/SR group) or who spontaneously resolved the first infection but became persistently infected upon reinfection (SR/CI group). HCV-specific CD8 T cells identified by MHC class I tetramer staining were sorted before, during and after reinfection. High-throughput sequencing technology was used to sequence the TCR beta chain repertoire of sorted cells. The TCR repertoire from naïve (CD8+ CD45RO-) T cells was sequenced as control. Functional avidity, defined by measuring the dose-dependent production of IFN-g in response to stimulation by the different viral sequences in an ELISPOT assay, was tested at the same time points.

Result(s): Preliminary results of TCR beta chain repertoire sequencing indicate that the T cell clonotypes forming the effector population at the peak of the immune response during reinfection in the SR/SR group were recruited from the memory population generated following the clearance of the primary infection. Indeed, no new T cell clonotypes were detected after reinfection, but a change in relative dominance between different clonotypes was observed. HCV-specific T cells in SR/CI patients demonstrated higher functional avidity for the epitopes present in the original reference sequences as compared to autologous sequences of the reinfecting virus.

Conclusion(s): These results suggest that HCV-specific effector CD8 T cell clonotypes associated with protection upon reinfection in SR/SR patients were recruited from the memory population rather than representing de novo responses. These clonotypes exhibited higher polyfunctional potential and are expected to have a superior functional avidity and flexibility.

Funding source(f): Supported by CIHR, FRQS and Alberta Innovates-Health Solutions

Poster number: 201

DYNAMIC INTERACTION OF THE HEPATITIS C VIRUS HELICASE WITH ITS NUCLEIC ACID SUBSTRATE

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Background: The hepatitis C virus (HCV) non-structural protein 3 contains a helicase (NS3h) activity in its C-terminal domain essential for viral replication. NS3h binds to single-stranded (ss) regions of nucleic acids and unwinds duplexes in an NTP-dependent manner. The mechanism by which NS3h disrupts secondary structure in the viral genome to make way for the replication machinery remains elusive. Several mechanisms have been proposed, which include an active mechanism whereby the helicase actively engages the ss/double-stranded (ds) junction of its nucleic acid substrate and disrupts the duplex, and a passive mechanism where the helicase binds and translocates along a ss nucleic acid overhang, taking advantage of transient melting of the ss/ds junction.

Purpose: Here, we investigate the dynamic interaction between the helicase and a nucleic acid substrate using a fluorescence-based assay in an attempt to establish where binding to the substrate occurs.

Method: Positioning of the helicase on a nucleic acid substrate with a ss/ds junction was monitored using a fluorescence-based assay. We use this approach to determine the location of the enzyme on the substrate based on the increased intensity of a fluorescence signal upon proximal binding of a protein to a fluorescent dye attached to the nucleic acid, a process referred to as protein induced fluorescence enhancement (PIFE).

Result(s): The helicase binds to the ss substrate with a footprint of approximately 6 bases. Designing a substrate fluorescently labeled at the ss/ds junction with a ss overhang of 6 bases ensures that a single helicase molecule will bind to the substrate and be positioned directly at the junction. Addition of NS3h to this substrate resulted in strong fluorescence enhancement, showing conclusively that the helicase bound at the junction. The length of the ss region of the substrate was then increased, providing the opportunity for the helicase to bind the ss substrate at an increased distance from the ss/ds junction. As the length of the ss overhang increased, fluorescence enhancement decreased, suggesting that the enzyme does not preferentially bind at the ss/ds junction, but rather can bind non-specifically along the ss overhang.

Conclusion(s): The work presented here validates the use of PIFE to study the positioning of the helicase relative to the ss/ds junction of the nucleic acid substrate. Furthermore, our studies offer insight into the dynamic interactions between the helicase and its substrate. NS3h appears to bind the ss overhang randomly, with no evidence for a specific complex that is trapped at the ss/ds junction. Based on our preliminary data, it appears that the helicase may bind the ss substrate and translocate until arriving at the ss/ds junction where it unwinds the duplex. The data supports a Brownian motor passive mechanism of unwinding, where the enzyme does not directly engage the ss/ds junction. A deeper understanding of the mechanism by which the helicase interacts with its substrate will help elucidate its role in the viral life cycle.

Funding source(f): C.A. is the recipient of a student award from the NCRTP-HepC, and this project was funded by a Grant from CIHR to M.G. and G.C.

Poster number: 202

REDUCED ACTIVITY OF CD8+ T CELLS IN RESPONSE TO IL-7 IN HCV MONO- AND HIV-HCV CO-INFECTION

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Background: Effective immune responses against hepatitis C virus (HCV) are dependent on CD8+ T cells, yet their function is impaired in chronic infection. CD8+ T cell impairment is also a feature of chronic HIV infection, where it is associated with decreased activity of IL-7. HCV is the most prevalent co-morbidity in HIV, yet the effect of HCV on HIV infection remains largely unknown. IL-7 is critical for CD8+ T cell development, and important for T cell homeostasis, memory cell generation, and cytolytic function. CD8+ T cell responses to IL-7 are dependent on the expression of IL-7 receptor alpha on the cell membrane (mCD127). Reduced mCD127 expression, increased plasma soluble CD127 (sCD127) levels, or cellular deficiencies in IL-7 signalling may contribute to impairment, as we reported in HIV infection.

Purpose: The purpose of this study is to determine if CD8+ T cell activity is impaired in chronic HCV infection in response to IL-7, and subsequently if this IL-7 response contributes to CD8+ T cell dysfunction in HCV infection. The hypothesis of this study is that HCV infection decreases CD8+ T cell activity, specifically IL-7 responsiveness, in both HCV and HIV-HCV infection.

Method: CD8+ T cells were isolated from blood from healthy donors (controls) as well as individuals with untreated HCV infection and HIV-HCV co-infected individuals on successful HAART treatment (< 50 copies/ml HIV RNA), provided by the Viral Hepatitis Clinic at the Ottawa Hospital-General Campus. Expression of mCD127 on CD8+ T cells and plasma sCD127 levels were measured by flow cytometry and immunobead assays, respectively. IL-7-induced signalling (STAT5 phosphorylation), proliferation, and production of the anti-apoptotic molecule Bcl-2 were measured by flow cytometry. Dose responses were assessed by regression analysis ($P < 0.05$).

Result(s): There was no significant difference in mCD127 expression on blood-derived bulk CD8+ T cells or plasma sCD127 levels between control, HCV and HIV-HCV infection. IL-7-induced STAT5 phosphorylation was significantly reduced ($p = 0.005$) in CD8+ T cells from HCV infection compared to controls, with no statistical difference between HCV mono- and HIV-HCV co-infection. There is a trend that cell division of CD8+ T cells cultured with suboptimal amounts of T cell stimulator (PHA) is of lower magnitude in HCV mono- and HIV-HCV co-infection than controls. Lastly, the production of Bcl-2 in response to IL-7 was significantly reduced in CD8+ T cells of HCV and HIV-HCV infected individuals compared to controls ($p<0.0001$ and 0.03, respectively).

Conclusion(s): These results suggest that CD8+ T cell impairment in HCV infection is characterized by decreased responsiveness to IL-7, independent of mCD127 expression, in contrast to what is observed in HIV infection. One mechanism of CD8+ T cell impairment may be through IL-7-stimulated signalling, as it is known that IL-7 functions depend largely on STAT5 signaling. Identifying the mechanisms of CD8+ T cell impairment in HCV infection has implications in the design of novel treatments, namely cytokine directed immunotherapies.

Funding source(f): Funding was provided by Canadian Foundation for AIDS Research, Ontario HIV Treatment Network, and J.P. Bickell Foundation.

Poster number: 203

HCV UPREGULATES T CELL EXPRESSION OF CD5 IN VITRO AND CHRONIC HEPATITIS C COINCIDES WITH CD5 OVEREXPRESSION IN T LYMPHOCYTES

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Background: Hepatitis C virus (HCV) infects and can productively replicate in cells of the immune system, including T lymphocytes (MacParland et al., JGV 2006;87: 3577 & Hepatology 2009;49: 133). CD5, an important pan T-cell-specific receptor modulating T cell development, activation and survival, has been identified to be essential for infection of human T lymphocytes with native, patient-derived HCV (Sarhan et al., JVI 2012 & Plos One 2013). T lymphocyte CD5 expression has not been investigated in HCV infection.

Purpose: To determine expression of CD5 in T lymphocytes, their CD4+ and CD8+ subsets and B cells from patients with progressing chronic hepatitis C (CHC) and in control healthy donors. To assess the effect of de novo infection of T cells with naturally occurring HCV on CD5 expression in vitro.

Method: Peripheral CD4+ and CD8+ T cells and B lymphocytes were purified from peripheral blood mononuclear cells (PBMC) isolated from treatment naïve patients with CHC infected with HCV G1 (n=9) and healthy donors (n=7) using stepwise Miltenyi microbead-based immunoaffinity approach. Jurkat T cells (ATCC TIB-152) were infected with plasma-derived HCV G1or exposed to the equivalent amount of normal human plasma (NHP) and cultured for 5 days in 4 independent experiments. CD5, CD81 and hypoxanthine phosphoribosyltransferase (HPRT) expression, and HCV RNA content in individual cell subsets were quantified by appropriate specific real-time RT-PCR assays.

Result(s): A significant increase of CD5 expression was found in T lymphocytes from patients infected with HCV compared to those derived from healthy controls ($P=0.003$), while CD5 expression in B cells from both study groups did not differ ($P=0.08$). Both CD4+ and CD8+ T cell subsets from infected patients displayed significantly augmented expression of CD5 when compared to the cells from healthy donors ($P<0.05$ and $P<0.01$, respectively). Overall, total T lymphocytes transcribed meaningfully more CD5 than B cells derived from either CHC patients or healthy individuals ($P<0.0001$). HCV RNA was detected at significantly greater levels in B cells than in CD4+ or CD8+ T cells of CHC patients ($P<0.03$). Similarly to primary T cells from patients with CHC, Jurkat T cells infected with patient-derived HCV showed a significant augmentation in CD5 transcription compared to cells exposed to NHP ($P=0.01$). In contrast, HCV significantly downregulated expression of CD81 in vitro infected T cells ($P=0.001$). This finding is currently being evaluated in primary T cells isolated from HCV-infected patients.

Conclusion(s): Due to multifarious T cell regulatory functions of CD5, its selectively augmented expression in T cells, but not in B cells, of patients infected with HCV and in in vitro infected T cell line suggests its importance in the HCV infection process. Upregulation of CD5 expression may protect T cells from apoptosis and allow for more prolonged and robust HCV replication in the cells infected. This event may also influence activation and proliferation of CD4+ and CD8+ T lymphocytes in HCV-infected or co-infected patients.

Funding source(f): Supported by CIHR operating grants MOP-77544 and MOP-126056 awarded to TIM, the Canada Research Chair Program 950-205222 and funds from the Canada Foundation for Innovation.

Poster number: 204

IFN-Λ3 FAVORABLE GENOTYPE CORRELATES WITH DECREASED EXPRESSION OF NKG2A AND IFN-Γ PRODUCTION BY NK CELLS DURING HCV INFECTION

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Background: Single nucleotide polymorphisms (SNPs) (rs12979860) located in the region of the IL28B gene encoding the type III interferon, IFN-λ3, can predict spontaneous resolution of acute hepatitis C virus (HCV) infection. The favorable genotype is defined as CC and the unfavorable genotype as CT or TT (*T). The predictive value of this SNP is enhanced when combined with polymorphisms in the killer cell immunoglobulin-like receptor (KIR) genes controlling the activity of natural killer (NK) cells and with plasma levels of the interferon gamma-induced protein 10 (IP-10), a chemokine that regulates lymphocyte migration to different tissues. This suggests that the IFN-λ3 polymorphism may act at the level of NK cell activation and lymphocyte recruitment.

Purpose: We hypothesized that polymorphism in the IL28B region may modulate the expression of type III IFNs during acute HCV, that may in turn modulate the induction and cross-talk between innate and adaptive immunity including the induction of innate immune genes, as well as activation and recruitment of NK cells and T cells to the liver.

Method: We performed longitudinal quantification of type III IFNs (IFN-λ3 and IFN-λ1 (IL29)) by ELISA in plasma samples collected from a cohort of injection drug users (n=29) during acute HCV infection that progressed to either spontaneous resolution or chronic infection. We used multiparametric flow cytometry to monitor the phenotype and the activity of NK cells.

Result(s): IFN-λ3 plasma levels were higher in HCV infected participants during acute infection than in naive. There was no difference between IFN-λ3 and IFN-λ1 plasma levels regarding IFN-λ3 genotype. We observed a positive correlation between plasma levels of IFN-λ3 and the expression of the inhibitory NK cell receptor NKG2A in individuals carrying the favorable IFN-λ3 genotype ($p<0.0001$). In addition, decreased expression of NKG2A on NK cells during follow-up phase was associated with both HCV spontaneous resolution and the favorable IFN-λ3 genotype. Decreased IFN-γ production by NK cells was observed in individuals with chronic evolution despite carrying the favorable IFN-λ3 genotype. Finally, we observed decreased frequency of NK cells expressing the degranulation marker CD107a that also produce IFN-γ during follow-up phase in individuals carrying the favorable IFN-λ3 genotype irrespective of the outcome of acute HCV.

Conclusion(s): These results suggest that in individuals with the favorable IFN-λ3 genotype, decreased expression of NKG2A might be predictive of spontaneous resolution whereas decreased production of IFN-γ might be predictive of chronic evolution. These results demonstrate that IFN-λ3 polymorphism affect the NK cell phenotype and function but that other factors may also act to determine the outcome of infection.

Funding source(f): NCRTP HepC, CIHR, FRSQ (Réseau SIDA-MI), NIDA

Poster number: 205

ARYLACETAMIDE DEACETYLASE: A NOVEL HOST FACTOR IMPORTANT IN THE LIPOLYSIS OF CELLULAR TRIGLYCERIDE STORES, VLDL ASSEMBLY AND HCV PRODUCTION.

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Background: The current model of HCV production involves the assembly of nascent virions on or near the surface of hepatocellular lipid droplets (LDs). Later stages of virion assembly are thought to occur on the luminal side of the endoplasmic reticulum (ER) membrane, where nascent virions can access the viral envelope E1 and E2 surface glycoproteins, then exit via the secretory pathway in association with very low density lipoproteins (VLDLs). VLDLs are triacylglycerol(TG)-rich lipoproteins assembled within the lumen of the ER. The majority of their TG cargo is derived from the lipolysis of TG stored in hepatocellular LDs. Because important roles for LDs and the VLDL secretory pathway in the cell culture production of infectious hepatitis C virus (HCV) have been established, we hypothesized that TG lipolysis and VLDL production are impaired during HCV infection so that these cellular processes can be diverted towards HCV production.

Purpose: In this study, we set out to examine the possibility that cellular LDs are diverted from their normal role as a VLDL substrate pool to support viral production.

Method: We used an HCV permissive cell culture system (JFH-1/Huh7.5 cells) to examine the relationship between TG lipolysis, VLDL assembly, and the HCV lifecycle using standard biochemical approaches.

Result(s): Lipolysis of cellular TG stores and the production of VLDL were found to be impaired in Huh7.5 cells during the early peak of HCV infection, when HCV had spread to >95% of the cell culture. Activity-based protein profiling and expression analysis established that infected cells had an apparent deficiency for a putative TG lipase, arylacetamide deacetylase (AADAC). Lipolysis of cellular TG stores was restored in infected cells by the re-introduction of AADAC, indicating a role for HCV-mediated downregulation of AADAC in this process. The lipolysis of cellular TG stores and VLDL production were also found to be defective in Huh7.5 cells stably expressing a short hairpin RNA targeting AADAC expression, proving AADAC-deficiency contributes to these defective pathways.

Paradoxically, we found that AADAC has an important role in the HCV replication cycle during the acute phase of HCV infection. We suggest that AADAC-deficiency, which occurred later in the more persistently infected cells present during the early peak of HCV infection, is aimed at limiting viral production. Because reduced lipolysis of cellular TG stores and reduced secretion of VLDL-TG are established causes for the development of hepatic steatosis, AADAC-deficiency may contribute to steatosis in the clinical setting of chronic HCV infection.

Conclusion(s): Very little is known about the cellular lipases that mediate the recruitment of cellular TG stores into the VLDL assembly pathway. This study is the first demonstration that endogenous AADAC has a role in this process, and in the HCV replication cycle. This novel insight into the biology of HCV infection, and possibly pathogenesis, identifies AADAC as a novel and translationally relevant therapeutic target.

Funding source(f): Operating grant from CIHR/IRSC awarded to Drs. Kneteman, Douglas and Lehner, the National CIHR Research Training Program (NCRTP) in Hepatitis C awarded to Dr. Mahra Nourbakhsh, CERC awarded to Dr. Michael Houghton.

Poster number: 206

EXTRACELLULAR MATRIX PROMOTES RESISTANCE OF HEPATOCELLULAR CARCINOMA AGAINST ANTI-CANCER AGENTS IRRESPECTIVE OF THE PRESENCE OF HEPATITIS C NON-STRUCTURAL PROTEINS

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Background: Hepatitis C virus (HCV) is a major risk factor for Hepatocellular Carcinoma (HCC) development. The strong association between advanced liver fibrosis and the development of HCC is well established but not well understood. We have demonstrated that type 1 collagen (COL1) induces a hepatoprotective response mediated by ERK1 pathway in normal hepatocytes.

Purpose: To evaluate whether COL1 is able to induce a state of resistance against anti-cancer agents and whether HCV proteins participate in this phenomenon.

Method: We used 3 HCC cell lines: HuH7 (devoid of HCV proteins), 9-13 (a HuH7 cell line stably transfected with a genotype-1 replicon expressing HCV non-structural proteins) and Tx (9-13 treated with interferon to remove HCV construct). Cell apoptosis was induced by 24h exposure to cisplatinum (CP) [25 µg/mL], a chemotherapeutic agent, on dishes plated or not with COL1 [13.9 µg/cm2]. Cell viability (MTT assay), count of cells showing morphological characteristics of apoptosis (apoptotic rate) and caspase 3 activity were measured. Cell proliferation (cell doubling time) and ERK1 expression by western blot were also evaluated. In order to evaluate the ability of cells to form colonies, a characteristic of neoplastic cells, individual cells were seeded in a soft agar gel containing or not COL1 [695 µg/cm3].

Result(s): Cell viability was significantly higher when HCC cell lines were plated on COL1 compared to plastic (Huh7: 80.2±4.2% vs 65.7±6.3%; $P<0.05$, 9-13: 68.1±3.5% vs 46.6±3.0%; $P=0.01$ and Tx: 74.4 ±5.1% vs 52.4±2.5%; $P<0.05$). HCC cell lines were significantly more resistant to apoptosis induced by CP when plated on COL1 than plastic (apoptotic rate: Huh7: 6.4±0.3% vs 20.3±0.2%; $P<0.01$, 9-13: 9.5±1.2% vs 15.8±1.8%; $P=0.01$ and Tx: 9.3±0.9% vs 22.2±3.4%; $P<0.05$). In addition, when Huh7 cells were plated on 3-fold and 7-fold COL1 concentration, ERK expression was increased respectively by a ratio of 1.2 and 2. Results were similar in 9-13 or Tx cells. Finally the protective effect of COL1 was abolished when cells were co-treated with CP and ERK1/2 inhibitor U0126 [20µM] (apoptotic rate: Huh7: 16.0±1.6%, 9-13: 15.9±2.7% and Tx: 22.2±1.4%). Results were similar when measuring caspase 3 activity. There was no difference in cell proliferation between HCC cell lines plated on COL1 or on plastic (Huh7: 53±6 vs 56±4h, 9-13: 63±4h vs 64±10h and Tx: 40±5h vs 38±3h). When the ability of cell lines to form colonies in soft agar was evaluated, far fewer Huh7 colonies were observed when cells were seeded in the absence of COL1 than in its presence (1.7±0.3 vs 12.7±1.3; $p=0.001$).

Conclusion(s): COL1 promotes resistance against the pro-apoptotic action of CP by an ERK1/2-mediated effect without any effect on cell proliferation. It also increases the tumorigenic potential of Huh cells. These observations seem unaffected by the presence of HCV non-structural proteins.

Funding source(f): NCRTP Program in Hepatits C

Poster number: 207

EFFECT OF RIBONUCLEOTIDE ANALOGS ON HUMAN MITOCHONDRIAL RNA POLYMERASE AND THEIR BIOCHEMICAL IMPACT ON ANTI-HEPATITIS C VIRUS DRUG DEVELOPMENT

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Background: Ribonucleoside triphosphate (rNTP) analog inhibitors represent an important class of compounds against the Hepatitis C virus (HCV) polymerase. Although highly effective against the virus, the structural similarities of these compounds to natural rNTPs may lead to off-target inhibition of human mitochondrial RNA polymerase (POLRMT) and subsequent mitochondrial toxicity.

Purpose: In this study, the structure-activity relationship between rNTP analogs and POLRMT-mediated RNA synthesis was explored. In parallel, we assessed incorporation of rNTP analogs by the HCV polymerase in order to identify chemical modifications that can increase selectivity for the viral polymerase. Finally, in silico modeling was performed to shed light on the role of specific structural elements in POLRMT active site that may affect discrimination against rNTP analogs.

Method: Incorporation profiles of over thirty rNTP analogs were assessed with purified recombinant POLRMT and HCV polymerase NS5B in cell-free RNA synthesis assays. Compounds investigated include inhibitors of HCV polymerase, investigational compounds, and commercially available rNTP analogs. Homology models of POLRMT were made using the crystal structure of the apoenzyme and the active site of the homologous T7 polymerase containing rNTP.

Result(s): Changes at the 2' and 3' positions of the nucleotide ribose moiety exerted a larger discriminatory effect on pyrimidine analogs as compared to purine analogs. Specifically, we also observed that POLRMT incorporation of GTP analogs with ribose moiety modifications were better tolerated over other rNTPs. Modeling suggests a stabilizing role for histidine residue 1125, which may interact with the C-2 amino group of GTP. Additionally, tyrosine residue 999 may provide stacking interactions with purine base moieties, thus allowing chemical changes on the ribose moiety to be tolerated. Finally, simple chemical modifications on the purine portion of GTP rendered this substrate inert against POLRMT while incorporation was still observed with HCV NS5B.

Conclusion(s): Our initial data provide a biochemical rationale for potential risk of increased mitochondrial toxicity with purine analogs. We have identified chemical modifications that can increase selectivity of compounds against POLRMT. These findings have important implications not only for rNTP analogs currently in development against HCV, but also for those in development against other RNA viruses.

Funding source(f): CFAR; NCRTP, American Liver Foundation

Poster number: 208

HCV REPLICATION REQUIRES THE RECRUITMENT OF THE AUTOPHAGY ELONGATION COMPLEX (ATG5-12/16) IN LC3 INDEPENDENT MANNER

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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. Recently, we showed that viral RdRp (NS5B) interacts with ATG5, a major component of autophagy initiation.

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

Result(s): We demonstrate that the elongation complex is recruited at the site of viral replication and acts as a proviral factor. Indeed, ATG5-12 as well as ATG16L1 colocalizes with the viral replicase in infected cells. Furthermore, we show that induction of autophagy-like structures by NS4B results in LC3-II colocalization in transfected cells but not in infected cells. Interestingly, LC3-I is not recruited to the elongation complex at the site of viral replication and no sign of colocalization of LC3-II with viral proteins was observed. Finally, using dominant negative forms of ATG5, ATG12 and ATG4B, we demonstrate that ATG5-12 conjugate is important for viral replication but not LC3-II formation.

Conclusion(s): These findings indicate that HCV uses the autophagy elongation complex as a proviral factor for its own replication but blocks the formation of a genuine autophagosome at the site of viral replication.

Funding source(f): This work was supported by a research grant from NSERC of Canada. Salary support is provided to PL by the FRSQ. AF and MB received fellowships from the NCRTP-HepC and the Fondation Armand-Frappier, respectively.

Poster number: 209

IDENTIFICATION OF RESIDUES WITHIN DOMAIN I OF HCV NON-STRUCTURAL 5A PROTEIN REQUIRED FOR MODULATION OF VIRAL TRANSLATION AND RNA BINDING.

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Background: Hepatitis C virus (HCV) non-structural 5A protein (NS5A) is a multi-functional viral protein that is essential for viral replication. NS5A is composed of three domains separated by regions of low complexity. Various regions of the individual NS5A domains have roles in modulating numerous processes such as viral replication, viral assembly and cellular signaling pathways. However, the role that NS5A and its individual domains may play in modulating viral translation has remained controversial. Previous studies have utilized translation reporter systems that may not accurately reflect the role of the viral 3'UTR in modulating viral translation. This is relevant as we and others have shown that NS5A binds to the poly-U/UC region of the 3'UTR. This protein-RNA interaction and the role of the 3'UTR in stimulating viral translation suggest the potential for modulatory effects on viral translation by NS5A.

Purpose: We set out to determine the role of NS5A and its individual domains in modulating viral translation and the role of the NS5A-poly-U/UC region interaction in this modulation.

Method: Two sets of reporter constructs were utilized: monocistronic RNA reporter constructs which contain the viral 5'and 3'UTRs, with or without the poly-U/UC region and an internal Renilla luciferase reporter gene; as well as full-length HCV genomic RNA reporters either with or without the poly-U/UC region. These reporters were used in combination with either NS5A expression plasmid or NS5A mRNA.

Result(s): We determined that NS5A specifically down-regulates viral translation in a dose-dependent manner through a mechanism dependent upon the presence of the poly-U/UC region of the viral 3'UTR. Additionally, we determined that domain I of NS5A is capable of modulating viral translation and this effect is also dependent upon the presence of the poly-U/UC region. We have identified a 61 aa. region within domain I that is sufficient for this translation down-regulation. Furthermore, we have identified a number of positively charged residues within this region involved in the modulation of viral translation, particularly arginine 112 (R112). This residue has previously been found to be present at the domain I dimer contact interface and forms an intermolecular hydrogen bond with E148. We found that both R112A and E148A mutations negate the ability of domain I to modulate viral translation and these mutations impede the formation of domain I dimers. Additionally, this R112A mutation appears to affect ability of domain I to interact with the poly-U/UC region of the viral 3'UTR alluding to the possible mechanism of translation modulation.

Conclusion(s): These findings suggest that in addition to being essential for viral replication, NS5A has an important role in modulating viral translation through a mechanism requiring the poly-U/UC region of the viral 3'UTR.

Funding source(f): NSERC, NCRTP-HepC

Poster number: 210

NON-INVASIVE DIAGNOSIS OF HEPATITIS C VIRUS-ASSOCIATED LIVER DISEASES BASED ON CIRCULATING MICRORNAS BIOMARKERS

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Background: Hepatitis C virus (HCV) is a globally important human pathogen afflicting more than 170 million people worldwide[1]. HCV infection is a major risk factor for liver cancer and the leading cause of liver transplantation in North America. Up to 80% of individuals who become infected with HCV do not resolve the infection allowing for a persistent "chronic" HCV infection of the liver. In the majority of cases chronic hepatitis C (CHC) infection goes unnoticed (asymptomatic) for up to two decades before liver diseases and cancer manifest, making HCV a "silent killer"[2]. Costs of HCV in Canada are estimated to exceed $650 million per year[3]. With the recent breakthroughs in anti-HCV drugs, CHC is expected to be "curable" in all patients, underlining the urgent need to implement a global CHC screening program that may aid in prioritization, prognostication and treatment planning on an individual and population level basis.

MicroRNAs have a great potential to serve as novel disease-specific biomarkers[4]. MicroRNAs are small non-coding ribonucleic acids that have recently emerged as the regulators of gene expression, while dysregulation of their homeostasis is associated with various human diseases including infectious diseases as well as lung, liver and kidney diseases. Moreover, microRNAs were found circulating in almost all body fluids in a cell-free stable form within small vesicles or as protein complexes[5]. Circulating microRNAs are secreted from healthy and damaged cells and appear to play highly important roles in cell signaling. Therefore, their expression patterns may reflect the development and progression of numerous pathological conditions. Thus, circulating extracellular microRNAs may also mirror different stages of liver disease progression rendering them as an attractive option for developing novel non-invasive disease biomarkers[6].

In this study we aim to investigate the potential of circulating microRNAs as the biomarkers of liver disease. The main objectives include correlating the relationship between microRNA profiles in patients chronically infected with HCV pre-, during and post- anti-HCV treatment. The changes in circulating microRNA profiles will be examined in patients at different stages of HCV-associated liver disease. Lastly, we will be exploring the effect of decrease and clearance of the viral RNA on the expression of circulating microRNAs.

The study involves a cohort of one hundred patients who have undergone treatment in British Columbia from whom stored plasma are available at baseline (pre-), during and at the end of the therapy. Prior to analysis, microRNA detection assays will be initially validated using stored samples undergoing routine HCV RNA quantitation and genotyping.

It is expected that successful identification of accurate biomarkers may help to identify individuals at greatest risk of disease progression. Even though treatment with the new drugs is expected to be greater than 90% curative, individuals those cured of their HCV infection may still benefit from biomarkers which could identify individuals at ongoing risk of cirrhosis and hepatocellular carcinoma[7]. Thus, microRNA-based prognostic tools could be of value both in identifying those who should be prioritized for treatment and identifying those at risk of progressing after treatment.

Poster number: 211

ONCOLYTIC VIRUSES AS THERAPY FOR HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is one of the most prevalent types of cancer in both men and women, and often is the result of infection with the hepatitis C virus (HCV). Despite studies into the pathogenesis of this disease, and advances in treatment, improvement in patient outcome has been marginal. Novel therapies are urgently needed. Oncolytic viruses (OVs) have shown potential against numerous types of cancer both in vitro and in clinical trials. As a therapy they demonstrate exquisite specificity since viral replication is limited to cancerous cells, which are known to have defects in their antiviral response. Oncolytic viruses function as endogenous vaccines, inducing tumour-specific immune responses, which can be further enhanced by OV-mediated delivery of antigens. Furthermore, they can be paired with other therapies to enhance their effect.

We investigated several animal viruses for their oncolytic potential against an in vitro model of HCC using a resazurin dye-based assay to measure cell viability. Additionally, cytopathic effect was observed by crystal violet staining. Preliminary results suggest Newcastle disease virus (NDV), and fowl adenovirus 9 (FAdV-9) offer promise as therapies against HCC. Results using NDV indicate it is an efficient oncolytic agent, as it showed activity in Huh7, Huh7.5 and HepG2 cells, at low multiplicities of infection. However, no cell death was observed in normal, non-cancerous cells, suggesting the use of NDV against HCC is both safe and specific. The cytopathic activity of NDV does not depend on stimulation of the RIG-I pathway. Instead, DAPI staining suggests that oncolysis is due to the fusogenic nature of the virus. By contrast, FAdV-9, did not show oncolytic activity against Huh7, Huh7.5 or HepG2 cells. However, a recombinant FAdV-9 variant that contained the gene encoding the enhanced green fluorescent protein was able to express this protein within these cells, indicating its potential as a vector for antigen delivery.

These studies show the potential use for OVs for targeted therapy against HCC, and for delivery of antigens. Future work will further investigate mechanisms of oncolytic activity of NDV, the potential synergy with anti-HCV therapies, and its applicability in more clinically relevant models of HCV infection and HCC.

Poster number: 212

EFFECT OF CHIMERIC RNA-DNA TEMPLATES ON RNA SYNTHESIS AND RESISTANCE TO NUCLEOSIDE ANALOGUE INHIBITORS

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Background: HCV NS5B is an RNA-dependent RNA-polymerase responsible for viral RNA replication. It exhibits a right hand structure with fingers, palm and thumb subdomains. The recently reported structure of HCV NS5B in complex with an RNA primer-template provides important information on the protein-nucleic acid interface during the elongation process (Mosley R et al, April 2012). The structure points to specific interactions with the 2'-OH group of bound RNA residues. However, previous studies have shown that HCV NS5B is able to utilize DNA templates, but with reduced efficiency.

Purpose: Here we investigate the effects of strategically introduced DNA residues in the template strand on: i) DNA elongation, ii) rates of incorporation of the nucleotide analogue 2'C-Methyl-CTP, and iii) its resistance conferring mutation S282T.

Method: HCV NS5b and S282T were expressed and purified. RNA synthesis to see activity and chain-termination was performed with the enzymes on modified RNA templates in a biochemical assay.

Result(s): NS5B is able to perform RNA synthesis both on RNA and DNA templates. However, pausing is observed when a nucleotide on the template is modified to dTTP, dUTP, and 2'F-UTP. 2'F-UTP adopts the RNA-like North conformation, which suggest that the lack of the 2'OH group and not the sugar pucker triggers pausing. Pausing is not seen with dGTP. S282T is sensitive to 2'C-Me-CTP when incorporated opposite dG. This effect is not superimposed by a pausing site. 2'-F-Riboguanosine shows likewise sensitivity to this compound.

Conclusion(s): From this data we can conclude that S282T which is totally resistant to 2'C-Me-CTP, shows sensitivity to the compound due to the lack of 2'-OH suggesting its role in establishing the resistant phenotype.

Funding source(f): NCRTP, CIHR

Poster number: 213

A NOVEL SEQUENCING METHOD USING CORE-HVR1 AND NS5B REGIONS FOR INVESTIGATING THE MOLECULAR EPIDEMIOLOGY OF HCV INFECTION: THE ATAHC STUDY

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Background: Sequencing is important for understanding the molecular epidemiology and viral evolution of HCV infection. To date, there is little standardisation among sequencing protocols, in-part been due to the high genetic diversity that is observed within the HCV species. This study aimed to develop a novel sequencing protocol including the Core and the hypervariable region 1 (HVR1) of E2 region of the HCV genome that could be used for molecular epidemiology. We also assessed whether concatenating the Core-HVR1 and NS5B regions improved the identification of clusters among participants with recent HCV infection.

Method: Participants were identified from the Australian Trial in Acute Hepatitis C (ATAHC) study, a prospective study of the natural history and treatment of recent HCV infection. Sequencing of the Core-HVR1 (nested PCR, 1534bp) and NS5b (389bp) and phylogenetic analysis were performed to identify clusters of patients sharing a related HCV virus. Phylogenetic trees were estimated using maximum likelihood methods and algorithms (RAxML) using the Core-HVR1, subregions within this amplicon, either alone or concatenated with NS5B. The percent and identity of subjects falling within a cluster, the bootstrap value and branch length of these trees were compared to assess the robustness of each condition. Full length sequences from treatment-naïve subjects within the Los Alamos National Laboratory database were trimmed to equivalent regions and included to assess the false positive rate of identifying subjects within a cluster. Clustering of the LANL subregions were also analysed in comparison to full length sequences.

Result(s): HCV RNA positive samples were available from 144 of 163 participants enrolled in the ATAHC study. Sequencing was successful in 82% of samples with a viral load >1,000IU/mL (113 of 138). The Core-HVR1 sequencing protocol amplified all HCV genotypes tested (1a, 1b, 2a, 2b, 3a and 6c-i). Phylogenetic analysis (bootstrap > 90%) with 5'UTR-HVR1 alone identified 11 clusters in Genotype 1a and 3a, while NS5b alone identified 6 clusters. Concatenation of both Core-HVR1 and NS5B produced the highest percentage of clusters and yielded a stronger bootstrap. Removing HVR1 decreased the average branch length among clusters suggesting that, despite the short length, HVR1 (81nt) is significantly influencing the phylogenetic analysis due to its high diversity. Core alone identified the minimum number of clusters compared to all other methods. Adding the LANL sequences decreased clustering for Core and NS5B in ATAHC but increased the percentage of clusters for all 5' regions (up to maximum of 50%). Using LANL sequences alone, concatenation of both Core-HVR1 and NS5B showed 10% clustering, the highest among all conditions, but the full length sequence (8962bp) showed 42% clustering which overrepresented the likely number of clusters within this database.

Conclusion(s): Concatenation of both Core-HVR1 and NS5B may provide the most robust sequence combination for clustering analysis. NS5B alone was less reliable and identified variable relationships between individuals. The inclusion of LANL sequences strengthened the relationships within the ATAHC cohort. This novel Core -HVR1 sequencing protocol and concatenation with NS5B amplicon could be a useful method for the study of HCV cluster analysis and viral evolution.

Poster number: 214

HIGH-RESOLUTION RENDERING OF HCV QUASISPECIES EVOLUTION DURING PREGNANCY.

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Background: HCV can be transmitted from mother to child during pregnancy and/or childbirth. Prevalence of chronic HCV infection in pregnant women ranges between 1% and 8% worldwide. Management of pregnant HCV-infected women is challenging because standard of care treatments are contraindicated during pregnancy. Serum ALT levels decline during the second and third trimesters of pregnancy, paralleled by an increase in HCV viral load. In contrast, ALT levels rebound after delivery along with worsening liver histopathology and a reduction in HCV viral load. HCV exists as a quasispecies within the host, with a large part of its genetic variability being located within hypervariable regions of E2 which are the targets of host immune responses. During pregnancy, selective pressure exerted on HCV is largely focused on solvent-exposed regions of E2, suggesting the involvement of humoral immune responses. These observations suggest that pregnancy-associated modulation of humoral immune responses can influence the course of hepatitis C.

Purpose: The objective of this study was to generate a detailed profile of HCV quasispecies evolution based on hypervariable regions of E2 during pregnancy using high throughput sequencing, and to correlate the evolution of the quasispecies with maternal humoral immune responses.

Method: Subjects (n=46) were enrolled at Centre hospitalier universitaire Sainte-Justine (Montreal, Canada) and the Women's Health Research Institute (Vancouver, Canada). Serum samples (140 time points) were obtained in the first, second and third trimesters of pregnancy and in the post-partum period. Viral RNA extracted from serum was amplified by RT-PCR using bar-coded primers and high fidelity polymerases. Amplicons were sequenced on a Roche 454 GS-FLX System with Titanium series reagents. Plasmid-derived amplicons were used to calculate amplification and sequencing error frequencies. Neutralizing antibody (NAb) titres in maternal serum were assessed by infecting Huh7.5 cells with genotype-matched HCVpp engineered to express autologous E2 segments.

Result(s): Analysis on 19 of 46 patients revealed dissimilar quasispecies profiles and evolution, some women exhibiting long-term conservation of major variants throughout pregnancy and others showing high diversity and prompt diversification of variant spectra. Neutralization assays using autologous HCVpp revealed that in some cases, specific NAb remained present throughout pregnancy even following complete disappearance of the cognate variant.

Conclusion(s): These results provide a high-resolution portrait of HCV quasispecies evolution throughout pregnancy and will yield one-of-a-kind insights into maternal HCV-specific immunity. Results from this study could lead to improved clinical care for pregnant women chronically infected with HCV and to the development of novel strategies to prevent mother to child HCV transmission.

Funding source(f): Canadian Institutes of Health Research (CIHR); Réseau SIDA et MI, Fonds de la recherche du Québec-santé (FRQS).

Poster number: 215

PRE-CLINICAL EVALUATION OF A HCV VACCINE DESIGNED TO ELICIT BROAD CROSS-NEUTRALIZING ANTIBODIES AND CROSS-REACTIVE CELLULAR IMMUNE RESPONSES

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Background: HCV clearance requires a protective role for virus neutralizing antibodies and virus-specific cellular immune responses. Accordingly, we are designing a vaccine formulation capable of eliciting such broad immune responses in humans. Previously we have shown that a recombinant envelope glycoprotein vaccine containing the gpE1/gpE2 heterodimer derived from a single HCV strain is protective in the chimpanzee challenge model against homologous and heterologous 1a strains. Vaccination of human volunteers in a phase 1 clinical trial elicited strong T helper responses and antibodies that neutralize the in vitro infectivity of all of the major HCVcc genotypes observed around the world. Cross-neutralization in clinical data appeared to favor genotypes 1, 4, 5 and 6 with significant but lower in vitro neutralization against genotypes 2 and 3.

Purpose: To determine an optimal HCV antigen for a global HCV vaccine and to investigate the effect of virion-associated apolipoproteins on neutralization.

Method: We have vaccinated animals with recombinant envelope glycoproteins derived from genotypes 1 and 2 and have determined their relative in vitro cross-neutralizing antibody titers. In additions, we utilized a newly published method to grow HCV in tissue culture (HCVcc) for neutralization assay using human serum, which produced virions with a greater resemblance to clinical isolates in terms of lipid content and buoyant density.

Result(s): Our data indicates that an optimal second generation vaccine should contain a cocktail of gpE1/gpE2 antigens derived from multiple HCV genotypes. We found that our vaccine-induced anti-sera showed similar efficacies in neutralizing both human serum-derived HCVcc and conventional bovine serum-derived HCVcc.

Conclusion(s): This provides encouragement that a global HCV is possible and these vaccine-induced antibodies remain functional in the presence of various apolipoproteins.

Funding source(f): Canada Excellence Research Chair (Houghton); Alberta Innovates Health Solutions; University of Alberta

Poster number: 216

SILYMARIN-INDUCED CELLULAR STRESS RESPONSES MODULATE CELLULAR METABOLISM TO INDUCE ANTI-INFLAMMATORY EFFECTS

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Background: Silymarin (SM) is a popular botanical medicine with purported liver protective effects. SM displays multiple effects in animal models and in cell culture including prevention of liver disease, reduction of inflammation, oxidative stress, and proliferation. Despite a plethora of data indicating that SM impinges on multiple cellular signaling pathways important in inflammation and disease, no unifying mechanisms have been forwarded.

Purpose: To define how SM elicits so many biological effects, the current study presents the first comprehensive transcriptional profiling study of human hepatoma cells treated with SM. The intention of the study was to focus on the early transcriptional events that are associated with SM-induced inhibition of proliferation and inflammation.

Method: Human hepatoma Huh7.5.1 cells were treated with SM (40 μM) or DMSO solvent for varying times and microarray analysis was performed on an Agilent platform. Gene changes were validated by quantitative real time RT-PCR. Protein expression and phosphorylation was further validated by western blots. Bioinformatic analysis using Ingenuity Pathway Analysis identified key genes and pathways that were modulated by SM, which were subsequently validated by signaling transduction studies in Huh7.5.1 cells and Jurkat T cells.

Result(s): At 4 hours, SM induced and activated genes involved in endoplasmic reticulum and cellular stress signaling (i.e., DDIT3, DDIT4). Several of these highly induced mRNAs detected at 4 hours were associated with activation of the transcription factor ATF-4. The rapid induction of ATF-4-dependent gene expression was associated with eIF-2α phosphorylation and induction of ATF-4 protein, hallmarks of ER and nutrient/energy deprivation stress responses. Furthermore, SM inhibited mammalian target of rapamycin (mTOR) signaling, a known the nutrient sensing pathway, via the induction of DDIT4 gene expression and inhibition of 4EBP1, P70S6K, and mTOR protein phosphorylation. In contrast, the anti-inflammatory effects of SM was reflected by significant up-regulation of inhibitors of NF-κB signaling (e.g., TRIB3) and down-regulation of NF-kB target genes including many cytokines and chemokines; these anti-inflammatory effects progressively increased over the 24-hour experiment. SM-induced anti-inflammatory effects were also observed by increased phosphorylation of FOXO3 protein.

Conclusion(s): Collectively, the data demonstrate that SM induces cellular stress, the slowing of cellular metabolism, leading to inhibition of cell growth and inflammation.

Funding source(f): Supported by NIH grant R01AT006842.

Poster number: 217

EXAMINING THE ALTERATIONS IN THE ACTIVITY OF HOST ENZYMES DURING HEPATITIS C VIRUS INFECTION

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Background: Host-pathogen interactions are indispensable for the replication of hepatitis C virus (HCV), and while numerous studies have demonstrated that HCV modulates various host protein levels, the systematic study of the virus's effect on the enzymatic activity has been relatively unexplored. Previous reports indicated that HCV hijacks the host lipid and membrane biogenesis pathways for its propagation.

Purpose: To identify differentially active host enzymes, which are essential for the replication of HCV for diagnostic and therapeutic purposes.

Method: We have applied activity-based protein profiling (ABPP), a technique which allows for the identification of differentially active enzymes in complex proteomic samples, to study the changes in the activity of essential host enzymes for HCV replication. ABPP employs active site-directed covalent probes that consist of small molecule inhibitors linked to reporter tags, which report on functional state of their target enzymes.

Result(s): We have used an activity-based probe (ABP) derived from Orlistat, a fatty acid synthase (FASN) inhibitor to probe FASN activity during HCV replication. FASN is a key enzyme in lipid biosynthesis. We observed an increase in the activity of FASN during viral replication in a cell culture model, as well as in chimeric SCID/Alb-uPA mice infected with HCV genotype 1a. Furthermore, we observed that the expression of certain HCV proteins, such as core and NS4B increase the expression and activity of FASN. Triglyceride levels were also elevated in accordance with FASN expression and activity. Moreover, immunofluorescence and ABPP imaging analyses confirmed our results regarding the increased expression and activity of FASN during HCV replication and allowed for tracking the localization of active FASN in the cell. Additionally, we have designed a novel PIK-93-derived ABP to investigate the activity of lipid kinases important for the HCV life cycle, such as phosphoinositide 3 kinase (PI3K), and phosphoinositide 4 kinase (PI4K). We have also observed increased activity, but not expression, of PI4KIIIβ during HCV replication.

Conclusion(s): These results will facilitate the discovery of new biomarkers and potential targets for therapeutic intervention of HCV infection.

Funding source(f): The Canadian Institutes of Health Research (CIHR).
National CIHR Research Training Program in Hepatitis C.

Poster number: 218

PROTEASE RESISTANT VIRUSES IN CELL CULTURE AND REVERSION CHARACTERISTICS

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Background: Hepatitis C virus affects 170 million people worldwide and until recently, therapeutic options have been limited. Novel and effective protease inhibitors (PI) recently became available in the clinic, but drug resistant variants are present at low levels in the quasispecies or quickly emerge in treated patients.

Purpose: The goal of this project is to analyze the effects of PI resistance mutations on viral fitness, to study the rate and mechanism by which these mutants revert to wild-type in the absence of drug pressure, and to analyze the potential for selection of these mutations under drug pressure in cell culture.

Method: Two common PI drug resistant variants: T54A, and R155K were generated in the JFH1T backbone through site-directed mutagenesis and viral fitness was assessed based on the levels of virus produced upon transfection of Huh-7.5 cells. Mutant viruses were cultured over 15 - 45 days and were sequenced in order to test the rate and mechanism by which they revert to wild-type virus. Resistance of the mutants to Telaprevir was assessed through QRT-PCR.

Result(s): The T54A and R155K mutations resulted in titres of approximately 1 log lower than wild type JFH1T. After passaging R155K and T54A for 45 and 30 days, respectively, the engineered mutations were maintained in cell culture. We developed a 6-well assay to assess EC50s in cell culture. We implemented this assay to determine the EC50 of the JFH1T virus, and to assess the level of resistance of respective mutants mentioned previously.

Conclusion(s): Here we describe a cell culture analysis of the impact of PI resistance mutations on HCV fitness in the context of a robustly replicating virus. Determination of the rates and mechanisms by which these mutant viruses revert to wild-type or possibly compensate for drug resistant mutations will help to explain why drug resistance rapidly develops and is maintained in patients treated with protease inhibitor therapy.

Funding source(f): CIHR, NCRTP-HepC

Poster number: 219

MIR-122 BINDING THE HCV 5' UTR AT SITE 2 IS MORE IMPORTANT FOR PROTECTION FROM XRN1 THAN BINDING SITE 1

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Background: miR-122 is a liver-specific and abundant microRNA that is critical to Hepatitis C Virus (HCV) replication in cell culture and in the human liver. It binds to two complementary sites on the 5' un-translated region (UTR) of the viral RNA, and has been implicated in preventing degradation of the viral RNA by the host RNA exonuclease Xrn1, but also appears to have a separate and unknown function required for the virus life cycle.

Purpose: We hypothesize that miR-122 binding to each site on the HCV genome has separate roles, and that by analyzing the impact of miR-122 binding to each site we will gain a better understanding of the mechanism by which miR-122 promotes the HCV life cycle.

Result(s): By using viral RNA genomes with intact or mutated miR-122 binding sites (either Site 1, Site 2, or both), we determined that each miR-122 binding site contributes equally to enhancing HCV RNA replication: miR-122 binding at either Site 1 or Site 2 increased replication ten-fold, while miR-122 binding at both sites increased replication 100-fold – the product of the effects of each site alone. In addition, binding of miR-122 to both sites also protected RNA from degradation by Xrn1, since Xrn1 knockdown rescued replication of HCV RNAs having mutations to either Site 1 or Site 2. However, Site 2 appears to have a more important role in protection from Xrn1 since we found that knockdown of Xrn1 had a greater impact on HCV RNA amplification levels when miR-122 was not bound to Site 2. Thus, Site 1, which overlaps the very 5' end of the viral RNA, is less critical for protection from Xrn1 than Site 2, which is further downstream. We also found that knockdown of Xrn1 rescued previously undetectable replication of the full-length HCV RNA construct to low but detectable levels when miR-122 binding was abolished. Knockdown of Xrn1 in the absence of miR-122 binding did not restore replication to miR-122-bound levels in any of our systems, thus confirming that miR-122 functions to promote HCV replication using a mechanism independent from Xrn1. We are currently verifying the effect of Xrn1 knockdown on viral RNA half-life to confirm a role for miR-122 binding to both sites on HCV genome stability.

Conclusion(s): miR-122 binding at either Site 1 or Site 2 has equivalent influence on promoting the HCV life cycle, and the effect of binding at both sites appears to be additive rather than synergistic. However, miR-122 binding at Site 2 appears to be more important for protection from Xrn1-mediated degradation of the viral RNA, suggesting that binding at Site 1 is more important for some other function of miR-122. Full-length HCV RNA can replicate, albeit poorly, in the absence of miR-122, following knockdown of Xrn1, which suggests to us that HCV is capable of inefficient replication in the absence of miR-122, but that the levels are too low for detection even with reporter viruses.

Funding source(f): NCRTP-HepC, NSERC, SHRF-RAPID.

Poster number: 220

A RECOMBINANT HCV ENVELOPE GLYCOPROTEIN VACCINE ELICITS ANTIBODIES THAT COMPETE WITH THE BINDING OF CROSS-NEUTRALISING ANTIBODIES AND BIND CROSS-NEUTRALISING EPITOPES

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Background: With millions of new infections occurring each year around the globe and with up to 12,000 new infections every year in Canada, there remains an urgent need to develop a Hepatitis C virus (HCV) vaccine. A promising candidate comprising a recombinant envelope glycoprotein heterodimer (gpE1/gpE2) derived from a single genotype 1a virus strain (HCV-1) has been shown previously to protect chimpanzees against experimental challenge and to elicit antibodies in guinea pigs, chimpanzees and man that inhibit the in vitro infectivity of all of the main HCV genotypes known to occur around the world.

Purpose: We wanted to confirm the ability of this vaccine candidate to elicit broad cross-neutralising antibodies by showing competition between a panel of defined monoclonal antibodies (known to be broadly cross-neutralising) and hyper-immunised animal antisera. These monoclonal antibodies exhibit a variety of epitopes in gpE1/gpE2. Secondly, we wish to show that hyper-immunised animal antisera binds directly to linear peptides known to represent part of the target domain of cross-neutralising monoclonal antibodies. Thirdly, we wish to explore if the vaccine elicits cross-neutralising antibodies targeting novel epitopes.

Method: We performed competition ELISAs using gpE1/gpE2 captured from cellular lysates with Galanthus nivalis antigen as a target antigen to detect if immunised animal antisera could prevent the binding of monoclonal antibodies. We used peptide ELISAs to detect binding to linear epitopes.

Result(s): Antisera from goats hyper-immunised with the gpE1/gpE2 vaccine was shown to effectively compete for the binding of the cross-neutralising monoclonal antibodies to gpE1/gpE2 antigen. Peptide mapping ELISAs using vaccinee antisera revealed binding to linear peptides known to be involved in cross-neutralising epitopes as well as to potentially novel neutralising epitopes. Peptide mapping experiments involving the panel of monoclonal antibodies are underway.

Conclusion(s): The clear binding competition demonstrated between hyper-immunised animal antisera and the monoclonal antibodies confirms the ability of the vaccine to elicit broad cross-neutralising antibodies. The hyper-immunised animal antisera was also shown to bind known cross-neutralising epitopes. Since various studies have indicated a protective role for cross-neutralising HCV antibodies, our work encourages the further development of a recombinant envelope glycoprotein-based HCV vaccine. Future work is aimed at further definition of the neutralising epitope profile elicited by the vaccine.

Funding source(f): National CIHR Research Training Program in Hepatitis C (Jason Wong); Canadian Liver Foundation Graduate Studentship (Jason Wong); Canadian Excellence in Research Chair (Michael Houghton).

Poster number: 221

THE EFFECT OF PTEN ON HCV INFECTION

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Background: Hepatitis C virus (HCV) infection causes serious global public health problems. The World Health Organization has established that there are more than 170 million chronic HCV patients worldwide. Hepatocellular carcinoma (HCC) is the most deadly clinical consequence of HCV infection. Phosphatase and tensin homolog (PTEN) is a tumor suppressor which 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. Two naturally occurring mutations on the phosphatase domain disrupt PTEN's phosphatase activity: C124S mutation, which abrogates both lipid and protein phosphatase activity, and G129E mutation, which abrogates lipid phosphatase only. PTEN acts a tumor suppressor, which can suppress one of the most critical cancer-promoting pathways: PI3K-Akt pathway. Moreover, PI3K-Akt pathway is shown to regulate SREBPs.

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

Method: We will characterize HCV infection or replication after PTEN overexpression or knocking down PTEN expression. We will determine whether PTEN interacts with HCV viral proteins as a mechanism for its effect on HCV infection or replication.

Result(s): In HCV JFH-1 genomic replicon cells, we showed that knocking down PTEN significantly enhanced HCV viral entry, NS5A protein expression, and viral replication. Consistently, PTEN overexpression significantly inhibited HCV entry and replication. We further showed that the phosphatase domain of PTEN was involved in HCV replication inhibition. Interestingly, PTEN with the lipid phosphatase defective mutation (G129E) could no longer inhibit HCV replication. In GST pull-down assays, we showed that HCV core protein interacted with PTEN. HCV core domain I aa. 42-59 and PTEN aa. 1-185 were required for the interaction.

Conclusion(s): The lipid phosphatase activity of PTEN is required for inhibiting HCV replication. HCV core interacts with PTEN, which may contribute to PTEN's effect on HCV replication. Our study may help justify further development of PTEN as a new drug target for HCV therapy.

Funding source(f): CIHR, NCRTP-HepC, SHRF

Behavioral Sciences

Poster number: 300

"IT GIVES ME A SENSE OF BELONGING": PROVIDING TREATMENT TO PEOPLE WITH HCV ENGAGED IN A PSYCHO-EDUCATIONAL SUPPORT GROUP.

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Background: The Toronto Community Hepatitis C Program (TCHCP) is a community-based model of HCV treatment offering weekly group support and access to HCV treatment for people who are active substance users and/or who have complex mental health, physical health and psychosocial needs. A previous retrospective study of the TCHCP model has demonstrated treatment initiation and success rates which are comparable to rates in traditional health care settings (Charlebois et al. 2012).

Purpose: The objective of this study was to explore the experiences of individuals engaged in the TCHCP's psycho-educational group. Groups last 16-18 weeks and are located at each of the program's three community-based health care settings.

Method: This phenomenological qualitative study consisted of semi structured in-depth interviews with twenty randomly selected program participants.

Result(s): Three dominant themes emerged: program structure, group cohesion and group as agent for change. The program's one-stop shopping model provided a stable foundation allowing for the development of group cohesion. This group cohesion was marked by the formation of intense relationships which created a safe and non-judgmental environment where participants could self-reflect, make social connections and feel cared for and accepted. Within the nurturing group environment, participants could challenge themselves and others, ultimately enabling positive life changes.

Conclusion(s): This study suggests that it is the formation of group cohesion that facilitated participants' behavior change. The structure of the group and the provision of multiple services in one location provided stability. The support from peers and staff allowed participants to see themselves in a new way and to develop and accomplish personal goals.

Funding source(f): Funded by South Riverdale Community Health Centre and a grant from the PSI Foundation.

References: Woolhouse, S., et al. "It gives me a sense of belonging": providing integrated health care and treatment to people with HCV engaged in a psycho-educational support group. International Journal of Drug Policy (July 2013), Epub ahead of print: http: //dx.doi.org/10.1016/j.drugpo.2013.05.018

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Epidemiology and Public Health

Poster number: 400

UNDERSTANDING THE ROLE OF PRIMARY CARE PHYSICIANS IN REDUCING HCV TRANSMISSION AMONG PERSONS WHO INJECT DRUGS

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Background: Hepatitis C virus (HCV) continues to disproportionately affect persons who inject drugs (PWID). Adequate access to primary care physicians (PCP) presents an ideal opportunity to offer HCV screening, counseling, assessment and treatment, strategies that are key in HCV prevention. Indirect evidence points to an inadequate access to primary healthcare services among this population, but little is known about the factors that influence access. Further, the effect of PCP exposure on HCV incidence has not been previously explored.

Purpose: The objectives of this study were to assess: i) factors associated with PCP access among active PWID living in a large cosmopolitan North-American city, and ii) the effect of PCP exposure on HCV incidence, while accounting for potential confounders.

Method: Data were collected as part of HEPCO, an ongoing prospective cohort of active PWID, established in Montreal, Canada (2004-2011). At each semi-annual visit, an interviewer-administered questionnaire elicited information on socio-demographic factors, drug use patterns and related behaviors, and healthcare services use. Blood samples were collected and tested for HCV antibodies. Using the Gelberg-Andersen Health Model, logistic regression analyses were carried out on baseline data to examine predisposing, need and enabling factors associated with PCP access. HCV incidence was calculated using the person-time method. To examine the relations between PCP exposure and HCV incidence, a time-updated Cox-regression model was conducted.

Result(s): Two-hundred and sixty-eight HCV-seronegative PWID (81.3% male, mean age: 34 years) were recruited and followed-up at least once during the study period. Visits to PCP were reported among 33% of participants. In logistic regression analyses, among predisposing factors, male gender (Adjusted Odds Ratio (AOR)=0.42, [0.21-0.84]), cocaine injection (AOR=0.47, [0.27-0.82]), and chronic homelessness (AOR=0.12, [0.02-0.91]) were negatively associated with PCP access. Perceived health and reports of being sick, markers of need, did not correlate with the outcome. Attending food banks (AOR=2.60, [1.43-4.75]) and reporting contacts with street nurses (AOR=3.68, [1.23-10.71]), enabling factors, were positively associated with access to PCP. Ninety-six participants seroconverted to HCV (incidence rate: 18.1 per 100 person-years, [14.8-22.0]. In univariate analyses, access to PCP was associated with a decreased risk of HCV seroconversion, although the association did not reach statistical significance (Crude Hazard Ratio=0.82, [0.53-1.27]; p=0.375). Results from Cox's univariate and multivariate model are presented in Table 1.

Conclusion(s): Suboptimal patterns of access to PCP appear to be the norm in the majority of PWID. While specific predisposing factors seem to render PWID less likely to benefit from adequate PCP access, community-based outreach services may play an important role in engaging these individuals into primary care. Further, findings suggest that PCP exposure, on its own, has a protective, yet not substantial impact on HCV transmission. Future research should explore the effect of PCP exposure on HCV incidence, as part of an integrated harm reduction approach.

Funding source(f): National CIHR Research Training Program in Hepatitis C; Canadian Institute of Health Research; Réseau Sida et Maladies Infectieuses du FRSQ

Poster number: 401

TYPOLOGY OF PEOPLE WHO INJECT DRUGS WITH CHRONIC HCV INFECTION: A NOVEL METHOD TO UNCOVER DETERMINANTS OF HCV TREATMENT UPTAKE

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Background: While specific barriers to HCV treatment have been identified among drug users, less attention has been given to combination of factors that could define distinct patient profiles relative to treatment uptake.

Purpose: To empirically identify profiles of HCV infected drug users relative to HCV treatment uptake, based on the Andersen Behavioural Model of Health Service Utilization.

Method: Enhancing Treatment for Hepatitis C in Opiate Substitution Settings (ETHOS) is a prospective observational cohort among drug users with chronic HCV infection. Recruitment was from July 2008 to December 2012 through six opiate substitution treatment (OST) clinics and three community health centres in NSW, Australia. Two-Step Cluster analysis was used to build this typology.

Result(s): Sample population: 386 participants; 71% males; mean age: 40 y.o. (SD 9); high school education: 19%; low weekly income: 75%; HCV treatment: 84 participants (22%). The cluster analysis yielded 4 classes. Sixty-seven percent of those treated belonged to Class 1 (n=84), comprising older participants, well educated (56% > high school), with the highest outcome and lowest opiate substitution therapy proportions of all class. Conversely, no treatment was initiated among Class 3 participants (n=92), which included 44% of all women and 100% of low education participants. Class 2 (14% treatment uptake) comprised predominantly male participants, with high social functioning, and alcohol/drug use in high proportions. Class 4 (19% treatment uptake) comprised low income and unstable housing participants, and included 54% of all aboriginals.

Conclusion(s): Specifically designed interventions for less educated women and disengaged aboriginal drug users could improve treatment uptake among these vulnerable sub-groups of drug users.

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Poster number: 402

VARIABLES ASSOCIATED WITH MENTAL AND PHYSICAL COMPONENTS OF QUALITY OF LIFE IN PEOPLE WHO INJECT DRUGS RECENTLY INFECTED WITH HCV

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Background: Compared to the general population, hepatitis C (HCV) infected patients have been found to have impaired health-related quality of life (HRQoL). Most studies on HRQoL and HCV infection were carried out among chronically infected patients, comparing different stages along disease progression. Studies targeting factors associated with HRQoL in recently infected HCV patients are lacking.

Purpose: The purpose of this study was to examine variables associated with the mental and physical components of quality of life (QoL) among PWIDs recently infected with HCV.

Method: The study population was recruited in IMPACT, a cohort study of PWIDs with a documented recent HCV infection (6 months or less), recruited in Montreal between 2004 and 2013. Eligibility criteria included being 18 years old or over, drug injection in the previous 6 months, and being HIV sero-negative. Socio-demographic characteristics, drug use patterns, and health care utilization were assessed by a behavioral questionnaire, administered by trained interviewers. Health related quality of life and depression were assessed using the SF-36, and the CES-D self-administered questionnaires, respectively. Two HRQoL outcomes were measured: i) mental component and ii) physical component of quality of life. Multiple linear regression models were conducted.

Result(s): Of a total of 76 participants, the mean duration between HCV infection disclosure and questionnaire administration was 44 days (SD: 37); 74% were males; 7% had a legal job; 22% deemed their health status as excellent or very good; 16% expressed depressive feelings; 9% reported prior suicide attempts; 61% had received. HepatitisA-B vaccine; 86% were on IV cocaine, 55% on alcohol, and 53% on IV heroin. The mean scores of mental and physical components of QoL were respectively 35.1 (SD: 13.7) and 46.3 (SD: 10.1). Being male was positively associated with a high mental QoL score; perceiving self-health as poor, feeling anxious, and feeling depressed were negatively associated. HepatitisA-B vaccination and having a legal job were positively associated with a high (good) physical score, while having used opioids and perceiving self-health as poor was negatively associated.

Conclusion(s): Socio-demographic variables (gender, job) and self-perceived comorbid conditions (mental health and physical problems), as well as drug use and healthcare service use may impact quality of life in PWIDs with recent HCV infection. Tailored programs, addressing health needs and perception, could help improve the wellbeing of recently infected PWIDS.

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SCREENING FOR HEPATITIS C EXISTENCE IN PRISON- 'SHEEP PROGRAMME' HMP CARDIFF

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Background: Hepatitis C, a blood borne virus transmitted via the receipt of infected blood, primarily via the use of infected needles during IV drug use, is estimated to infect 216,000 people in the UK (circa 0.35% of the British population), including 12,000 in Wales. Chronic infection may result in liver cirrhosis after 20 years, with a large proportion consequentially developing hepatocellular carcinoma resulting in the need for liver transplantation.

Ribavirin and pegylated interferon alpha is the usual treatment regime for a hepatitis C positive individual causing sustained virologic response (SVR) in up to 80% of those with genotype 2 and 3 and between 33% and 42% in those with genotype 1.

Boceprevir and Telaprevir, new protease inhibitors NICE-approved in April of this year are particularly effective against genotype 1a, found most commonly in prisoners, significantly improving SVR when used alongside ribavirin and interferon therapy making possible hepatitis C findings even more treatable than before.

From October 2010 to September to 2010, 767 hepatitis C screening results were obtained from a cohort of people seen by substance misuse services of which 77% had been involved with injecting drugs. 9% in the Cardiff and Vale area were found to be hepatitis C positive (17% less than the national average) of which 54% had previously been in prison.

A large proportion of prisoners indulge in IV drug use, presenting the need to establish prevalence in these institutions. The optimal screening approach is to screen those with an identifiable risk factor for increased hepatitis C prevalence. Screening has now been initiated in HMP Cardiff in line with Blood Borne Viral Hepatitis Action Plan for Wales 2010- 2015.

Purpose: To establish the prevalence of Hepatitis C in Cardiff prison, enhancing the epidemiological understanding of Hepatitis C within communities in South Wales and elucidating how the infection may have taken place in line with BBV Hepatitis action plan, Wales. Those recognised as Hepatitis C positive will be referred for suitable treatment, either whilst in prison or upon release.

Method: Offer Hepatitis C screening to eligible HMP Cardiff prisoners using dried blood spot (DBS) testing to identify prisoners with positive viral antibodies, confirming positive results with PCR testing to establish genotype, whilst educating prisoners on the subject of BBVs.

Result(s): 59 of 795 eligible prisoners (7.4%) underwent screening from 28th May to 29th June 2012. Of those screened, 10.2% tested positive for Hepatitis C antibodies and after PCR testing. Of those screened who had indulged in IVDU, 20.7% tested positive.

Conclusion(s): Hepatitis C prevalence data collected in this study has re-enforced the importance of screening programmes in incarceration institutions to establish prevalence and commence treatment for those who require it, using recently licensed drugs to cause SVR and ultimately reduce hepatitis C prevalence. Further efforts to improve uptake such as opt out strategies will reduce health service costs, benefit the individuals testing positive as well as the communities they are part of.

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THE EFFECT OF INSULIN SENSITIZING AGENTS ON TREATMENT AND LIVER-RELATED OUTCOMES IN HCV-INFECTED PATIENTS: A SYSTEMATIC-REVIEW AND META-ANALYSIS.

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Background: The presence of insulin resistance (IR) and type 2 diabetes (T2DM) in HCV has been associated with poor response to interferon/ribavarin (IFN/Rib) therapy for HCV, acceleration of liver fibrosis, increased risk for hepatocellular carcinoma (HCC), and higher rates of liver transplantation. With the development of HCV protease inhibitors, sustained virological response (SVR) rates have improved significantly. However due to cost, access and other comorbidities, IFN/Rib remains the mainstay of HCV antiviral therapy in many circumstances.

Purpose: To assess the effectiveness and safety of insulin sensitizers (IS) in improving treatment response rates with IFN/Rib therapy and liver-related outcomes (liver fibrosis, HCC and liver transplants rates) in HCV-infected patients with IR or T2DM.

Method: Medline and Embase databases were systematically searched to identify relevant studies between January 1989 and February 2013. Only randomized controlled trials (RCT) were included for treatment-related outcomes. Observational studies were included for liver-related outcomes. A random-effects model was used to calculate a pooled risk estimate and estimate differences in treatment-related outcomes.

Result(s): Of the 190 studies identified in the literature search, there were 4 RCTs that focused on the potential of IS to improve SVR rates. A pooled analysis of these studies did not show a statistically significant improvement overall (RR 1.20, 95% CI 0.86-1.67). However, pre-specified sensitivity analyses based on risk of bias and type of insulin sensitizer did demonstrate that these pharmacologic agents and particularly metformin may have the potential to augment SVR when combined with IFN/Rib therapy for the treatment of HCV genotype 1/4. (RR 1.39, 95% CI 1.11, 1.73, RR 1.33, 95% CI 1.02, 1.72 respectively). This correlates with a number needed to treat of 7 patients. There were no studies that examined the benefit of these treatments in genotype 2/3. There were no serious adverse events associated with the use of IS in any of these studies.

Although a trend towards improvement in HCC events was noted based on the two studies identified for liver-related outcomes (1 case-control, 1 cohort study), these results were not pooled due to differences in methodology, quality, and exposure rates [case-control OR 0.39 (95% CI 0.13-1.27), cohort-study OR 0.20 (95% CI 0.04-0.92)].

There were no studies that investigated the impact of insulin sensitizers on preventing the progression of liver fibrosis.

Conclusion(s): Although IR has been consistently associated with reduced SVR, increased fibrosis and increased risk for HCC and liver transplant, there are very few studies that have examined the benefits of IS in improving these outcomes. These pharmacologic agents and particularly metformin are safe, well-tolerated, accessible and relatively inexpensive. This study provides some evidence to suggest that IS may improve SVR rates in IFN/ribavarin treated patients and may lead to decreased morbidity and mortality in chronically infected patients. This study highlights the need for larger, high quality studies to further evaluate this benefit and understand the mechanisms by which IR may impact outcomes in this population.

Poster number: 405

TEMPORAL CHANGES IN HEPATITIS C VIRUS GENOTYPE 3A DISTRIBUTION AMONG PEOPLE WHO INJECT DRUGS IN VANCOUVER, CANADA

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Background: The availability of interferon (IFN)-free directly acting antiviral (DAA)-based therapy has improved the feasibility of hepatitis C virus (HCV) treatment as prevention among people who inject drugs (PWID). However, IFN-free DAA-based therapies have reduced efficacy among people with HCV genotype 3a infection. We characterized trends in HCV genotype 3a infection and associated factors among PWID recruited between 1996 and 2012 in Vancouver, Canada.

Method: Data were derived from two ongoing prospective cohorts of PWID in Vancouver (VIDUS and ARYS). Participants that were HCV antibody positive at baseline, or had HCV antibody seroconversion during follow-up were tested for HCV RNA. HCV RNA positive samples were sequenced using the Core-HVR1 and NS5B regions. Year of infection was estimated as one year after self-reported initiation of injecting. Trends in HCV genotype distribution were evaluated. Factors associated with HCV genotype 3a infection (vs. non-3a) were assessed using logistic regression.

Result(s): Among 1,107 HCV RNA positive participants, 818 (74%) had available HCV genotyping. The HCV genotype prevalence was: G1a: 52% (n=422), G1b: 6% (n=46), G2a: 3% (n=22), G2b: 6% (n=53), G3a: 32% (n=263), G4a: <1% (n=4), G6a: 1% (n=7) and G6e <1% (n=1). The mean age was 33.8 years (SD, 9), 37% were female and 21% were HIV positive. Overall, 36% (n=288) were estimated to have been infected prior to 1980, 44% (n=354) infected between 1980 and 1995, and 21% (n=167) infected between 1995 and 2010. HCV genotype 3a was more prevalent in females (38% vs. 30%, P=0.040) and those without HIV infection (34% vs. 25%, P=0.021). The prevalence of HCV genotype 3a infection increased from 28% among those infected prior to 1980 to 40% among those infected between 1995 and 2010 (P=0.009). Factors independently associated with HCV genotype 3a infection included female sex [adjusted odds ratio (AOR) 1.45; 95%CI 1.03, 2.03], HIV co-infection (AOR 0.65; 95%CI 0.44, 0.95) and more recent estimated year of infection (vs. <1980; 1980 to 1995 AOR 1.21, 95%CI 0.85, 1.70; 1995 to 2010 AOR 1.56, 95%CI 1.03, 2.34).

Conclusion(s): The prevalence of HCV genotype 3a infection appears to have increased among PWID in this setting. This has important implications for strategies focused on HCV treatment as prevention, given reduced efficacy of IFN-free DAA-based therapy in people with HCV genotype 3a. Further studies investigating the molecular epidemiology of HCV transmission are needed to inform HCV treatment as prevention trials among PWID.

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Poster number: 406

THE PILOT PROJECT "HEALTH BREAK/PAUSE-SANTE": EXPERTS JOINING FORCES TO ALLOW AND OPTIMIZE STANDARDS OF HEP C CARE OF HOMELESS PATIENTS.

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Background: Management of homeless Hepatitis C (HepC) patients remains an unmet need. Mission Old Brewery has been involved since 1889 in providing essential cares and lodging to the homeless Montreal population. CAPAHC is a Quebec organism specializing in HepC community care and services since 2003. A Global approach to community work is currently being evaluated through the Health Break Pilot project design to optimize chronic HepC treatment specifically in the homeless patient's population.

Purpose: What happens when two groups of experienced stakeholders in the HepC community share expertise and join forces to maximize the management of homeless patients? As inherent symptomatic HepC treatment challenges add up to the homeless daily harsh reality, special attention to homeless patients' needs has to be paid to provide the most appropriate treatment conditions. Doctors generally do not want to deal with the homeless population due to their unstable lifestyle, their drug use, side effects of treatment and costs associated with it. The Health break project allows this population to get cured from hepc. Beyond offering an appropriate setting for patients undergoing therapy, building trust, providing robust humanistic support have determinant impact on chronic treatment success and adherence.

Method: A team of health care providers involving physicians, nurses, social workers, nutritionists and pharmacists joined expertise providing a Therapy Hall (corridor de services) to support 14 homeless patients in their chronic HepC treatment regimen. An ancillary support team ensured sustained social reinsertion attending daily patients' needs and provided counselling. A holistic approach was implemented.

Result(s): After six months, results confirm a higher treatment success is reach. 11 of 12 patients had successful treatment. Patients with genotype 1 have shortened treatment to 28 weeks instead of 48. The adherence rate to treatment was particularly high and the majority of patients admit that without this project and entourgae, they would never received treatment.

Conclusion(s): Raising standards of care for the homeless HepC patients is possible when experts work in a unified front to surround the patients with adapted cares and environment. On the long-term, funding will be determinant to sustain such holistic treatment strategy and success of patients management.

Funding source(f): The main source of funding was from Service Canada who has funded the renovation of the building. Old brewery Mission is busy providing meals and the majority of human resources. CAPAHC hired a social worker as project coordinator and a nurse to provide treatment (injections and lab) directly in the home. Participants pay a portion of their welfare as service charges. Several donations were made by stores and a pharmacy. Pharmaceutical companies have furnished a treatment room for the nurse.
To ensure the durability of this CAPAHC project is now seeking funds.

Poster number: 407

PHYLODYNAMIC ANALYSIS OF A REGIONAL HEPATITIS C VIRUS EPIDEMIC

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Background: Phylogenetic inferences drawn from viral sequence data can identify signatures of past and present processes that describe the evolution of an epidemic. Scaling the branches of phylogenetic trees in proportion to time and combining this information with patient attribute data enables the chronology of key epidemiological parameters contributing to an epidemic to be inferred. In British Columbia, the Hepatitis C virus (HCV) epidemic poses a serious public health problem and mirrors what is seen across North America. The highest HCV prevalence is in baby boomers, generally at low risk of onward transmission but susceptible to premature morbidity and mortality. In contrast, transmission is ongoing in younger populations who are typically engaged in injection drug use (IDU).

Purpose: To investigate factors contributing to the HCV epidemic in BC and to reconstruct the epidemic history of HCV using anonymized sequence data from patients diagnosed at the BC Centre for Disease Control in 2011.

Method: One hundred time-scaled phylogenetic trees were reconstructed using 536 HCV NS5B sequences from 522 individuals. The origin of the HCV epidemic was estimated using the root age of each phylogenetic tree in our distribution. We also visualized the diversification of HCV infections through time in males versus females, in two age groups (50-70 yrs and 20-50 yrs) and with each of the various HCV subtypes using lineage through time plots.

Result(s): Our analyses suggest a median age of the HCV epidemic of approximately 2000 years with an initial slow rate of expansion followed by a rapid increase in sequence diversity beginning approximately 60 years ago. Examining lineage diversification of the various HCV genotypes over time shows the highest diversity rate increase in genotype 1a, and in males compared to females. Lineage diversity through time analysis of 50-70 yrs versus 20-50 yrs highlights that although HCV prevalence is high in baby boomers, this cohort is not contributing significantly to ongoing transmission. Analysis also confirms that the net increase in HCV epidemic growth continues to occur in the younger age category likely due to IDU practices.

Conclusion(s): Examination of HCV sequence diversity using lineage through time plots can be highly informative for describing viral epidemics and can highlight factors contributing to epidemic growth. Such information can supplement traditional surveillance data to enable the development of more robust measurements of transmission dynamics. Our analyses of BC sequence data reinforces the need for targeting harm reduction and prevention strategies to at-risk youth, especially in males, who remain the major contributors of onward HCV transmission.

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